Review Article

RAS mutation: site of disease and recurrence pattern in colorectal cancer

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Abstract: Somatic mutation status in metastatic colorectal cancer (CRC), and namely mutational activation of the Kirsten rat sarcoma viral oncogene homolog (KRAS) oncogene, is becoming more and more relevant in clinical practice. In this review, we describe the current data about the importance of associations between the mutational activation status of the KRAS oncogene and clinical outcomes, prognosis and metastatic patterns of CRC. The presence of a KRAS mutation is detected in approximately 30–50% of CRC and represents a powerful predictor of oncologic outcomes. It is associated with low response to systemic chemotherapy and for insensitivity to the anti-EGFR antibodies in the preoperative setting. It is more frequently associated with right colon cancer. In non-metastatic patients, KRAS mutation leads to more aggressive disease with shorter recurrence free survival (RFS) and more lung recurrences. After resection of CRC liver metastases (LiM), KRAS mutation is directly associated with increased risk of recurrence, worse overall survival (OS), and a distinct metastatic pattern with more invasive intrahepatic recurrence and increased recurrence outside of the liver, particularly in the lung, the peritoneum, and even in uncommon metastatic sites such as the brain and bones. As metastasectomy with curative intent is increasingly considered, a comprehensive approach of tumor biology is required to face the specific challenge of patients with metastatic CRCs. Thus, as it represents one of the strongest predictors of oncologic outcomes, integrating the KRAS mutational status at all the different stages of patient care appears crucial in order to adapt both medical and surgical strategies.

Keywords: Kirsten rat sarcoma viral oncogene homolog (KRAS); colorectal cancer (CRC); metastases; chemotherapy

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Introduction

Colorectal cancer (CRC) represents the third leading cause of cancer-related death worldwide. Approximately 15% to 25% of patients present with synchronous metastasis at diagnosis and 25% to 50% will develop metachronous distant disease and distant recurrence often occurs within 3 years. The most common site of CRC metastases is the liver, followed by lungs and peritoneum. This recurrence pattern will directly guide the optimal surveillance strategy after curative treatment of CRC, namely in the metastatic setting. Advances in cytotoxic agents and targeted therapies have led to major control of metastatic disease, allowing curative intent surgery and resulting in real improvement in overall survival (OS) for patients with metastatic CRC (1).

Carcinogenesis of CRC is directly linked to activating mutations in oncogenes. In CRC, different signal pathways can be affected such as the mitogen-activated kinase (MAPK) pathway or the phosphatidylinositol 3-kinase (PI3K) pathway. Among the MAPK pathway genes, Kirsten

rat sarcoma viral oncogene homolog (KRAS) mutations are the most prevalent predictive and prognostic activated oncogene, detected in approximately 30–50% of CRCs. Currently, evaluation for mutations in KRAS in metastatic CRC is part of standard of care in order to select patients to treatment targeting the epidermal growth factor receptor (EGFR), as the presence of a KRAS mutation predicts for insensitivity to the anti-EGFR antibodies (2,3). Furthermore, it is now well established that it is associated with poor recurrence free (RFS) and OS after liver resection, making RAS mutation status as a powerful predictor of oncologic outcomes (4,5). In addition, the somatic mutation profile may also predict the pattern of metastatic spread in metastatic CRC and future prognosis. Metastasectomy with curative intent becomes increasingly considered and possible in metastatic CRC (6-8). Understanding and considering tumor biology as a powerful predictor of outcome may seem crucial in a modern and tailored approach to guide patient selection, treatment and surveillance in both pre and post therapeutic workups for CRC patients (1,9,10).

Therefore, in this review, we describe the current data about the importance of associations between the mutational activation status of the KRAS oncogene and clinical outcomes, disease prognosis and metastatic patterns of CRC.

Impact of RAS mutation in non-metastatic CRC

In nonmetastatic CRC patients, prevalence of KRAS mutation ranges from 30% to 38%. Patients with mutated KRAS seem more associated with right colon cancer than left colon cancer (60% *vs.* 40%, OR 2.05, P<0.001), low grade tumor (OR 0.73, P=0.007) and have less deficient mismatch repair status (OR 0.21, P<0.001). They are also less likely to have a first degree relative with CRC or to be a smoker (11). Similar results concerning the association between KRAS mutation and right colon cancer were reported (12,13).

Oncologic outcomes associated with RAS mutation in non-metastatic patients

Molecular testing and genotyping do not represent standard for non-metastatic patients (14,15). The prognostic impact of RAS mutation in this population is inconsistent (2,16,17). Stage I CRC has excellent prognosis with 5-year OS up to 95%. However, Reggiani Bonetti *et al.* (18) evaluated the impact of RAS mutational status in 62 stage I CRC. A RAS mutation was present in 40% of patients and was statistically associated with worse 5-years OS (P=0.019). Yoon *et al.* studied in a large cohort of 2,478 patients with resected stage III CRC receiving adjuvant FOLFOX alone or combined with cetuximab the impact of RAS mutation. A RAS mutation in codon 12 was present in 31% of patients and 8.9% had mutation in codon 13. KRAS mutations in either codon 12 (HR 1.52, P<0.0001) or 13 (HR 1.36, P=0.0248) were associated with shorter DFS (19). Similar results were obtained in another large cohort of 2,720 patients with 35% having a RAS mutation. Wild-type patients had 70.7% 5-year DFS versus 61% in mutated patients (16). It seems also that mutational status appears as a predictive biomarker of the benefit of adjuvant chemotherapy. Indeed, Deng *et al.* observed no benefit in 3-year DFS of an adjuvant FOLFOX in stage III CRC among patients showing wild-type RAS (84.3% *vs.* 82.0%, P=0.661), whereas adjuvant treatment significantly improved outcomes in patients with RAS tumors (74.4.0% *vs.* 50.2%, P=0.020) (20).

Finally, KRAS mutation not only impacts time of recurrence but also its patterns. Tie *et al.* showed that RAS mutation in stages II and III CRC was associated with more lung recurrences (HR 2.1, P=0.007). However, it was not associated with liver relapse (21).

Thus, it seems that tumor biology, namely RAS mutation profile, provides important prognostic information as well in non-metastatic CRC that could guide adjuvant treatments or surveillance modalities and therefore needs further investigations.

Impact of RAS mutation in metastatic CRC

Epidemiology of RAS mutations in metastatic CRC

Prevalence of KRAS mutation among metastatic CRC patients range from 25% to 52% (22).

Concordance between primary tumor and metastases concerning overall oncogene mutational status is high ranging between 85% to 100%, irrespective of patient medical history or treatment duration, highlighting that evaluation of the primary tumor appears as a sufficient and reasonable surrogate to establish the therapeutic strategy in the metastatic setting (23-27).

At diagnosis of metastatic disease, *RAS* mutant and wild-type tumors differed in the pattern of metastatic involvement. Among a cohort of 918 patients from Memorial Sloan Kettering Cancer Center, *RAS* mutant

patients exhibited a higher incidence of lung metastasis at diagnosis compared to the wild-type cases. Liver, lung, bone, and brain involvement at the time of diagnosis of metastatic disease occurred in 75%, 13%, 0.6%, and 0.2% of *RAS* wild-type, respectively, and in 74%, 22%, 0.9%, and 0.5% of *RAS* mutant patients, respectively. Metastases were limited to the liver at the time of diagnosis in 303 (64%) *RAS* wild-type and 245 (56%) *RAS* mutant cases (P=0.015) (13).

Impact of RAS mutation in liver metastases (LiM)

Approximately, 15% to 25% of patients present with LiM at diagnosis, and another 25% to 50% will develop metachronous hepatic disease within 3 years. Among them, KRAS mutant represents 18% to 41% of patients (1). It is now well established that KRAS mutant metastatic CRC is associated with worse oncologic outcomes with a higher risk of recurrence and decrease OS following curative resection of LiM (4,5,10,22,28). From the experience of the MD Anderson Cancer Center, Vauthey *et al.* found that patients with KRAS mutant metastatic CRC experienced worse RFS (HR 1.9, P=0.005) and OS (HR 2.3, P=0.002) compared with KRAS wild-type patients who underwent single-regimen modern chemotherapy before resection of LiM. The 3-year RFS and OS after curative resection were 33.5% and 81% for *RAS* wild-type patients and 13.5% and 52.2% for *RAS* mutant (P=0.001 and P=0.002) (4). In a cohort of 169 patients from Memorial Sloan Kettering Cancer Center, Kemeny *et al.* found similar results with 3-year RFS and OS of 30% and 81% in KRAS mutated patients versus 46% and 95% in wild-type patients with resected LiM and adjuvant hepatic arterial infusion plus systemic therapy (5). Presence of KRAS mutations does not only affect the time of recurrence after resection of LiM, it also determines its patterns. Indeed, in both cohorts, RAS mutation was associated with an increased incidence of recurrence in lung, bone and brain in comparison to wild-type patients (4,5). Yaeger *et al.* confirmed that RAS mutant was predictive of involvement of these sites (HR 1.5, 1.6 and 3.7, respectively). Cumulative incidences at 2 years were 32.5% versus 19% for lung (P=0.001), 8.8% versus 4.4% for bone (P=0.024), and 1.4% versus 0.2% for brain metastasis (P<0.01) (13). However, the cumulative incidence of liver metastasis did not vary by *RAS* mutation status (12% versus 14.3%, P=0.78). RAS mutation appears also associated with more aggressive recurrences not amenable to second or salvage curative treatments. Okuno *et al.* studied 566 patients with recurrence after hepatectomy for LiM, of whom 309 (54.6%) underwent chemotherapy only, 189 (33.4%) surgical resection, 47 (8.3%) ablation and 21 (3.7%) radiation therapy. Local therapy was statistically associated with major improved OS compare to chemotherapy only, and RAS mutation was associated with recurrence not amenable to local therapy (HR 1.49, P=0.001). It was also associated with worse survival in both patients who received local therapy and those who received chemotherapy only (29).

Secondly, several clinical scores and nomograms mainly based on clinicopathological factors were created in order to guide selection of patients who would benefit from resection of LiM (30-33). As RAS mutation status may represent a direct measure of tumor biology and appears strongly linked to oncologic outcomes, it has been recently included in a new and modified predictive score in order to offer a better potential guide for patients selection. Indeed, replacing traditional clinicopathological factors such as disease free survival, number of metastases and CEA level with RAS mutation in addition to lymph node positive primary status and size of metastases in the Memorial Sloan Kettering Clinical Score (traditional clinical score, t-CS) resulted in an modified clinical score (m-CS) that outperformed the t-CS, and thus providing a quick and easy preoperative assessment of the expected survival benefit (10). Similarly, especially for patients with RAS mutated LiM, Passot *et al.* proposed a predictive model defining and combining three risk factors—node-positive primary tumor, largest LiM >3 cm and >7 cycles of preoperative chemotherapy—in order to help selection of candidates to hepatectomy. High-risk patients with the 3 risk factors demonstrated poorer median OS of 21.5 months versus 57 and 41 months for patients with 1 or 2 risk factors, respectively. Thus, alternative therapies or further systemic therapy would be preferable for those patients (34). Finally, as next-generation sequencing technology becomes widely available, multigene analysis is possible and could provide a more accurate risk stratification based directly on tumor biology. For instance, a concomitant RAS and TP53 mutation is associated with decreased survival after resection than RAS mutation only, and patients with a high evolutionary action score TP53 mutation showed even a worse prognosis (9). Those results underline that it is time to change the paradigm of traditional poor prognostic factors, such as multiple LiM or extrahepatic disease. Such patients could be considered for surgery if their mutational status is favorable. Further investigations using high-throughput genomic analysis are needed to validate those results and to optimize patient selection for surgery.

Finally, tumor biology could be also directly integrated in the surgical strategy. Indeed, non-anatomical resections and parenchymal sparring represent standard of care for patients with LiM. In the era of modern chemotherapy, it appears that a 1 mm resection margin could be sufficient to obtain acceptable oncologic outcomes (35-37). Furthermore, it seems that a positive resection margin does not worsen survival in patients with a major pathologic response to preoperative chemotherapy (38). However, RAS mutations are associated with less optimal radiologic morphologic response and major pathologic response after modern chemotherapy that included bevacizumab before resection of LiM (39). In a study including 633 patients who underwent surgery for LiM, of whom 229 had mutant RAS, RAS mutation was significantly associated with positive resection margin rate 11.4% versus 5.4% for wild-type RAS patients (P=0.007), suggesting a more aggressive intrahepatic growth pattern. A positive margin (HR 3.36) and RAS mutation (HR 1.629) were independently associated with worse OS (40). Similarly, presence of RAS mutation is associated for more diaphragmatic invasion by liver metastasis requiring major hepatic resection and diaphragmatic resection (41). Margonis *et al.* suggested that anatomical resections with more extensive surgical margins could counterbalance this adverse and more invasive genetic profile associated to RAS mutation (42). Another concept for limiting systemic toxicity while intensifying treatment in the adjuvant setting for such patients is hepatic arterial infusion (5,43). However, these different strategies for controlling hepatic recurrence in RAS mutated patients with LiM need further investigations in randomized trials.

Impact of RAS mutation in lung metastases (LuM)

LuM will eventually develop in 5–15% of patients with mCRC and prognosis after metastasectomy ranges between 41% and 56% (44). The presence of a *KRAS* mutation appears directly associated to LuM. In non-metastatic patients with resected stage II or III CRC, RAS mutated patients experienced more lung recurrence (HR 2.1, P=0.007) (21). In a large Australian cohort of 5,967 patients with mCRC, RAS mutation was significantly associated with lung-only metastases (HR 1.4, P=007) (45).

Secondly, in mCRC, KRAS mutation influences directly oncologic outcomes. In patients with resected LiM, RAS mutation is associated with worse lung RFS (4,5,13). Presence of a KRAS mutation represents also a strong predictive factor of poor OS in case of LuM. Ghidini *et al.* studied lung specimens from 75 mCRC among whom 36% had KRAS mutation. Median OS was 60.9 for wild-type patients versus 36.6 months in mutated patients (P=0.035). In multivariate analysis, presence of a KRAS mutation was statistically associated with worse OS (HR 2.17, P=0.012) (46). Similar results were obtained by Renaud *et al.* in a cohort of 180 patients with lung metastasectomy. Molecular analysis revealed mutated KRAS in 93 patients (51.7%) and mutated BRAF in 19 patients (10.6%). The 5-year OS was 0% for mutated BRAF, 44% for mutated KRAS and 100% for wild-type, with corresponding median OS of 15, 55 and 98 months, respectively (P=0.001) (47). In mutated patients, it seems also that according to KRAS amino-acid substitution, different signaling pathways are activated, resulting in different tumor evolution and clinical outcomes. After lung metastasectomy, KRAS exon 2 codon 13 mutation is associated with, better OS (82 *vs.* 54 months, P=0.009) and lung RFS (78 versus 56 months, P=0.008) than codon 12 (48). Similarly to LiM, Renaud *et al.* showed also that anatomical resection with segmentectomy compared to wedge resections of LuM could improve OS in RAS mutated patients. However, in wild-type patients, the type of resection did not impact OS (8).

Impact of RAS mutation in peritoneal metastases (PM)

In CRC, up to 15 % of patients will develop PM that carry a worse prognosis than other metastases (49). However, since a few decades, development of cytoreductive surgery (CRS) with or without peroperative hyperthermic intraperitoneal chemotherapy (HIPEC) leads to prolonged survival with median survival ranging from 30 to 45 months in comparison to dismal prognosis associated to systematic treatment only (50,51). Survival is undoubtedly linked to the crucial surgical endpoint: completeness of CRS, which is directly associated to the extent and distribution of PM (7,52). However, the role of tumor biology and RAS mutations in the context of PM remained unclear until recent studies (53-57). RAS mutation is associated with peritoneal recurrence after resection of LiM (41) and prevalence of RAS mutations appears higher in PM than in LiM, up to 58% (55). In 524 patients who underwent CRS and HIPEC for CRC PM, 378 had known RAS/RAF status. Among them, 186 (49.2%) had a RAS/RAF mutation. KRAS (HR 1.46) and BRAF (HR 3.97) were both associated with impaired OS and also shorter RFS. Based on those results, a point-based risk score termed BIOSCOPE, including RAS/RAF mutational status, PCI, and N- and G-status of the primary tumor was developed to determine 4 risk groups with distinct prognosis in order to

guide patient selection (56). Similarly, Arjona-Sanchez *et al.* reported a significant decrease in OS for patients with RAS mutated tumors (HR 2.024, P=0.045). Thus, they associated RAS mutational status to PSDSS, the most widely used and validated score to select patient for CRS and HIPEC, and created a new score, RAS-PSDSS, that also outperformed the former PSDSS (57).

Impact of RAS mutation in bone metastases (BoM)

BoM in patients with CRC are relatively uncommon and incidence occurs in 3% to 7%. Median OS after diagnosis of BoM ranged from 5 to 21 months. Risk factors usually described are rectal cancer, primary lymph node invasion and lung metastases (58). KRAS status appears also to be predictive of BoM. Kemeny *et al.* found a cumulative recurrence for BoM by 3 years of 13.4% in KRAS mutated versus 2% in KRAS wild patients (5). At 2 years, Yaeger *et al.* showed similar results with a cumulative incidence of BoM of 8.8% with RAS mutated tumors versus 4.4%, in wild-type patients (P=0.024). RAS mutation remained an independent predictor of BoM in multivariate analysis (HR 1.62, P=0.012) (13).

Impact of RAS mutation in brain metastases (BM)

BM represent an uncommon metastatic site in CRC. However, consequences for affected patients are major. They are reported to develop late in the disease and patients normally have metastases to other organs at diagnosis, namely in the lung (59). Incidence of BM ranges from 0.6% to 3.2% (60). However, in selected patients, resection or radioablation of oligometastatic disease may provide benefits with median survival ranging from 2 to 9 months for non-resected patients versus 10 to 16 months for patients with loco-regional treatments (61). KRAS mutation is directly associated with higher prevalence of BM from CRC and several studies investigated this potential association (27,61-63). Tie *et al.* found that 56.5% of patients with BM had RAS mutations (21). Yaeger *et al.* showed that patients with RAS mutated tumors had higher incidence of BM (6.1% versus 1.9%) than wild-type patients (HR 3.7, P<0.01) (13). After resection of LiM, Kemeny *et al.* found a cumulative recurrence by 3 years of 14.5% in KRAS mutated versus 2% in KRAS wild patients (5). KRAS mutation was an independent predictor of spread to the brain in both studies. Thus, an understanding of this specific pattern of spread and recurrence may alert physicians to look for specific neurologic symptoms and to perform cerebral CT scans in *RAS* mutant metastatic CRC.

Conclusions

In both non-metastatic and metastatic CRCs, RAS mutations not only predict strongly oncologic outcomes with less response to chemotherapy, worse RFS and OS, but also have direct impact on the site of disease and recurrence patterns. RAS mutated status is more frequently associated with right side colon cancer, and mutations in the primary tumor remain concordant with distant metastasis. It seems not directly associated with LiM but appears more frequent in LuM or PM and uncommon metastatic sites such as BoM and BM. Integration of RAS mutations in the selection of patients for curative intent surgery in metastatic CRC appears crucial and may render traditional clinicopathological risk factor obsolete. Further investigations using namely high-throughput genomic analysis are needed to validate this new paradigm.

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Footnote

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