Journal of Gastrointestinal Surgery (2021) 25:1591–1600
https://doi.org/10.1007/s11605-021-04962-x

REVIEW ARTICLE

Prognostic and Therapeutic Implications of Tumor Biology, Including Gene Alterations, in Colorectal Liver Metastases

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Received: 25 November 2020 / Accepted: 10 February 2021 / Published online: 19 March 2021

Abstract

Background For patients with colorectal liver metastases (CLM), the combination of surgical resection with other therapeutic options is essential. This article shows how recent advances in knowledge of tumor biology, including genetic alterations, affect the choice of therapeutic approach for patients with CLM.

Methods We reviewed the literature on recent advances in knowledge about CLM tumor biology including genetic profiles, clinical risk score models for CLM, preoperative therapy for CLM, and liver-directed therapy for CLM.

Results Studies showed that *RAS* alteration is a negative prognostic factor in addition to traditional clinical risk factors (e.g., larger diameter and higher number of CLM, spread of the primary tumor to regional lymph nodes). Although the response to preoperative chemotherapy is an important predictor of survival, poor response is not a contraindication to surgical resection. The combination of surgical therapy and percutaneous ablation can be considered in marginally resectable cases; however, a wider ablation margin is required for *RAS*-mutant CLM. More recently, genetic analysis using next-generation sequencing showed the negative prognostic impact of alterations in *TP53*, *SMAD4*, *FBXW7*, and *RAS*/*BRAF* in patients with CLM. In *RAS*-mutant CLM, intensive follow-up is required in patients who remain recurrence free 2 years after surgery.

Discussion In patients with CLM, *RAS* mutation status is important in predicting postoperative survival, selecting the treatment approach, and tailoring postoperative follow-up. In addition, more recent genetic analyses of CLM have identified additional predictors of survival.

Keywords Colorectal liver metastases · Somatic gene mutations · Percutaneous ablation

Introduction

Colorectal liver metastases (CLM) occur in approximately 30% of patients with colorectal cancer. Because CLM are a major cause of death in patients with colorectal cancer, control of CLM is crucial to achieve cure of colorectal cancer.

Recent advances in surgical technique, including portal vein embolization and two-stage hepatectomy, and improved understanding of surgical complexity[1–3] have expanded the use of surgery in patients with CLM. Medical therapy for colorectal cancer has also advanced dramatically during the past two decades and has improved the survival of patients with CLM. Currently, the combination of surgical resection and perioperative medical therapy is the standard of care for this patient group. While the efficacy of alternative locoregional therapies for CLM (e.g., ablation and radiation therapy) has recently been reported,[4, 5] surgical resection remains the optimal locoregional therapies to cure CLM.

CLM is a heterogeneous disease in terms of tumor burden and somatic gene alteration status. Thus, medical providers need to understand how best to individualize management of CLM. This article highlights the importance of tumor biology, including somatic gene alterations, in selecting the therapeutic approach for individual patients with CLM. The information in this article is based on our review of the literature on recent advances in knowledge about genetic profiles of CLM, clinical risk score models for CLM, preoperative therapy for CLM, and liver-directed therapy for CLM.

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Prediction of Prognosis After CLM Resection

Accurate prediction of prognosis in patients undergoing CLM resection is useful for selecting therapeutic approaches. Various clinical risk score models have been reported that were able to predict survival after CLM resection (Table 1).

Nordlinger et al. assessed 1568 patients who underwent CLM resection and identified seven risk factors associated with overall survival (OS): age ≥ 60 years, primary tumor extension into serosa, spread of the primary tumor to regional lymph nodes ("primary lymph node metastases"), disease-free interval after primary resection <2 years, number of CLM ≥ 4, largest CLM diameter > 5 cm, and surgical margin <10 mm. These factors were incorporated into a clinical risk score model in which the total number of risk factors is used to stratify patients with respect to OS .[6]

To address the limitations of the Nordlinger et al. model, which included a postoperative factor, Fong et al. assessed 1001 patients undergoing CLM resection and reported another clinical risk score model with five risk factors that are available before surgery and were associated with recurrence-free survival (RFS): carcinoembryonic antigen level > 200 ng/mL, largest CLM diameter > 5 cm, multiple CLM, primary lymph node metastases, and synchronous CLM (defined as disease-free interval < 1 year).[7] The so-called Fong score has become the most widely adopted clinical risk score model for CLM in the past two decades.

The prognostic value of somatic gene alterations in patients with CLM has been increasingly recognized. Our group showed that among patients who underwent CLM resection, patients who had *RAS* alteration had worse RFS (hazard ratio [HR], 1.92; 95% confidence interval [CI], 1.21–3.03; p = 0.005) and worse OS (HR, 2.26; 95% CI, 1.13–4.51; p = 0.002) than patients who had *RAS* wild-type.[8] Later, Brudvik et al. reported a new clinical risk score that integrated two clinicopathologic factors, largest CLM diameter > 5 cm and primary lymph node metastases, and *RAS* alteration .[9]

Margonis et al. also developed a clinical risk score model for OS; their model included primary lymph node metastases, carcinoembryonic antigen level before surgery ≥20 ng/mL, extrahepatic disease, resection margin <1 mm, *KRAS* alteration, and higher tumor burden score, which combines tumor size and number .[10] Both the clinical risk score by Brudvik et al. and the clinical risk score by Margonis et al. performed better in predicting OS than did the Fong score (C-index, 0.69 vs. 0.57 and 0.65 vs. 0.58, respectively).

The clinical risk score models mentioned above categorized patients with CLM into 3 to 7 risk groups on the basis of dichotomized variables. Dichotomization underestimates the extent of risk variation and is associated with substantial loss of statistical power compared with use of continuous variables. As such, development of a new prognostic model based on continuous number and diameter of CLM for patients undergoing CLM resection is desirable in the future.

Preoperative Medical Therapy

In 2012, a multidisciplinary international group reported outcomes of more than 14,000 patients who underwent CLM resection and showed that the 5-year OS rate was significantly better in patients who underwent curative resection of CLM than that in patients who did not undergo CLM resection (42% vs. 8%; p < 0.001). The 5-year OS rate was 33% in patients who had initially unresectable CLM converted to resectable status after chemotherapy .[11] Owing to recent advances in medical therapy, the combination of preoperative medical therapy and surgical resection has become the standard of care for patients with CLM.

Regimens including 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or 5-fluorouracil, leucovorin, and irinotecan with molecular-targeted agents are commonly used for patients with colorectal cancer. *RAS* alteration status is used

Table 1 Studies of clinical risk score models in patients who underwent resection of colorectal liver metastases (CLM)

Reference	Year	No. of patients	Outcome	No. of groups	Risk factors included in model
Nordlinger[6]	1996	1568	OS	3	Primary LN metastases, extension of primary tumor into serosa, age ≥ 60 years, DFI < 2 years, no. of CLM ≥ 4, largest CLM diameter > 5 cm, surgical margin <10 mm
Fong[7]	1999	1001	RFS	6	Primary LN metastases, DFI < 12 months, multiple CLM, largest CLM diameter > 5 cm, CEA level > 200 ng/mL
Brudvik[9]	2019	564	OS	4	Primary LN metastases, largest CLM diameter > 5 cm, *RAS* alteration
Margonis[10]	2018	502	OS	7	Primary LN metastases, extrahepatic disease, CEA level > 20 ng/mL, positive surgical margin, higher tumor burden score,[a] *RAS* alteration
Lang[40]	2019	139	RFS	4	Primary LN metastases, largest CLM diameter > 5 cm, *RAS* alteration, *SMAD* alteration

CEA, carcinoembryonic antigen; *DFI*, disease-free interval; *LN*, lymph node; *OS*, overall survival; *RFS*, recurrence-free survival.

[a] Tumor burden score is based on the size and number of CLM

as a biomarker for predicting the response to molecular therapy targeting anti-epidermal growth factor receptor.

The efficacy of preoperative chemotherapy for resectable CLM remains a subject of debate. The EPOC trial was a randomized controlled trial that compared patients who received perioperative FOLFOX and surgery with patients who underwent surgery alone. In the intention-to-treat analysis, the 3-year progression-free survival (PFS) rate did not differ significantly between patients who received chemotherapy followed by surgery and patients who underwent surgery alone (35.4% and 28.1%, respectively; HR, 0.79; 95% CI, 0.62–1.02; $p = 0.058$). In the per-protocol analysis, the 3-year PFS rate was significantly higher in patients who received perioperative chemotherapy and surgery than that in patients who underwent surgery alone (36.2% vs. 28.1%; HR, 0.77; 95% CI, 0.60–1.00; $p = 0.041$) .[12]

Subsequently, the same group conducted another randomized controlled phase 3 trial, the New EPOC trial, in which 257 patients with *KRAS* wild-type resectable or suboptimally resectable CLM received perioperative chemotherapy with cetuximab ($n = 129$) or without cetuximab ($n = 128$) and underwent resection of CLM according to the same criteria. The trial showed that perioperative chemotherapy with cetuximab was associated with worse OS than perioperative chemotherapy without cetuximab (median OS, 55.4 months vs. 81.0 months; HR, 1.45; 95% CI, 1.02–2.05; $p = 0.036$) .[13] Median PFS did not differ significantly between the groups (15.5 months with cetuximab vs. 22.2 months without cetuximab; HR, 1.17; 95% CI, 0.87–1.56; $p = 0.304$).

The response to preoperative chemotherapy is regarded as an important predictive factor for survival after CLM resection. Adam et al. reported that the 5-year OS rate was higher in patients who had stable disease than that in patients who had progressive disease: 30% vs. 8% .[14] Vigano et al. identified three prognostic factors in patients with progressive disease after preoperative chemotherapy: number of tumors >3, tumor diameter > 5 cm, and carcinoembryonic antigen level > 200 ng/mL at diagnosis. These authors showed that the 3-year OS rate was less than 10% in patients with two or more risk factors or carcinoembryonic antigen level > 200 ng/mL at diagnosis. In contrast, patients who did not have any of the three risk factors had a 3-year OS rate of 60.5% regardless of progressive disease after chemotherapy. Therefore, poor response to preoperative chemotherapy should not be a contraindication for surgery.[15]

Although response to chemotherapy has been evaluated using the size and number of tumors (i.e., the Response Evaluation Criteria for Solid Tumors), our group reported that pathologic response to chemotherapy, which is independent of change in tumor size, was associated with prognosis.[16]

Mise et al. reported that *RAS*-mutant CLM is an independent risk factor for poor pathologic response to preoperative chemotherapy (HR, 2.61; 95% CI, 1.17–5.80; $p = 0.019$).[17] Resection remains a standard of care for patients with technically resectable CLM, and preoperative chemotherapy is useful for testing tumor biology; however, preoperative chemotherapy lasting longer than 3 months has been reported to increase hepatic toxicity.[18] Currently, preoperative chemotherapy is given to 88% of patients undergoing CLM resection at our institution. Among patients with resectable CLM, our preferred regimen is four cycles of chemotherapy (Fig. 1a). For patients with marginally resectable CLM, it is important to consider genetic and clinical information, patients' performance status, and the response to preoperative chemotherapy prior to proceeding with surgical treatment.

Liver-Directed Therapy

Patients with CLM have various options for liver-directed therapies: liver resection, ablation, stereotactic body radiation therapy, yttrium-90 radiation, and proton beam radiation.

Recently, associations of *RAS* alterations with surgical margin status have been reported. Brudvik et al. reported that *RAS* alterations were associated with positive surgical margins (HR, 2.44; 95% CI, 1.30–4.58) and narrower surgical margins .[19] Margonis et al. showed that in patients with *KRAS*-mutated CLM, anatomic liver resection was associated with better PFS compared to non-anatomic resection (HR, 0.42; 95% CI, 0.23–0.78; $p = 0.006$) .[20] However, Mise et al. reported that parenchyma-sparing hepatectomy does not negatively impact postoperative outcome and is associated with a greater chance of repeat resection in case of recurrence than major hepatectomy (68% vs. 24%; $p < 0.01$),[21] and Vreeland et al. reported that there was no difference in OS or liver-specific RFS between the anatomic resection and non-anatomic resection groups, regardless of *RAS* alteration status.[22] Given these findings, the basic surgical approach for CLM at MD Anderson Cancer Center has transitioned from major hepatectomy to parenchyma-sparing hepatectomy, although we still pursue curability by extended major hepatectomy in aggressive cases (Fig. 1b).

For patients with unresectable CLM, liver-directed therapies other than liver resection may be used. A randomized phase II trial that compared percutaneous ablation vs. systemic therapy alone showed that the 5-year OS rate was 43.1% with percutaneous ablation and 30.3% with systemic therapy alone ($p = 0.01$).[4] An adequate ablation margin is critical for achieving effective local tumor control. Shady et al. reported that ablation margin ≤5 mm was a risk factor for local recurrence (also defined as local tumor progression) (HR, 11.6; 95% CI, 3.1–42.7; $p < 0.001$), regardless of the ablation modality. Additionally, these authors did not observe local tumor progression in patients with ablation margin >10 mm.[23]

Tumor biology may affect the minimum ablation margin. Odisio et al. reported that *RAS* alteration (HR, 3.01; 95% CI, 1.60–5.77) and minimal ablation margin <5 mm (HR, 2.48; 95% CI, 1.31–4.72) were risk factors for local tumor progression .[24] Figure 2 shows local tumor progression stratified by the largest CLM diameter and *RAS* status. Early local tumor

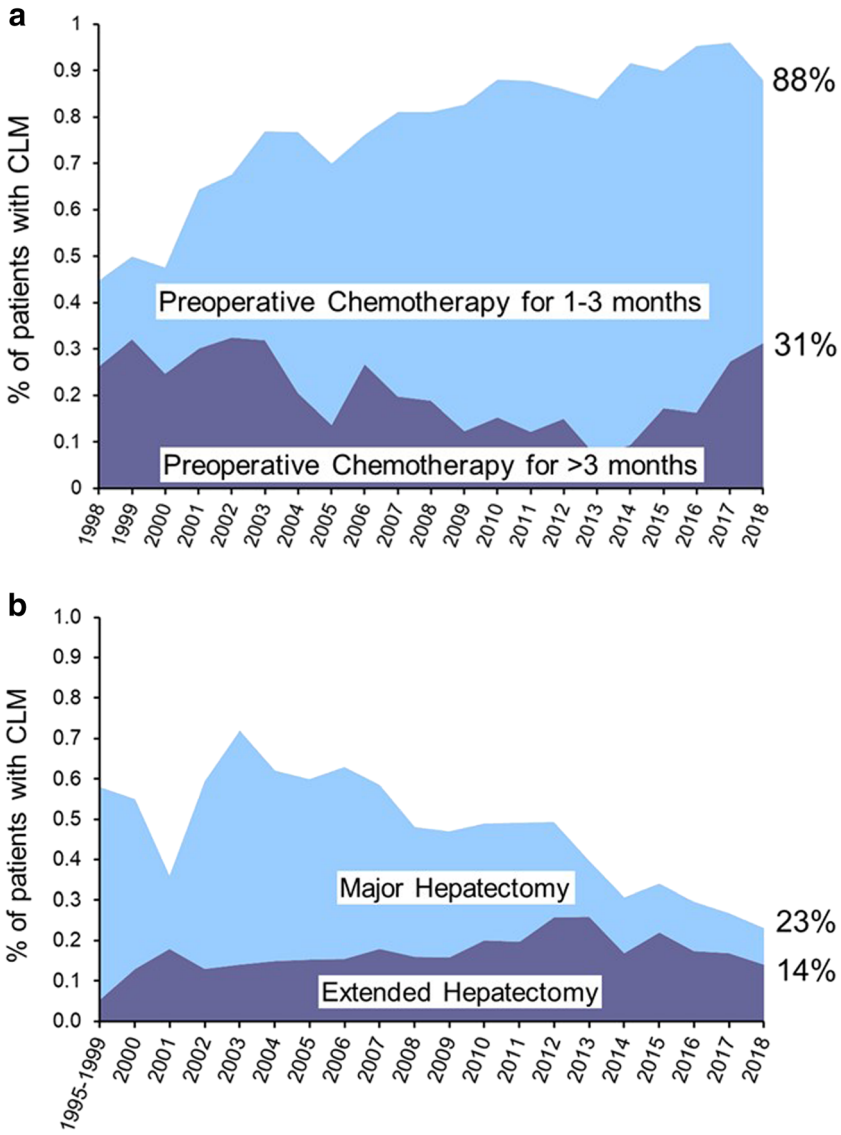

Fig. 1 Time trends in treatment of patients with CLM at MD Anderson Cancer Center, 1998–2018. **a** Proportions of patients treated with preoperative chemotherapy for 1–3 months and > 3 months. **b** Proportions of patients treated with major and extended major hepatectomy

progression was identified in *RAS*-mutant CLM, even when the CLM were < 2 cm.

On the basis of these findings, we recommend an accurate approach to percutaneous ablation margin using cross-sectional imaging guidance with computed tomography for three-dimensional assessment of minimal ablation margins rather than intraoperative ultrasound-guided concomitant ablation (Fig. 3). In our recent experience, we have used percutaneous ablation after resection as part of a "completion ablation" approach using postoperative computed tomography technique .[25] A recent study indicated significantly lower rates of local tumor progression with this "completion ablation" approach than those with CLM resection and intraoperative concomitant ablation[26] (Fig. 4).

Other options for liver-directed therapies are stereotactic body radiation therapy,[5] yttrium-90 radiation,[27] and proton beam radiation.[28] However, these therapies are not considered first-line therapies at this time.

Decision at Recurrence After Surgery

Although the 5-year OS rate after CLM resection is high, ranging from 20 to 60% ,[29, 30] approximately 70 to 80% of patients undergoing CLM resection experience recurrence. The liver is the most common site of recurrence after CLM resection. Studies have shown that repeat resection of recurrent CLM is effective and has the potential for cure. Andreou et al. reported that the 5-year OS rate after repeat resection of CLM was 73%.[31]

RAS alteration status can be used to predict prognosis after repeat resection of recurrent CLM and after two-stage

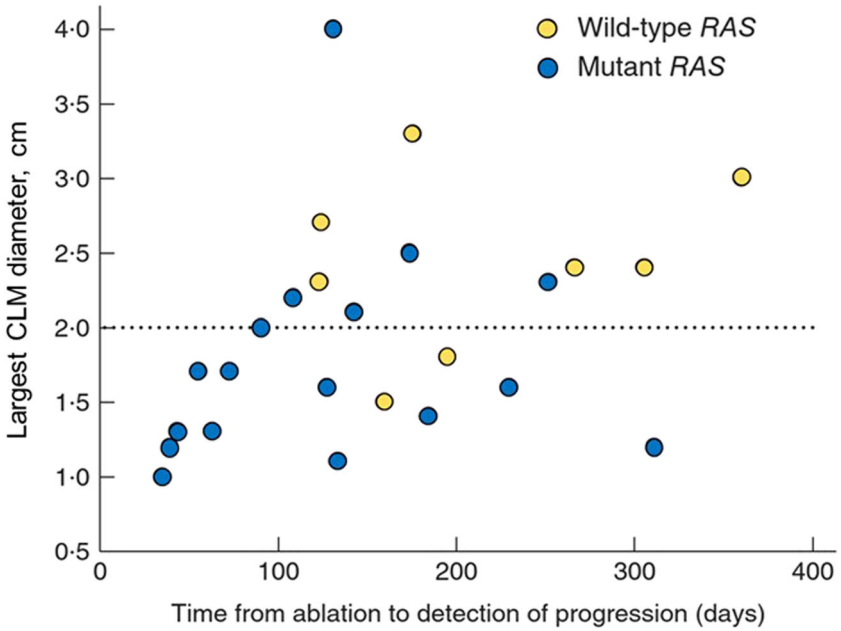

Fig. 2 Time from ablation to local tumor progression among 25 patients with CLM stratified by *RAS* status and CLM diameter. (Odisio B, et al. Br J Surg 2017. Used with permission)

hepatectomy for bilateral CLM. In patients undergoing repeat resection of recurrent CLM, RFS and OS were significantly worse in patients with *RAS* alteration than those in patients with *RAS* wild-type. Median RFS was 6.1 months in patients with

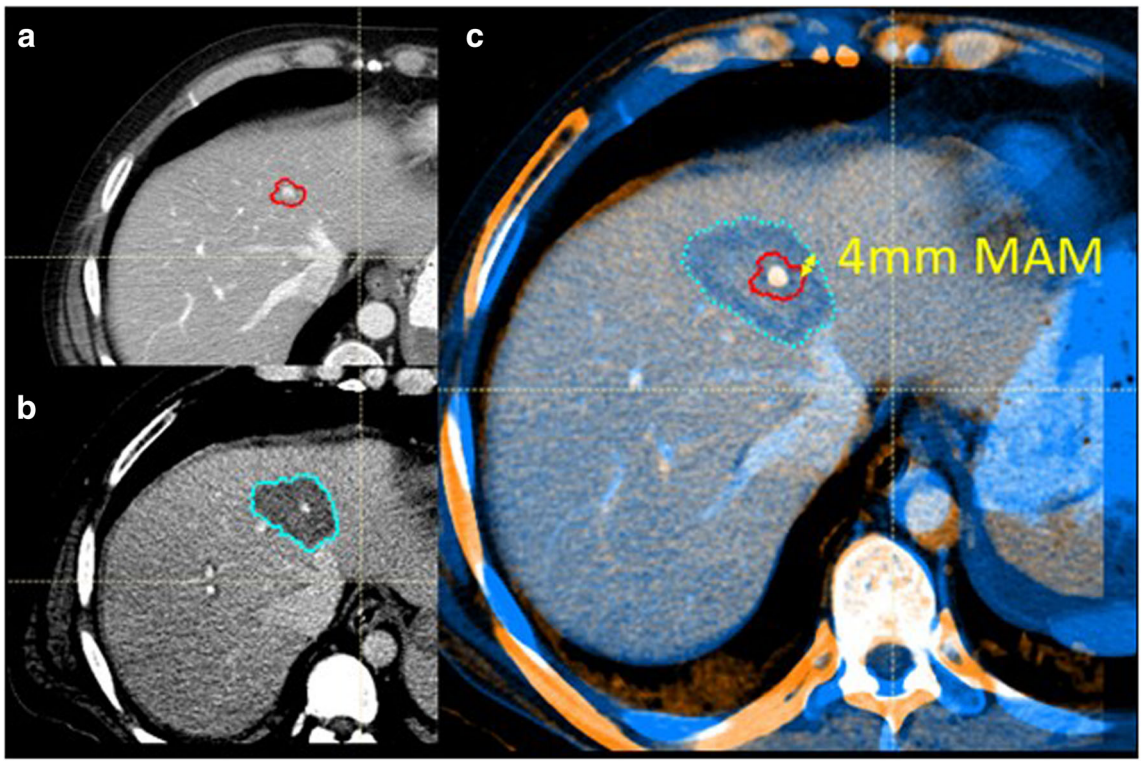

Fig. 3 Use of an advanced deformable registration model (Morfeus) for CT imaging fusion during ablation in a patient with a colorectal liver metastasis. **a** Pre-ablation contrast-enhanced CT depicting the gross tumor volume (area circled in red). **b** Immediate post-ablation contrast-enhanced CT demonstrating the ablation zone (area circled in blue). Note that the gross tumor volume is indistinguishable from the ablation zone given similarities in attenuation. **c** Fusion of pre- and post-ablations contrast-enhanced CT scans using a biomechanical model (Morfeus). Three-dimensional imaging evaluation revealed a suboptimal minimal ablation margin of 4 mm in the medial aspect of the ablation zone (yellow arrow), indicating the need for further ablation in this area to expand the ablation margins to >10 mm. Courtesy, Kristy Brock, PhD, and Brian Anderson

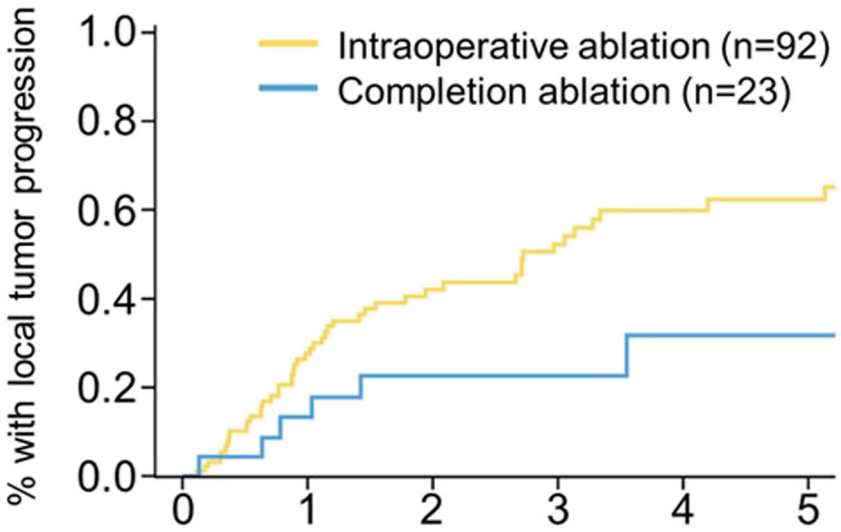

Fig. 4 Cumulative incidence of local tumor progression at the ablation site in patients who underwent intraoperative and postoperative (completion) ablation of CLM. The 5-year local tumor progression rate was significantly lower in patients who underwent completion ablation (32% vs. 62%, p = 0.030). (Okuno M, et al. Eur J Surg Oncol 2020. Used with permission)

RAS alteration vs. 12.1 months in patients with *RAS* wild-type (HR, 1.69; 95% CI, 1.03–2.72; p = 0.037). Median OS was 26.6 months in patients with *RAS* alteration vs. 42.5 months in patients with *RAS* wild-type (HR, 2.11; 95% CI, 1.11–3.98; p = 0.024).[32] In patients who experienced recurrence after two-stage hepatectomy for bilateral CLM, repeat resection of recurrent CLM improved OS (HR, 0.25; 95% CI, 0.10–0.54; p < 0.001). For this patient group, *RAS* alteration was associated with decreased OS (HR, 2.25; 95% CI, 1.16–4.50; p = 0.016) .[33]

Genetic Profile of CLM: Beyond *RAS* Alteration Status

Although studies showed that patients with *RAS* alteration had a poor prognosis after CLM resection, *RAS* alteration should not be a contraindication for CLM resection.

Beyond *RAS* alteration, other genetic alterations may have prognostic utility in the treatment of CLM. The substitution of valine for glutamate in codon 600 (*BRAF*

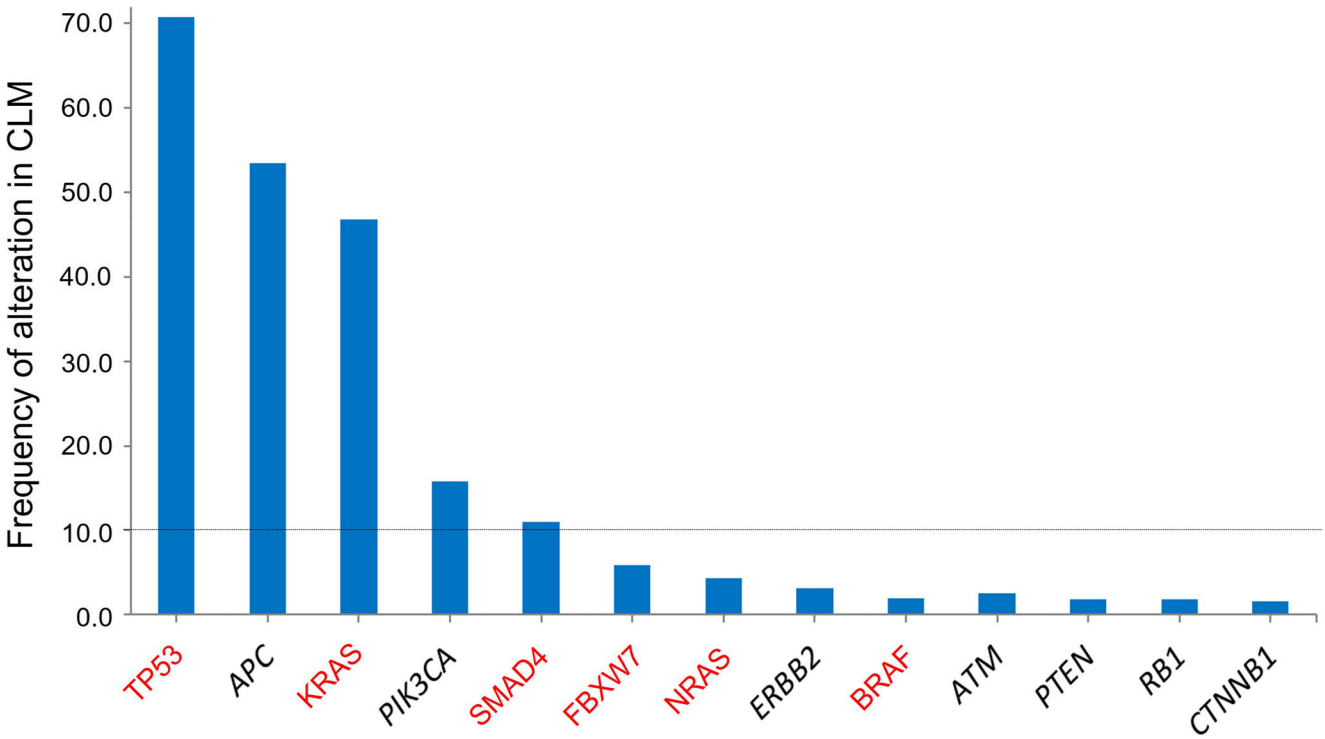

Fig. 5 Frequency of somatic gene alterations in CLM. (Kawaguchi Y, et al. Clin Cancer Res 2019. Used with permission)

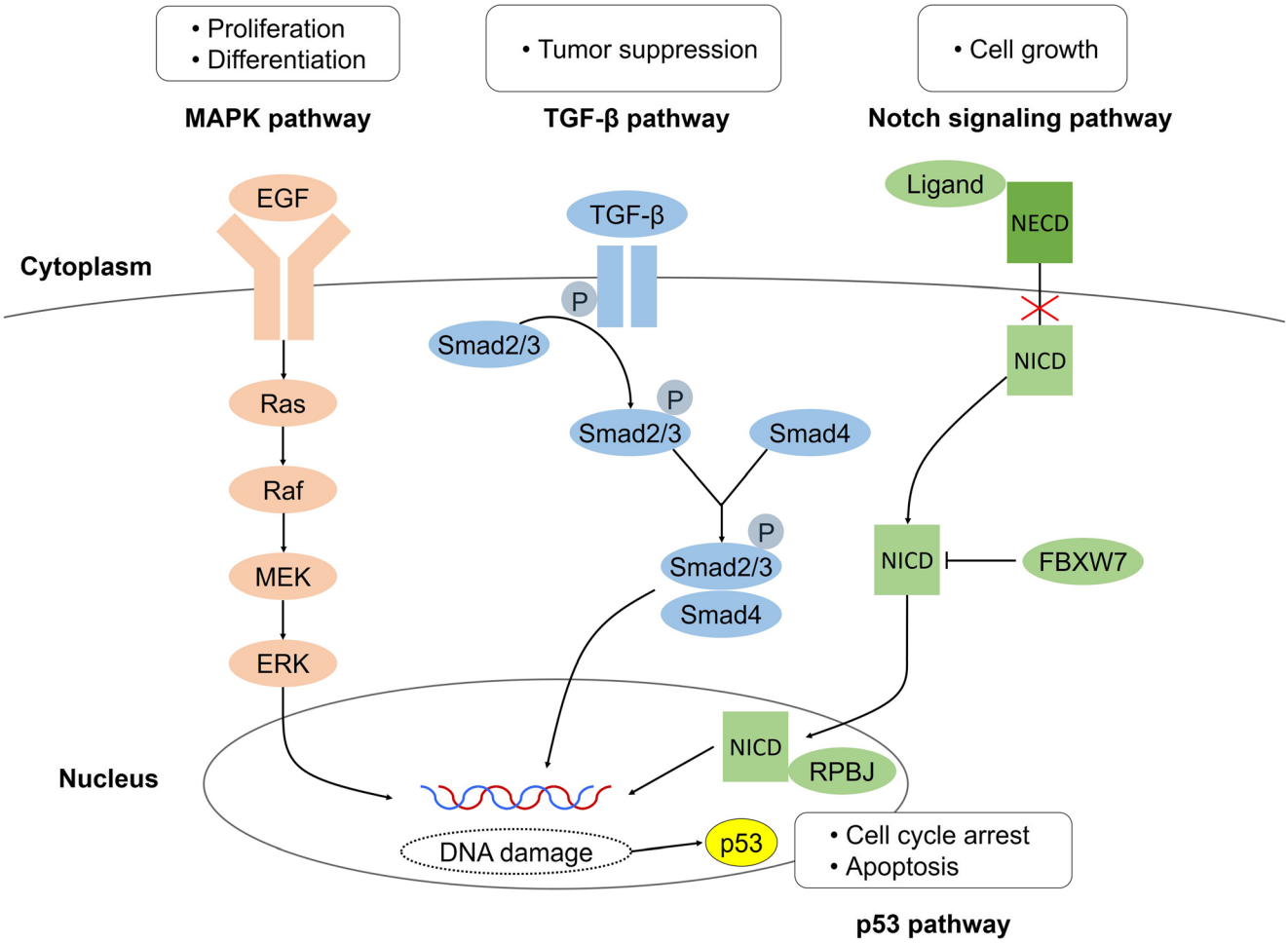

Fig. 6 Four cancer-related signaling pathways associated with prognosis after CLM resection

V600E) is a well known negative prognostic factor in patients with colorectal cancer. Schirripa et al. reported that the negative impact of *BRAF* alteration on prognosis (HR, 3.07; 95% CI, 2.12–22.94; $p = 0.002$) was greater than the negative impact of *RAS* alteration (HR, 1.47; 95% CI, 1.05–2.07; $p = 0.025$) .[34] The association of *BRAF* V600E with prognosis in surgical cohorts is unclear because patients with *BRAF* V600E generally present with multiple extrahepatic sites of disease and rarely undergo surgical treatment. In a recent multi-institutional study that included 853 patients, *BRAF* V600E alteration was identified in 43 patients (5.0%). RFS and OS after CLM resection were worse in patients with *BRAF* V600E than those in patients with *BRAF* V600E wild-type (RFS: HR, 2.04; 95% CI, 1.30–3.20; OS: HR, 2.76; 95% CI, 1.74–4.37).[35]

A recent study of The Cancer Genome Atlas reported that genetic mutations of cancer cells could be understood in the context of 10 oncogenic signaling pathways: *RTK/RAS*, *p53*, *Wnt*, *TGF-β*, *Notch*, *PIK3*, *Hippo*, *Myc*, cell cycle, and *Nrf2* .[36] Our group used genetic analysis with next-generation sequencing in patients undergoing CLM resection and showed that at least one genetic alteration was found in 95.5% of patients with CLM .[37] We also found that the following five genes had a frequency of somatic mutation higher than 10% in patients with CLM (Fig. 5): *TP53* (70.8%, member of the *p53* pathway), *KRAS* (46.7%, member of the *MAPK* pathway), *APC* (53.5%, member of the *Wnt* pathway), *PIK3CA* (15.8%, member of the *PIK3* pathway), and *SMAD4* (11.0%, member of the *TGF-β* pathway) .[38] Co-mutation of *RAS* and *TP53* was associated with worse OS than *RAS* alteration alone, and median RFS was lower for patients with *RAS/TP53* co-mutation than for those with *RAS/TP53* wild-type, even among patients who were free of recurrence at 1 year (1.5 years vs. 2.8 years; $p = 0.006$) or who were free of recurrence at 2 years (3.0 years vs. 5.9 years; $p = 0.024$) .[30] Somatic gene alterations in *RAS* (HR, 1.47; 95% CI, 1.20–1.82; $p < 0.001$), *TP53* (HR, 1.40; 95% CI, 1.11–1.78; $p = 0.005$), and *SMAD4* (HR, 1.62; 95% CI, 1.20–2.20; $p = 0.002$) were associated with worse OS after CLM resection, and alterations in more than one of these three genes were associated with worse OS and RFS than alteration in only one or none of

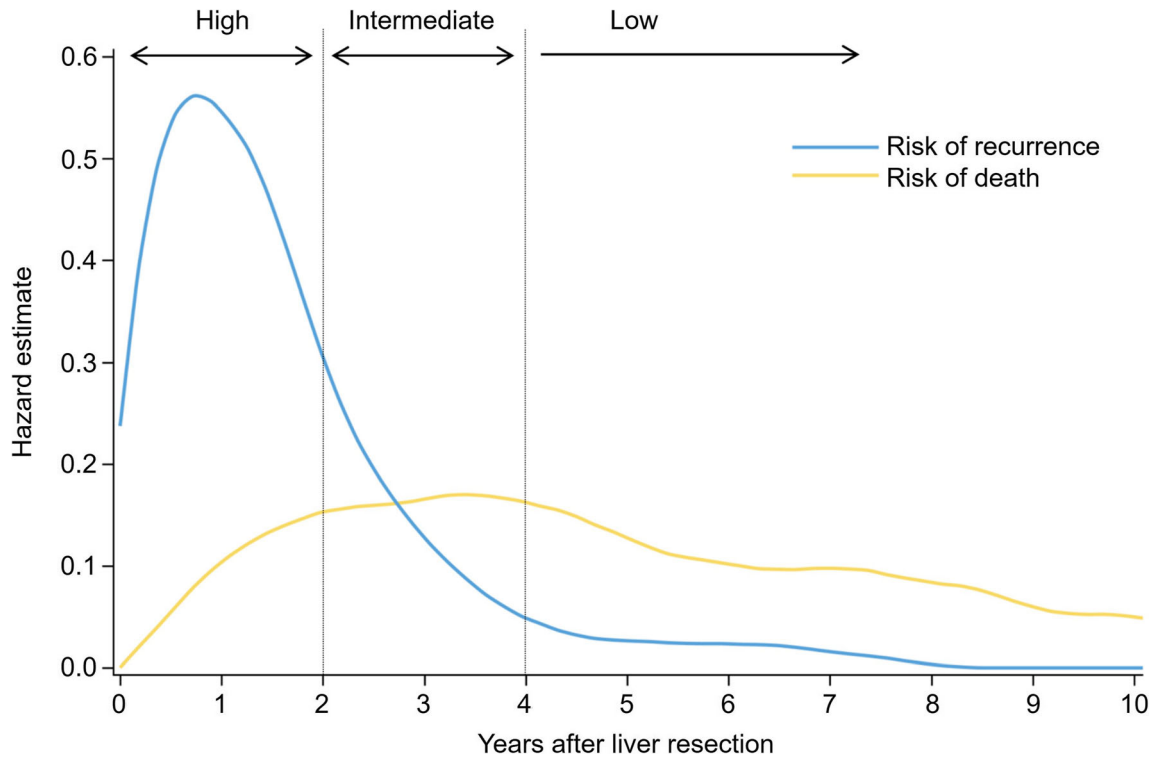

Fig. 7 Risk of recurrence and death over time after CLM resection. (Kawaguchi Y, et al. J Natl Compr Canc Netw 18:11;1500-1508; used with permission)

them. Additionally, OS and RFS did not differ significantly between patients with *RAS* alteration and wild-type *TP53* and *SMAD4* and patients with wild-type *RAS* .[38]

Our recent study showed that *FBXW7* somatic gene alteration was the sixth most common alteration in patients with CLM and was associated with prognosis .[39]

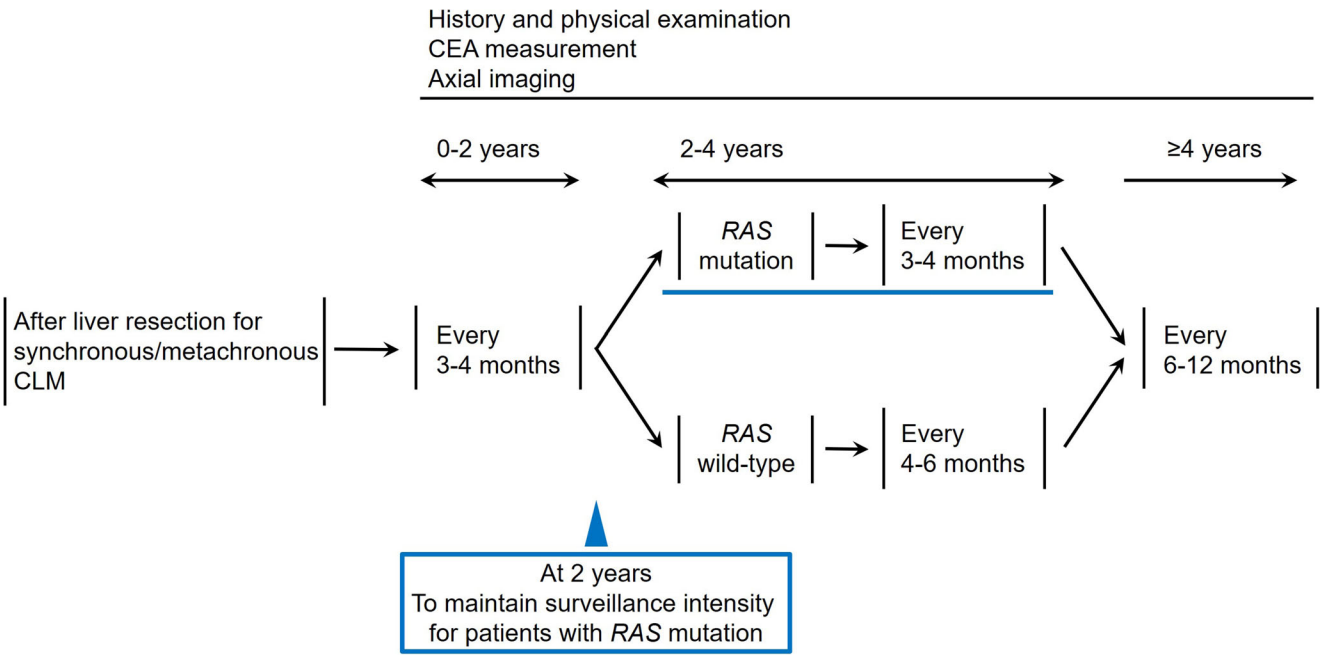

Fig. 8 Surveillance algorithm tailored by the changes in recurrence risk and stratified by *RAS* mutation status. (Kawaguchi Y, et al. J Natl Compr Canc Netw 18:11;1500-1508; used with permission)

From the point of view of signaling pathways, alteration in *RAS*/*BRAF* (MAPK pathway) contributes to the deregulation of cell proliferation and differentiation. *TP53* is a tumor suppressor gene in the p53 pathway, which is activated by DNA damage and induces apoptosis and cell cycle arrest, and *TP53* mutations alter these protecting functions. *SMAD4* is a tumor suppressor gene in the TGF-β pathway, which regulates cell proliferation. *FBXW7* inhibits the Notch pathway, and its mutation results in uncontrolled cell growth (Fig. 6).

Lang et al. identified four clinicopathologic and genetic risk factors for relapse in patients with CLM on the basis of next-generation sequencing: largest CLM diameter > 5 cm, primary lymph node metastases, *RAS*/*BRAF* alteration, and *SMAD* alteration (Table 1). The authors showed that a new clinical risk score integrating these four risk factors stratified prognosis by number of existing risk factors .[40]

Further understanding of the genetic profile of colorectal cancer may be helpful for selecting patients with high risk for decreased OS .[41] For such patients, whether CLM resection is warranted should be carefully determined considering the response to preoperative chemotherapy.

Surveillance After Resection of CLM

National Comprehensive Cancer Network guidelines currently recommend a computed tomography scan every 3 to 6 months until 2 years and every 6 to 12 months from 2 to 5 years in patients with stage IV colorectal cancer. However, the surveillance algorithm for patients undergoing resection of synchronous or metachronous CLM has not been established yet. The goal of surveillance for patients with CLM is to detect early manifestations of CLM recurrence and permit timely reintervention to achieve cure. Recently, our group reported that the probability of recurrence peaked at approximately 1 year and diminished thereafter .[30] Additionally, the risk of recurrence changes over time by the interval free from recurrence after surgery (Fig. 7). At the time of CLM resection, *RAS* alteration, number and diameter of CLM, and primary lymph node metastases were all risk factors for recurrence; however, for patients free from recurrence at 2 years after CLM resection, only *RAS* alteration was associated with recurrence. Thus, it is reasonable to stratify surveillance intensity by *RAS* alteration status after 2 years. Our group recently proposed a surveillance algorithm in which surveillance is tailored according to the changes over time in recurrence risk and risk factors (Fig. 8).

Conclusion

Understanding the heterogeneity of the tumor burden and genetic profile of CLM is important to accurately predict prognosis after CLM resection and select the best treatment approach for individual patients. *RAS* alteration is a risk factor for poor survival in addition to traditional clinical risk factors (e.g., number and diameter of CLM, primary lymph node metastases). *RAS* alteration status can be used not only to predict survival after initial CLM resection but also to select treatment for recurrent CLM and to tailor postoperative follow-up. Recent studies using genetic sequencing have shown *TP53* and *SMAD4* alterations are associated with poor prognosis as well. Currently, somatic gene alteration status should not be interpreted as a contraindication for CLM resection. Instead, clinicians should use genetic and clinicopathologic risk factors to help guide decision-making regarding surgery and other forms of therapy.

Abbreviations CI, Confidence interval; CLM, Colorectal liver metastases; FOLFOX, 5-Fluorouracil, leucovorin, and oxaliplatin; HR, Hazard ratio; OS, Overall survival; PFS, Progression-free survival; RFS, Recurrence-free survival

Declarations

Conflict of Interest The authors declare no competing interests.

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