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Gene mutation and surgical technique: suggestion or more?

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Abstract

Advancements in chemotherapy and molecular targeted therapy have improved long-term outcomes for patients with resectable colorectal liver metastases (CLM). *RAS* mutation status was an original focus as a molecular biomarker as it predicted treatments response to anti-epidermal growth factor receptor agents. More recently, studies have incorporated somatic mutation data in analyses pertaining to surgical outcomes and prognosis. This evidenced-based review covers the implications of somatic mutations in patients undergoing resection of CLM.

Keywords

somatic gene mutation; multiple gene mutation; colorectal liver metastasis

1. Introduction

Colorectal liver metastases (CLM) are found in approximately 15–30% of patients with colorectal cancer [1]. Liver resection has a survival benefit over chemotherapy alone and provides 5-year overall survival (OS) rates that range from 40% to 58% [2–4]. Modern chemotherapy and molecular targeted therapy can downsize CLM and have increased the number of patients eligible for curative resection [5]. Indeed, chemotherapy regimens that include anti-epidermal growth factor receptor (EGFR) agents have improved long-term outcomes in patients with unresectable metastases from colorectal cancer [6]. However, it was quickly noted that patients with mutations in the *RAS* gene family (*KRAS, NRAS*, and *HRAS*) exhibited lack of response to anti-EGRF therapy [7–9]. Subsequent studies found association between mutations in *RAS* and *BRAF* and worse prognosis after CLM resection. With the recent development of next generation sequencing, testing of multiple somatic mutations can occur in the context of clinical practice. This article reviews the association of somatic gene mutations with prognosis and surgical outcomes after CLM resection to facilitate better clinical decision-making.

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2. Common somatic gene mutation and prognosis

2.1. *RAS* mutation

The *RAS* oncogene (*KRAS, NRAS*, and *HRAS*) is a key member of the mitogen-activated protein kinase (MAPK) pathway and contributes to deregulation of tumor-cell growth, programmed cell death and invasiveness, and induction of new blood-vessel formation [10]. An important clinical implication of the *RAS* mutation is resistance to anti-EGFR therapy [11]. EGFR belongs to a family of receptor tyrosine kinases that includes three other members (erbB2/HER-2, erbB3/HER-3, and erB4/HER-4) [12, 13]. The binding of epidermal growth factor or other ligands to EGFR initiates a mitogenic signaling cascade through the MAPK signaling pathway and the phosphatidylinositol 3-kinase (PI3K) signaling pathway [11]. Mutations in *RAS* result in continuous activation of the downstream MAPK signaling pathway, even if the EGFR is pharmacologically blocked [7, 14].

Recently, studies have reported an association of *RAS* mutation with prognosis in patients undergoing CLM resection (Table 1). Based on these series, anywhere from 15 to 50% of patients have a *RAS* mutation. Many studies report that *RAS* mutant patients have shorter OS and recurrence-free survival (RFS) than *RAS* wild-type patients. However, the prognostic impact of *RAS* mutation is inconsistent across the literature. Recently, our group demonstrated that a “triple mutation” in RAS, *TP53,* and *SMAD4* was independently associated with worse OS and RFS in 507 patients undergoing CLM resection [15]. The study showed that a subset of patients with only a *RAS* mutation has similar long-term outcomes as *RAS* wild-type patients. OS and RFS in patients with *RAS* mutation and wild-type *TP53* and *SMAD4* were not significantly different from OS and RFS in patients with *RAS* wild-type. For example, the median OS for patients with *RAS* mutation and wild-type *TP53* and *SMAD4* was 7.3 years compared to 7.0 years for *RAS* wild-type patients ($P = 0.858$). This finding may explain the inconsistency in terms of long-term outcomes in patients with *RAS* mutation, and suggests that information regarding *RAS* mutation alone is perhaps insufficient.

2.2. *BRAF* mutation

Similar to *RAS*, the *BRAF* oncogene is an important member of the MAPK pathway [16] and a mutation in *BRAF* results in continuous activation of the downstream MAPK signaling pathway [17]. *BRAF* is mutated in approximately 10% of all patients with colorectal cancer [18]. The prognostic role of a *BRAF* mutation in patients with colorectal cancer is well established and associated with poor survival outcomes [19, 20]. Based on surgical series, *BRAF* is mutated in only 1.0-6.1% of patients undergoing CLM resection, likely given its associated poor prognosis [21–26]. Similar to patients with colorectal cancer, *BRAF* mutant patients undergoing CLM resection have been shown to have shorter survival than *BRAF* wild-type patients [21–25, 27]. It should be noted that the single institution studies have been able to analyze anywhere from three to twelve patients with *BRAF* mutations because of the low mutation frequency in this patient cohort [22–25]. Recently, two multi-institutional studies analyzed 35 *BRAF* mutant patients out of 1497 total patients [27] and 45 *BRAF* mutant patients of 853 patients [21] (Table 2). Both studies showed that

BRAF mutant patients had significantly worse OS and RFS than *BRAF* wild-type patients [21, 27].

Of all the *BRAF* mutations, 80% were V600E (1799T>A) [28]. For patients with unresectable colorectal cancer, two multi-institution studies showed that the non-V600E *BRAF* mutation is a distinct molecular subset compared to the V600E *BRAF* mutation [29,30]. Patients with a V600E *BRAF* mutation had a worse prognosis; however, patients with non-V600E *BRAF* mutations had a similar survival to patients with *BRAF* wild-type [29, 30]. The rarity of *BRAF* mutation (all, 10%; V600E, 8%; non-V600E, 2%) is a barrier to ensuring statistical power and avoiding the type II error in clinical studies. To detect a difference of 5% between *BRAF* wild-type and non-V600E *BRAF* mutation in patients with colorectal metastases, more than 18,000 events may be needed based on the sample size analysis reported by Lakatos [31] using the following parameters (alpha, 0.05; beta, 0.20; non-V600E *BRAF* mutation, 2%; 5-year OS in *BRAF* wild-type patients, 30%; non-V600E *BRAF* mutant patients, 25%) [30].

2.3. *TP53* mutation

TP53 is a tumor suppressor gene in the p53 pathway and encodes p53 protein. Malignancy-associated stress signals activate p53, which inhibits tumor-cell growth either through cell-cycle arrest or induction of apoptosis [32, 33]. *TP53* is mutated in approximately 40–70% of patients undergoing CLM resection (Table 3). Currently, the literature remains divided as to the prognostic role of *TP53* in patients undergoing CLM resection. In 1999, Tullo et al. reported that patients with a *TP53* mutation had shorter RFS than *TP53* wild-type patients [34]. In contrast, in 2000, Yang et al. reported that OS and RFS were better in *TP53* mutant patients than in TP53 wild-type patients [35]. Subsequently, four studies have shown worse OS and/or RFS in *TP53* mutant patients compared to *TP53* wild-type patients [15, 36–38], whereas, in five studies, *TP53* mutation was not significantly associated with prognosis [25, 39–42].

2.4. *PIK3CA* mutation and prognosis

The *PIK3CA* gene encodes a catalytic subunit of class IA PI3Ks [43]. PI3Ks activate serine/threonine-protein kinases and other downstream effector pathways. Serine/threonine-protein kinases activate the mammalian target of rapamycin. Through these activation processes, the PI3K signaling pathway play a key regulatory role in cell survival, proliferation, angiogenesis and differentiation [43, 44]. *PIK3CA is* mutated in approximately 12–13% of CLM patients (Table 3). However, the prognostic role of *PIK3CA* mutation is not well described. Two studies have reported that OS and RFS did not significantly differ between *PIK3CA* mutant and *PIK3CA* wild-type patients. The previously mentioned study of 507 patients from our institution also showed that *PIK3CA* mutation status was not associated with OS or RFS [15].

2.5. *SMAD4* mutation and prognosis

SMAD4 is a tumor suppressor gene in the transforming growth factor-β pathway, involved in the regulation of cell proliferation, differentiation, migration, and apoptosis [45, 46]. *SMAD4* is mutated in approximately 10% of patients undergoing CLM resection [42, 47].

Two studies have shown a negative prognostic role of *SMAD4* in patients undergoing CLM resection with worse OS and/or RFS than *SMAD4* wild-type patients (Table 3) [15, 47].

3. Association of *RAS* mutation with surgical outcomes

RAS mutation status has been widely tested because of its clinical relevance in regards to the use of anti-EGFR therapy. As such, studies have also reported the associations of *RAS* mutation with various surgical outcomes. The following section summarizes the implication of *RAS* mutation status in regards to surgical margin, ablation margin, repeat hepatectomy, and two-stage hepatectomy.

3.1. Resection margin

A positive resection margin is associated with worse prognosis in the era of modern preoperative chemotherapy [48]. Two studies have investigated the impact of *RAS* mutation status on surgical margin [49, 50]. Brudvik et al. reported that independent predictors for positive resection margin were *RAS* mutation (hazard ratio [HR] 2.44, 95 % confidence interval [CI] 1.30–4.58, $P = 0.005$) and carcinoembryonic antigen level ≥ 4.5 ng/mL (HR 95 % CI 1.09–3.89, $P = 0.026$) [50]. In patients who developed liver-first recurrence, the median width of the resection margin was significantly smaller in *RAS* mutant patients than in *RAS* wild-type patients: 4 mm (0–70 mm) vs. 7 mm (0–67 mm), $P = 0.031$. Margonis et al. also demonstrated a difference in the effect of surgical margin on surgical outcomes between *KRAS* mutant and *KRAS* wild-type patients [49]. For *KRAS* wild-type patients, a resection margin ≥ 1 mm was associated with better OS than a resection margin < 1 mm. In contrast, for *KRAS* mutant patients, OS did not differ significantly between a resection margin < 1 mm and ≥ 1 mm. These studies show that the prognostic effect of surgical margin may differ between patients with *RAS* mutation and those who are *RAS* wild-type.

3.2. Ablation margin

Three studies have described an association between *RAS* mutation and ablation margin. Odisio et al. showed that local tumor progression-free survival after percutaneous ablation for CLM was worse in patients with *RAS* mutation (35% at 3 years) than in those who were *RAS* wild-type (71% at 3 years) ($P < 0.001$). Of 25 ablated CLMs with local tumor progression, patients with *RAS* mutation had earlier progression than patients with *RAS* wild-type. In a series of 218 ablated CLMs, Calandri et al. showed that *RAS* mutation status and ablation margin ≤ 10 mm were associated with local tumor progression-free survival: *RAS* mutation, HR 2.85, 95% CI 1.74–4.69, $P < 0.001$; ablation margin ≤ 10mm, HR 1.80, 95% CI 1.11–2.89, $P = 0.017$. Finally, Jian et al. analyzed 154 ablated CLM and also showed that *KRAS* mutation status and ablation margin were associated with local tumor progression [51].

3.3. Repeat hepatectomy

Liver resection has been regarded as a gold standard for patients with colorectal liver metastases. However, most patients experience recurrence [2–4, 52]. Studies have shown that repeat hepatectomy for recurrence of liver metastases can improve survival in selected patients [53, 54]. Denbo et al. reported that the median RFS after repeat hepatectomy for

recurrent CLM is lower in *RAS* mutant patients than in *RAS* wild-type patients: 6.1 months vs. 12.2 months, $P = 0.03$. *RAS* mutation was an independent risk factor for both OS and RFS in patients who underwent repeat hepatectomy for recurrent CLM (OS: HR, 1.69, 95% CI, 1.03–2.72, $P = 0.04$; RFS: HR, 2.11, 95% CI, 1.11–3.98, $P = 0.02$). This study suggests that *RAS* mutation status can be used for decision-making regarding the use of repeat resection or medical therapy in patients who experience recurrence after initial CLM resection.

3.4. Two-stage hepatectomy

Two-stage hepatectomy for bilateral CLMs was described in the early 2000s as a technique for improving resectability [55, 56] because patients with bilateral CLM were often excluded from curative intent resection due to an insufficient future liver remnant [57]. Passot et al. showed the importance of *RAS* mutation status in regards to patient selection for two-stage hepatectomy [58]. In this series, the 5-year OS rate was 67% in patients with *RAS* wild-type, compared to only 12% in patients with a *RAS* mutation.

3.5. Repeat surgery for recurrence after two-stage hepatectomy

Recurrence after two-stage hepatectomy is frequent because this strategy is generally used for patients with multiple bilateral CLMs [59, 60]. A recent study by Lillemoe et al. assessed the feasibility and safety of repeat surgical resection for recurrence after two-stage hepatectomy for CLM [61]. In 83 patients who developed recurrence after two-stage hepatectomy, 31 patients (37%) underwent resection for recurrence. *RAS* mutation and first recurrence in multiple sites were associated with worse survival. Specifically, *RAS* mutant patients undergoing repeat surgery for recurrence had shorter OS than *RAS* wild-type patients undergoing repeat surgery (5-year OS: 38% vs. 86%, $P = 0.019$). In contrast, for patients who did not undergo resection for recurrence after two-stage hepatectomy, OS did not differ significantly between *RAS* mutant patients and *RAS* wild-type patients ($P = 0.517$) [61]. Thus, *RAS* mutation status remains an important prognostic factor in advanced disease and should be considered when determining treatment.

3.6. Synchronous liver and lung metastases

Lung metastases are the most frequent type of extrahepatic metastasis of colorectal cancer [62]. As such, for patients with both lung and liver metastases, clarifying the impact of the lung metastases is key to maximize the benefit of CLM resection. Patients with a *RAS* mutation have a higher propensity for developing lung metastases than patients with *RAS* wild-type [26, 63]. Mise et al. demonstrated that in patients undergoing resection of CLM without resection of lung metastases, *KRAS* mutation (HR, 2.10, 95% CI, 1.21–3.64, $P < 0.001$) and rectal primary tumor (HR, 1.72, 95% CI, 1.02–3.64, $P = 0.039$) were associated with worse OS [64]. The authors showed that the 3-year OS rate for patients with no risk factors (*KRAS* wild-type and colon primary tumor) was 76.9%, compared to 36.7% for patients with one risk factor and 13.5% for patients with two risk factors.

4. Conclusions

Mutations in the *RAS* oncogene family were the original focus of genetic sequencing in patients with CLM due to the clinical relevance in regards to anti-EGFR therapy resistance. Recently, the association of *RAS* mutation with prognosis after CLM resection has been increasingly reported, with most studies reporting substantially shorter OS in *RAS* mutant patients compared to *RAS* wild-type patients. *RAS* mutation status has also been evaluated in the context of other parameters related to CLM resection. Studies have found associations with *RAS* mutations and surgical margin, ablation margin, and long-term outcomes after repeat hepatectomy and two-stage hepatectomy. Similar to patients with primary colorectal cancer, mutations in *BRAF* are also associated with a poor prognosis. However, it should be noted that *BRAF* mutations are rare in this patient population (at most 5% of patients undergoing CLM resection), making it difficult to evaluate its prognostic importance. Finally, *TP53, APC, PIK3CA,* and *SMAD4* are commonly mutated in patients undergoing CLM resection. As genetic sequencing becomes more accessible, more data will arise regarding the prognostic implication of these mutations. Continued advancements in the realm of tumor biology based on next generation sequencing will further improve outcomes and clinical decision making for patients with CLM.

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ABBREVIATIONS

CLM	colorectal liver metastases
OS	overall survival
EGFR	epidermal growth factor receptor
MAPK	mitogen-activated protein kinase
PI3K	phosphatidylinositol 3-kinase
RFS	recurrence-free survival
HR	hazard ratio
CI	confidence interval

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Table 1.

Studies of *RAS* mutation in patients who underwent resection of colorectal liver metastases *

Reference	Year	Gene analyzed	No. of patients	Frequency	Association of *RAS* (*KRAS*) mutation with prognosis	
					OS	RFS
Nash et al. [65]	2010	*KRAS*	188	51 (27%)	Worse	-
Teng et al. [24]	2012	*KRAS*	292	111 (38%)	No association	-
Vauthey et al. [26]	2013	*RAS*	193	34 (17.6%)	Worse	Worse
Karagkounis et al.[66]	2013	*KRAS*	202	58 (29%)	Worse	Worse
	2014	*KRAS*	154	43 (28%)	No association	-
Lin et al. [67]	2015	*RAS*	309	160 (52%)	No association	No association
Scirripa et al.[22]	2016	*KRAS*	512	190 (37%)	-	No association
Margonis et al. [68]	2016	*RAS*	633	229 (36%)	Worse	-
Brudvik et al. [50]	2017	*RAS*	342	19 (44%)	Worse	Worse
Amikura et al. [69]	2017	*KRAS*	300	110 (37%)	Worse	-
Wang et al. [70]	2019	*RAS*	507	257 (51%)	Worse	Worse
Kawaguchi et al. [15]						

Abbreviations: OS, overall survival; RFS, recurrence-free survival.

* More than 150 patients and a Cox proportional hazards model analysis

Table 2.

Studies of *BRAF* mutation in patients who underwent resection of colorectal liver metastases [*]

Reference	Year	No. of patients	Frequency	Multivariable analysis	Association of *BRAF* mutation with prognosis	
					OS	RFS
Gagniere et al.[27]	2018	1497	35 (2%)	No	Worse	Worse
Margonis et al.[21]	2018	853	43 (5%)	Yes	Worse [†]	Worse [†]

Abbreviations: OS, overall survival; RFS, recurrence-free survival.

[*] More than 20 patients.

[†] V600E *BRAF* vs. wild-type *BRAF*

Table 3.

Studies of other somatic gene mutations in patients who underwent resection of colorectal liver metastases

Gene analyzed	Reference	Year	No. of patients	Frequency	Multivariable analysis	Association of gene mutation with prognosis	
						OS	RFS
TP53	Tullo et al. [34]	1999	40	19 (48%)	No	-	Worse
	Yang et al. [35]	2001	39	16 (41%)	No	Better	Better
	Saw et al. [39]	2002	60	35 (58%)	No	No association	-
	De Jong et al[40]	2005	44	16 (36%)	No	No association	No association
	Mollevi et al. [36]	2007	91	46 (51%)	Yes	Worse	-
	Pilat et al. [38]	2015	76	42 (55%)	No	Worse *	-
	Loes et al. [25]	2016	164	99 (60%)	Yes	No association	No association
	Fankel et al. [41]	2017	165	95 (58%)	No	No association	-
	Chun et al. [42]	2019	401	263 (66%)	No	No association	-
	Kawaguchi et al. [15]	2019	507	359 (71%)	Yes	Worse	Worse
PIK3CA	Loes et al. [25]	2016	164	22 (13%)	Yes	No association	No association
	Fankel et al. [41]	2017	165	20 (12%)	No	No association	No association
	Kawaguchi et al. [15]	2019	507	80 (16%)	Yes	No association	No association
SMAD4	Mizuno et al. [47]	2018	278	37 (13%)	Yes	Worse	-
	Kawaguchi et al. [15]	2019	507	56 (11%)	Yes	Worse	Worse

Abbreviations: OS, overall survival; RFS, recurrence-free survival.

* 51 patients who received preoperative chemotherapy

Table 4.

RAS mutation and surgical outcomes in patients undergoing resection of colorectal liver metastases

Reference	Year	Gene analyzed	No. of patients	Frequency	Findings
Surgical margin					
Brudvik et al. [50]	2016	*RAS*	633	229 (36%)	*RAS* mutation is associated with positive and closer surgical margin.
Margonis et al. [49]	2016	*KRAS*	411	153 (37%)	OS in *RAS* mutant patients was similar between R0 and R1 resections.
Ablation margin					
Odisio et al. [71]	2017	*RAS*	92	36 (39%)	LTPFS after ablation was worse in *RAS* mutant patients.
Calandri et al. [72]	2018	*RAS*	136	54 (40%)	*RAS* and margin > 10 mm are predictors for LTPFS.
Jian et al.[51]	2019	*KRAS*	76	38 (50%)	*KRAS* and margin are predictors for LTPFS
Repeat hepatectomy					
Denbo et al.[73]	2017	*RAS*	98	34 (35%)	*RAS* mutation was associated with worse OS and RFS after repeat hepatectomy
Two-stage hepatectomy					
Passot et al. [58]	2016	*RAS*	93	40 (43%)	*RAS* mutation was associated with worse OS and RFS in patients undergoing two-stage hepatectomy.
Repeat surgery for recurrence after two-stage hepatectomy					
Lillemoe et al. [61]	2018	*RAS*	83	36 (46%)	*RAS* mutation was associated with worse OS in patients undergoing resection after two-stage hepatectomy.
Synchronous liver and lung metastases					
Mise et al. [64]	2015	*KRAS*	98	44 (45%)	*KRAS* mutation was associated with worse OS in patients undergoing CLM resection without resection of synchronous lung metastases.

Abbreviations: OS, overall survival; LTPFS, local tumor progression-free survival; RFS, recurrence-free survival; CLM, colorectal liver metastases.