Review Article

Impact of somatic mutations on patterns of metastasis in colorectal cancer

Marla Lipsyc, Rona Yaeger

Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
Correspondence to: Rona Yaeger, MD. Memorial Sloan Kettering Cancer Center, 300 E 66th Street, New York, NY 10065, USA.
Email: yaegerr@mskcc.org.

Abstract: Somatic mutation status in metastatic colorectal cancer (mCRC) is becoming increasingly clinically relevant as it may be correlated not only with response to biologic therapies, but also with site-specific pattern of metastatic spread and outcome. In this review, we describe our current understanding of associations between mutational activation of the *KRAS*, *BRAF*, *PIK3CA*, and *NRAS* oncogenes and clinical outcomes and metastatic patterns of mCRC. The presence of a *KRAS* mutation is associated with a distinct pattern of metastatic spread with decreased liver metastases and increased lung, brain, and bone metastases. In patients who undergo resection of colorectal liver metastases (CLM) with curative intent, *KRAS* mutation is associated increased risk of recurrence, worse survival, and increased recurrence outside of the liver, particularly in the lung, but also in the brain and bone. *BRAF* mutation, a poor prognostic factor in mCRC, is associated with decreased liver-limited metastasis and increased peritoneal and distant lymph node metastases. *PIK3CA* mutation does not clearly affect outcomes in the metastatic setting, but is associated with concurrent *KRAS* mutations, and has been associated with an increased incidence of lung and brain metastases, metastatic sites preferentially involved in *KRAS* mutant mCRC. *NRAS* mutation may confer worse survival and early studies suggest *NRAS* mutation may promote tumorigenesis in the setting of colorectal inflammation. As metastasectomy with curative intent is increasingly considered in patients with mCRC, understanding patterns of metastasis associated with tumor mutations may help focus medical treatment, surgical management, and surveillance in patients with mCRC.

Keywords: Colorectal cancer (CRC); metastasis; RAS; BRAF; phosphatidylinsolitol 3-kinase (PI3K)

Submitted Dec 23, 2014. Accepted for publication Mar 23, 2015.
doi: 10.3978/j.issn.2078-6891.2015.045
View this article at: http://dx.doi.org/10.3978/j.issn.2078-6891.2015.045

Introduction

It has long been noted that outcomes for patients with metastatic colorectal cancer (mCRC) vary widely. As sequencing technology has become less expensive and tumor genotyping has become standard practice for mCRC, clinicians now often have information on the mutational status of oncogenes, including the *KRAS*, *BRAF*, *PIK3CA*, and *NRAS* oncogenes. Many of these mutations represent early events occurring in the adenoma or adenoma-adenocarcinoma transition (1,2), but recent data suggest these mutations may affect the metastatic behavior of tumors and patterns of metastatic spread. In addition to the prediction of response to targeted agents, an understanding of the association between these somatic mutations and site-specific pattern of metastatic spread in mCRC is important as metastasectomy with curative intent is increasingly considered in patients with mCRC and as this may correlate with disease prognosis. Moreover, knowledge of clinical features associated with somatic mutation in mCRC may help focus treatment and surveillance for mCRC patients. In this review, we describe our current understanding of associations between mutational activation of the *KRAS*, *BRAF*, *PIK3CA*, and *NRAS* oncogenes and clinical outcomes and metastatic patterns of mCRC.

KRAS oncogene

KRAS is the most commonly activated oncogene in colorectal cancer (CRC). Approximately 30-50% of CRCs harbor somatic *KRAS* mutations, most frequently in exon 2 at codon 12 or 13 and less often at codons 61 or 146 (3). *KRAS* is a member of the RAS oncogene family. RAS proteins are small GTPases that are active when bound to GTP and regulate cell proliferation, survival, and differentiation. Point mutations in *KRAS* lead to constitutive activation by preventing hydrolysis of GTP. Currently, evaluation for mutations in *KRAS* is part of standard of care for mCRC to guide the use of the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab as the presence of a *KRAS* mutation predicts for insensitivity to these agents (4-8).

KRAS mutant mCRC has been associated with a higher risk of recurrence following resection of hepatic metastases with curative intent, a procedure performed in about 25% of patients with colorectal liver metastases (CLM). Karagkounis *et al*. found that *KRAS* mutation status was an independent predictor of recurrence-free survival (RFS) and overall survival (OS) after surgical resection of CLM. Patients with *KRAS* mutant mCRC experienced worse RFS (HR 1.89) and OS (HR 2.13) after hepatectomy for CLM (9). Similarly, Vauthey *et al*. found that *RAS* (*KRAS*/*NRAS*) mutation was associated with worse OS (HR 2.3, P=0.002) and overall RFS (HR 1.9, P=0.005) after resection of CLM in multivariate analyses (10). In their dataset of 193 patients who underwent single-regimen modern chemotherapy before resection of CLM with curative intent, the 3-year RFS was 33.5% for *RAS* wild-type cases and 13.5% for *RAS* mutant cases (P=0.001). In a population of patients undergoing CLM resection plus adjuvant hepatic arterial infusion (HAI) and systemic therapy, Kemeny *et al*. identified a significant reduction in RFS at three years for *KRAS* mutant mCRC compared to *KRAS* wild-type mCRC (30% *vs*. 46%, P=0.005) and a trend towards decreased 3-year OS in the *KRAS* mutant mCRC cases (81% *vs*. 95%, P=0.07) (11).

The presence of a *KRAS* mutation may impact recurrence patterns. *KRAS* mutation has been associated with increased risk for lung recurrence (HR 2.1, P=0.007) in patients with resected stage II and III colorectal tumors (12). In patients undergoing resection of CLM with curative intent, *RAS* mutation has been associated with worse lung RFS on multivariate analysis (HR 2.0, P=0.01), and in patients undergoing resection of CLM plus adjuvant HAI therapy with curative intent, *KRAS* mutation was associated with an increased cumulative incidence of recurrence in the lung (58% *vs*. 33%, P<0.01), brain (14.5% *vs*. 2%, P=0.05), and bone (13.4% *vs*. 2%, P<0.01) in comparison to patients with *KRAS* wild-type tumors (11).

Among all patients with mCRC, the presence of a *KRAS* mutation appears to influence the pattern of metastatic spread. Tie *et al*. analyzed the frequency of *KRAS* mutations in a series of liver, lung, and brain metastases (12). They found that *KRAS* mutations were less prevalent in liver metastases (32.3%), but more prevalent in lung (62.0%) and brain (56.5%) colorectal metastases (P=0.003). At the time of diagnosis of mCRC, *RAS* mutant mCRC is more likely to have spread to the lungs compared to *RAS* wild-type mCRC (22% *vs*. 13%, P<0.01) (13). *RAS* mutation is associated with a significantly higher cumulative incidence of lung, bone, and brain metastases after diagnosis of metastatic disease and is an independent predictor of metastasis to these sites (HR 1.5, 1.6, and 3.7 for lung, bone, and brain respectively) (13).

The mechanism by which RAS activation affects metastatic patterns is still unknown. RAS activation has been associated with vascular invasion and hematogenous metastases (14). A recent study focusing on the mechanism of sequential metastasis from the liver to the lung in *KRAS* mutant colon cancer cell line models found that downregulation of p38 MAPK signaling led to increased lung colonization through increased expression of the cytokine parathyroid hormone-like hormone (PTHLH), contributing to tumor cell extravasation to the lungs through PTHLH-inducted, caspase-independent apoptosis of endothelial cells in the lung microvasculature (15).

BRAF oncogene

BRAF mutations occur in 5-15% of mCRC, and over 95% of these mutations consist of a conversion of valine to glutamic acid at codon 600 (V600E) that leads to constitutive activation of *BRAF* (5,16). *BRAF* and *RAS* mutations in CRC are nearly always mutually exclusive. *BRAF* mutation is associated with tumor development through the serous serrated pathway, rather than the classic adenoma-carcinoma pathway (17,18).

BRAF mutation has been found to be a poor prognostic factor in multiple clinical trials. While the median survival for patients with mCRC overall has improved to over two years, reported median survival for *BRAF* mutant mCRC remains less than 1 year (6,19,20). *BRAF* mutant CRC

more frequently demonstrates adverse histologic features such as lymphatic invasion, mean number of lymph node metastases, perineural invasion, and high tumor budding (21). *BRAF* mutant mCRC is also associated with poorly differentiated morphology, mucinous histology, and signet ring histology (21-23).

BRAF mutant mCRC exhibits a distinct pattern of metastatic spread. These tumors are less likely to present with liver-limited metastasis and are associated with increased incidence of peritoneal and distant lymph node involvement (19,20,22,23), a pattern of metastatic spread that may contribute to the poor outcomes of *BRAF* mutant mCRC. Patients with *BRAF* mutant mCRC less commonly undergo metastasectomy (10,19), and *BRAF* mutation confers a poor prognosis in patients who undergo resection of metastases with curative intent (23). *BRAF* mutation is also associated with atypical distant lymph node metastasis (24). The mechanism of increased lymph node metastasis in *BRAF* mutant mCRC is under investigation. Interestingly, a recent study in patients with CRC identifies overexpression of BRAF-activated long non-coding RNA (BANCR) in specimens from patients with *BRAF* mutant CRC and finds that this overexpression induces the epithelial-mesenchymal transition (EMT) and correlates with increased lymph node metastasis (25).

PIK3CA oncogene

PIK3CA encodes the p110α catalytic isoform of phosphatidylinsolitol 3-kinase (PI3K) and exhibits activating, hotspot mutations in 15-20% of CRCs (16,26). Mutation of *PIK3CA* is thought to occur during the adenoma-carcinoma transition in the classic adenoma-carcinoma sequence of development of CRC and commonly co-occurs with mutations in *KRAS* or *BRAF* (5). About 70% of *PIK3CA* mutant mCRC cases have concurrent mutations in the classic mitogen-activated protein kinase pathway, predominantly *KRAS*.

PIK3CA mutation alone has not been found to correlate with patient survival in the metastatic setting (5,27,28). The effect of *PIK3CA* mutation on metastatic pattern is unclear and is complicated by the high frequency of concurrent *KRAS* mutations. Our group did not find a correlation of *PIK3CA* mutation with the cumulative incidence of liver, lung, or bone metastasis, but did find an increased incidence of brain metastasis in mCRC with mutant *PIK3CA* (1.4% *vs*. 0.8%, P=0.0013) (13). The association of *PIK3CA* mutation with brain metastasis appeared to be driven by the high concurrent frequency of *KRAS* mutation and the increased incidence of brain metastasis in *KRAS* mutant mCRC as six of the seven cases of brain metastasis that developed in *PIK3CA* mutant mCRC had concurrent *KRAS* mutations. *PIK3CA* mutation has also been associated with lung metastases in mCRC (23% *vs*. 8.7%, P=0.004), another metastatic site associated with *KRAS* mutation (22).

NRAS oncogene

NRAS is mutated in approximately 3% of CRCs (5,13). Activating mutations in *NRAS* are mutually exclusive with *BRAF* and *KRAS* mutations in CRC and also predict for lack of activity of anti-EGFR antibodies (6).

NRAS mutation has been associated with decreased OS in small series (29). NRAS activation has been suggested to lead to colorectal tumor development in the context of inflammation (29). Activated NRAS may suppress stress-induced apoptosis in CRC cells. A recent study suggests that in CRC, NRAS signals through STAT3, a transcription factor that normally requires IL-6 to promote growth and survival in a cytokine-independent pathway (29).

Conclusions

Increasing data suggest that the presence of mutations in the *RAS* and *BRAF* oncogenes impacts patterns of metastasis. Increased lung, brain, and bone metastasis may be seen in *RAS* mutant mCRC in addition to increased recurrence after hepatectomy. This recurrence is associated with non-liver metastatic sites, such as the lung. *BRAF* mutation is associated with increased peritoneal involvement, distant lymph node metastasis, and decreased incidence of liver-limited metastasis, which may contribute to the overall poor prognosis seen in *BRAF* mutant mCRC. Our expanding understanding of the correlation of somatic mutations with metastatic patterns should contribute to the clinical care of mCRC patients by focusing treatment, defining the role of metastasectomy, and guiding surveillance strategies for patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.
2. Whitehall VL, Rickman C, Bond CE, et al. Oncogenic PIK3CA mutations in colorectal cancers and polyps. Int J Cancer 2012;131:813-20.
3. Janakiraman M, Vakiani E, Zeng Z, et al. Genomic and biological characterization of exon 4 KRAS mutations in human cancer. Cancer Res 2010;70:5901-11.
4. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-34.
5. 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 2010;11:753-62.
6. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34.
7. 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;26:374-9.
8. Peeters M, Douillard JY, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. J Clin Oncol 2013;31:759-65.
9. 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 2013;119:4137-44.
10. 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 2013;258:619-26; discussion 626-7.
11. Kemeny NE, Chou JF, Capanu M, et al. KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. Cancer 2014;120:3965-71.
12. Tie J, Lipton L, Desai J, et al. KRAS mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res 2011;17:1122-30.
13. Yaeger R, Cowell E, Chou JF, et al. RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer. Cancer 2015;121:1195-203.
14. Tanaka M, Omura K, Watanabe Y, et al. Prognostic factors of colorectal cancer: K-ras mutation, overexpression of the p53 protein, and cell proliferative activity. J Surg Oncol 1994;57:57-64.
15. Urosevic J, Garcia-Albéniz X, Planet E, et al. Colon cancer cells colonize the lung from established liver metastases through p38 MAPK signalling and PTHLH. Nat Cell Biol 2014;16:685-94.
16. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
17. Rustgi AK. BRAF: a driver of the serrated pathway in colon cancer. Cancer Cell 2013;24:1-2.
18. Kalady MF. Sessile serrated polyps: an important route to colorectal cancer. J Natl Compr Canc Netw 2013;11:1585-94.
19. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 2011;117:4623-32.
20. Yokota T, Ura T, Shibata N, et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br J Cancer 2011;104:856-62.
21. Pai RK, Jayachandran P, Koong AC, et al. BRAF-mutated, microsatellite-stable adenocarcinoma of the proximal colon: an aggressive adenocarcinoma with poor survival, mucinous differentiation, and adverse morphologic features. Am J Surg Pathol 2012;36:744-52.
22. Russo AL, Borger DR, Szymonifka J, et al. Mutational analysis and clinical correlation of metastatic colorectal cancer. Cancer 2014;120:1482-90.
23. Yaeger R, Cercek A, Chou JF, et al. BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. Cancer 2014;120:2316-24.
24. Lipsyc MD, Yaeger R, Dengel LT, et al. Axillary Lymph Node Involvement, a Unique Pattern of Metastasis in BRAF-Mutant Colorectal Cancer. JAMA Oncology 2015; doi:10.1001/jamaoncol.2015.0569.
25. Guo Q, Zhao Y, Chen J, et al. BRAF-activated long non-coding RNA contributes to colorectal cancer migration by inducing epithelial-mesenchymal transition. Oncol Lett 2014;8:869-75.
26. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science 2004;304:554.

27. Karapetis CS, Jonker D, Daneshmand M, et al. PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer--results from NCIC CTG/AGITG CO.17. Clin Cancer Res 2014;20:744-53.
28. Tol J, Dijkstra JR, Klomp M, et al. Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab. Eur J Cancer 2010;46:1997-2009.
29. Wang Y, Velho S, Vakiani E, et al. Mutant N-RAS protects colorectal cancer cells from stress-induced apoptosis and contributes to cancer development and progression. Cancer Discov 2013;3:294-307.

Cite this article as: Lipsyc M, Yaeger R. Impact of somatic mutations on patterns of metastasis in colorectal cancer. J Gastrointest Oncol 2015;6(6):645-649. doi: 10.3978/j.issn.2078-6891.2015.045

