

Surgery for colorectal liver metastases: The evolution of determining prognosis

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Abstract

Despite improvements in the multi-modality treatment of colorectal liver metastasis (CRLM), survival after resection remains varied. Determining prognosis after surgical resection has historically been predicated on preoperative clinicopathological factors such as primary tumor stage, carcinoembryonic antigen levels, number of liver metastases, presence of extrahepatic disease, as well as other factors. While scoring systems have been developed by combining certain preoperative factors, these have been inconsistent in accurately determining prognosis. There has been increasing interest in the use of biologic and molecular markers to predict prognosis following CRLM. The role of markers such as KRAS, BRAF, p53, human telomerase reverse transcriptase, thymidylate synthase, Ki-67, and hypoxia inducible factor-1 α and their correlation with accurately predicting survival after surgical resection have been supported by several studies. Furthermore, other elements such as pathological response to chemotherapy and the presence of circulating tumor cells have shown promise in accurately determining prognosis after resection for colorectal liver metastasis. We herein review past, pres-

ent, and possible future markers of prognosis among colorectal cancer patients with liver metastasis undergoing resection with curative intent.

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Key words: Colorectal; Metastasis; Prognosis; Risk score; Molecular markers; Outcomes

Core tip: Historically, prognosis after resection has been largely assessed based on preoperative clinicopathologic features. Data validating the prognostic value of patient and tumor specific factors have been mixed, with many recent studies showing these scoring systems to correlate poorly with survival. Rather, there has been an emerging interest in biological or molecular markers of prognosis to more effectively assess patient prognosis after resection of colorectal liver metastasis. In this review, we discuss past, present, and possible future markers of prognosis among colorectal cancer patients with liver metastasis undergoing resection with curative intent.

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INTRODUCTION

Colon cancer is the 3rd most common cancer worldwide. It has an estimated incidence of 42.5 per 100000 with over 140000 estimated new cases expected in the United States in 2013 as reported by the Center for Disease Control^[1,2]. About 14%-25% of patients with colorectal cancer will have liver metastasis at presentation and up to

Table 1 Studies of prognostic clinicopathological factors

Study	Primary stage	CEA level	Size of major metastasis	Number liver metastases	Disease free interval	Extrahepatic disease	Surgical margins
Scheele <i>et al</i> ^[11]	P	NA	P	NP	P	P	P
Nordlinger <i>et al</i> ^[10]	P	P	P	P	P	NA	P
Fong <i>et al</i> ^[9]	P	P	P	P	P	P	P
Mann <i>et al</i> ^[12]	P	P	P	NP	NP	NA	NA
Rees <i>et al</i> ^[15]	P	P	P	P	NA	P	P
John <i>et al</i> ^[21]	NP	P	NP	NP	NA	NP	P
Docì <i>et al</i> ^[27]	P	NP	NP	NP	NP	NA	NA
Hughes <i>et al</i> ^[34]	P	P	P	P	P	NA	NA
Gayowski <i>et al</i> ^[37]	P	NA	NP	P	NP	P	P

CEA: Carcinoembryonic antigen; P: Prognostic; NP: Non prognostic; NA: Non available.

60% of patients will develop metastasis at some point after diagnosis^[3-6]. Surgical resection remains the only hope for cure. Contemporary series have demonstrated that surgical therapy for colorectal liver metastasis (CRLM) is associated with a low operative mortality of 1% to 2%^[7,8]. The reported 5- and 10-year survival does vary, however, ranging from 25% to 74% (median 38%) and 9% to 50% (median 26%), respectively, depending on the era from which the data were reported and the underlying patient population. Historically, prognosis after resection has been largely assessed based on preoperative clinicopathologic features. Data validating the prognostic value of patient and tumor specific factors have been mixed, with many recent studies showing these scoring systems to correlate poorly with survival. Rather, there has been an emerging interest in biological or molecular markers of prognosis to more effectively assess patient prognosis after resection of CRLM. In this review, we discuss past, present, and possible future markers of prognosis among colorectal cancer patients with liver metastasis undergoing resection with curative intent.

CLINICAL MARKERS

Numerous clinical prognostic factors have been identified in an attempt to estimate overall prognosis among patients with CRLM. The most relevant factors have been included in clinicopathological scoring systems, proposed in the late 90s and now widely used by many clinicians^[9,10]. The role of each of these factors in determining the prognosis of patients with CRLM is still, however, a matter of some debate. Furthermore, there remains no consensus regarding which of these clinicopathological factors has the “best” prognostic value (Table 1).

Primary tumor stage

Advanced primary tumor stage has been considered a negative prognostic factor by multiple investigators. Scheele *et al*^[11] initially proposed a correlation between the primary tumor grade and overall survival (OS) as well as disease free survival (DFS). Primary tumor stage was later incorporated into clinical prognostic scoring systems^[9,10]. Specifically, Fong *et al*^[9] proposed the stage of the primary tumor as an adverse prognostic factor, concluding that

the nodal status of the primary cancer was highly predictive of outcome^[9,12-15]. A subsequent meta-analysis reported an association between primary tumor stage, nodal metastasis, and worse outcomes following resection of CRLM^[13-15]. Tranchart *et al*^[16] similarly noted that primary tumor lymph node metastasis was an independent predictor of adverse OS and DFS. Previously Bennett *et al*^[17] analyzed the prognostic value of perihepatic lymph node micrometastases in patients with CRLM. Patients with at least one perihepatic lymph node with metastases had a shorter recurrence free survival.

Preoperative carcinoembryonic antigen level

The role of carcinoembryonic antigen (CEA) as a robust predictor of long-term survival following resection of CRLM remains poorly defined^[9,10,12,18-22]. Among many patients, CEA can be an effective marker to monitor for recurrence, as well as to assess response to systemic therapy^[18,21]. CEA levels can correlate with the radiological response to preoperative chemotherapy; however, other data have suggested that the absolute change in CEA level with chemotherapy may not correlate with long-term outcome^[23]. As a pre-operative prognostic factor, Mann *et al*^[12] reported that CEA levels did correlate with 5-year survival (CEA levels < 200 ng/mL: 48.9% *vs* > 200 ng/mL: 0.0%). Other studies have similarly noted that preoperative CEA > 200 ng/mL was an independent factor of poor OS and disease specific survival (DSS), respectively^[18,21]. In a one study, Park *et al*^[19] looked at both tissue CEA and serum CEA concentration after resection for CRLM and noted that CEA expression was an independent prognostic factor for OS and DFS. Of note, patients with elevations in both tissue CEA expression and serum CEA had a worse OS and DFS compared with patients who had only one CEA category elevated^[19]. Despite these data, other studies have noted that CEA level was not a significant predictor of survival or recurrence after hepatic resection for metastatic colorectal cancer^[24-27]. The reason for the disparate finding from various studies may be due to the different cut-off values used for CEA, as well as differences in how the statistical models were constructed (*e.g.*, which other competing risk factors were put into the model, how many patients in any given study had a particular factor, *etc.*).

Number of liver metastases

Several studies have reported that a higher number of CRLM lesions is a poor prognostic factor^[28-32]. A recent large meta-analysis examining nearly 10000 patients reported a 5-year survival of only 17.1% for patients with four or more CLMs^[28]. Other studies have found no difference in survival based on the number of tumors with 5-year survival ranging from 40%-50% regardless of tumor burden^[9,27,29-32]. The reason for these differences may be related to patient selection, differences in surgical approach (resection only, resection plus ablation, *etc.*), as well as differences in the use of neoadjuvant chemotherapy. For example, in a study by Pawlik *et al.*^[33] the 5-year survival among patients with 4 or more CRLM was 50.9%, however many of the patients had been pretreated with neoadjuvant chemotherapy and response to neoadjuvant therapy was strongly associated with survival. As such, the impact of tumor number on prognosis needs to be considered in light of other important clinical and therapeutic information. While the limit of hepatic involvement that precludes a patient from being “operable” is still a matter of debate, the general consensus is that tumor number should not be used as an absolute contraindication to surgery. When all the lesions can be resected with a microscopically negative margin (R0) in the setting of an adequate future liver remnant (FLR), surgery should at least be contemplated. Considering that as the number of tumor metastases increases, a curative resection becomes more technically challenging, the number of liver tumors may impact survival when all tumors are not able to be completely removed.

Size of liver metastases

The size of the largest metastasis is another clinical factor that has long been considered a prognostic factor. Mann *et al.*^[12] reported that 5-year survival was 51.6% among patients undergoing surgery for CRLM ≤ 5 cm compared with 27% for those patients with a tumor > 5 cm. In other studies, patients with CRLM measuring > 5 cm were similarly noted to have a worse survival^[15]. Specifically, Aldrighetti *et al.*^[22] reported that patients with a CRLM lesion measuring > 5 cm had a survival of only 18.8% *vs* 30% for patients with smaller tumors. In a separate study, Rees *et al.*^[15] similarly reported that CRLM diameter > 5 cm was an independent predictor of survival. As such, tumor size > 5 cm has been adopted by several investigators as a predictor of adverse long-term outcome, evidenced by the inclusion of tumor size in multiple clinical scoring systems^[9,11,14,34-36]. However, several other studies have been unable to find any differences in recurrence and survival with relation to tumor size^[20,24,27,37]. Modern era chemotherapeutic agents are now frequently able to cytorreduces or downsize metastasis. In this context, it is not clear if tumor size continues to hold important prognostic information. Response to chemotherapy - as evidenced by change in tumor size - may be a more important and relevant prognostic marker than initial CRLM tumor size^[38,39].

Synchronous metastases and disease free interval

Approximately 25% of patients have a synchronous presentation of their primary tumor and CRLM at the time of diagnosis^[1]. Some authors have found an association between the presence of synchronous metastasis and a worse prognosis^[9-11,34,40], while others have not noted that synchronous presentation has an effect on survival^[12,20,27]. Similarly, there is no consensus regarding the impact of disease-free interval on outcomes. Some authors have reported that a short disease-free interval did not impact disease-free or OS^[12], however other investigators consider disease-free interval a reliable prognostic factor^[9,22]. Fong *et al.*^[9] concluded that disease-free interval of < 12 mo after resection of the colorectal primary was predictive of adverse outcomes, and included this factor in the clinical risk score. Tan *et al.*^[18] similarly noted that a disease-free interval < 12 mo was an independent predictor of disease-specific survival (DSS) at 3 years. The prognostic role of disease-free interval is still controversial. One reason why the impact of disease-free interval may have changed over time is that there is more effective adjuvant treatment for patients with advanced colorectal cancer. More effective chemotherapy may prolong the disease-free interval among these patients and may contribute to why studies conducted in the past might not be comparable to the ones conducted in the era of modern chemotherapy.

Extrahepatic disease

Traditionally extrahepatic disease (EHD) has been considered a contraindication to hepatectomy for CRLM due to the unfavorable prognosis previously noted in multiple studies^[10,34,41-43]. While the presence of EHD has clear prognostic implications, the impact of the extent and location of the EHD and its effect on prognosis has been debated. In a study by Elias *et al.*^[44], the investigators argued that the total number of metastases was more prognostically important than the site of EHD. While other groups have shown that multiple EHD sites is clearly associated with a worse survival^[45,46], the site of EHD also has prognostic importance. Specifically, Pulitanò *et al.*^[46] noted that the location of EHD was associated with prognosis, as patients having pulmonary metastasis had the best prognosis and patients with retroperitoneal/aortocaval lymph node metastasis had the worse prognosis. Pulmonary metastasectomy has been demonstrated to prolong survival in selected patients and has a clear benefit in patients with solitary or oligometastatic disease^[47-49]. Specifically, 5-year survival after pulmonary resection of colorectal metastasis has been reported to be as high as 48.0%^[50]. In contrast, regional lymph node involvement has been correlated with a worse survival, with observed 5-year OS of 25% for pedicular, 0% for celiac, and 0% for para-aortic lymph node involvement^[51].

Surgical margin status

Microscopically negative surgical margins (R0) have traditionally been considered an important prognostic factor

Table 2 Survival based on the clinical risk cumulative score (adapted from Fong *et al.*^[9])

Cumulative score	1 yr	2 yr	3 yr	4 yr	5 yr	Median, mo
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22
Prognostic factor	Score 0	Score 0	Score 0	Score 1	Score 1	Score 1
Node-positive primary	negative	negative	negative	positive	positive	positive
Disease-free interval	≥ 12 mo	≥ 12 mo	≥ 12 mo	< 12 mo	< 12 mo	< 12 mo
Number of liver metastases	1	1	1	> 1	> 1	> 1
Size of major liver metastases	≤ 5 cm	≤ 5 cm	≤ 5 cm	> 5 cm	> 5 cm	> 5 cm
CEA (ng/mL)	< 200 ng/mL	< 200 ng/mL	< 200 ng/mL	> 200 ng/mL	> 200 ng/mL	> 200 ng/mL

CEA: Carcinoembryonic antigen.

following resection of CRLM. Most authors have indeed reported that an R1 (microscopically positive) and R2 (macroscopically positive) margin are associated with worse long-term OS^[9,15,20,21,52-55]. While there has been some lack of consensus as to what constitutes a “truly” microscopically negative margin^[56-59], Pawlik *et al.*^[60] demonstrated in a large cohort of patients that margin width > 1 mm was not associated with overall risk or pattern of recurrence. Kokudo *et al.*^[30], using a sensitive genetic analysis detecting *KRAS* and *p53* mutations, found micrometastases in the liver parenchyma surrounding CRLM in only 2% of patients, all within 4 mm of the tumor border. Andreou *et al.*^[61] did report that it was important to achieve an R0 margin as patients who had an R1 resection were noted to have a worse outcome. Some investigators have argued, however, that it is biology, not millimeters that dictate prognosis following resection^[62]. Specifically, these investigators note that margin status is often confounded by the extent of intrahepatic disease. Patients with a larger intrahepatic tumor burden are most at risk for an R1 margin; it is these patients who also have worse overall tumor biology and overall recurrence. To this point, de Haas *et al.*^[23] did not find a difference in OS among patients undergoing an R0 *vs* R1 resection. These data may suggest that, in an era of more effective chemotherapy options, leaving microscopic disease behind may result in increased local failure but not necessarily a worse OS. The impact of margin status on outcomes may therefore be influenced by patient and tumor factors, as well as the utilization of chemotherapy^[61]. Regardless of the impact of margin status on prognosis, complete macroscopic and microscopic removal of all lesions with negative resection margins should remain the gold standard in the surgical treatment of CRLM^[23].

Operative and post-operative factors

There is no consensus regarding the impact of blood loss, transfusion, or postoperative complications on survival following resection of CRLM^[63-66]. The most convincing prognostic factor seems to be the effect of infections and other postoperative complications^[40,67]. Specifically, Mavros *et al.*^[68] reported that postoperative complications

were independently associated with decreased long-term survival after surgery for CRLM with curative intent. The effect of complications on long-term survival may be due to the immune modulating effects of sepsis, impaired immune system and consequent metastatic spread. Moreover, a high rate of complications, longer hospital stays and the delayed wound healing may cause a postponement or avoidance of necessary adjuvant treatments, which in turn may have implications for long-term survival.

Clinical scoring system

One of the first preoperative prognostic scoring systems was described by Nordlinger *et al.*^[10] in 1996. In this scoring system, one point was given to each of the following factors: age, size of largest metastasis, CEA level, stage of the primary tumor, disease-free interval, number of liver nodules, and resection margin^[10]. Subsequently, Fong *et al.*^[9] proposed a “clinical risk score” to predict long-term outcome and recurrence. In a cohort of 1001 patients treated with resection of CRLM, the authors identified 5 criteria as significantly impacting prognosis: nodal status of the primary tumor, disease-free interval, number of hepatic metastases > 1, preoperative CEA level > 200 ng/mL, and size of the largest metastasis > 5 cm^[9]. One point was assigned to each factor (Table 2) and the total score was reported to be highly predictive of long-term outcome (Figure 1). This score has been widely utilized; while some groups have validated the scoring system, other investigators have questioned its prognostic accuracy^[12,25,26,69-72]. In a separate study, Iwatsuki *et al.*^[73] proposed a different prognostic score that included tumor number ≥ 3, tumor size > 8 cm, time to hepatic recurrence ≤ 30 mo as well as the presence of bilobar tumors. The prognostic score, calculated by summing these prognostic factors, was suggested to predict 5-year survival. When comparing the Fong score^[9] with other described clinical scoring systems, including the Nordlinger score^[10], Iwatsuki score^[73], Mayo Clinic scoring system and Basingstoke index, several authors have found that only the Fong and the Iwatsuki scores provide a statistically significant stratification of disease specific survival^[9,10,15,70,71,73,74]. In 2008, the Memorial Sloan Kettering Cancer Center (MSKCC) proposed

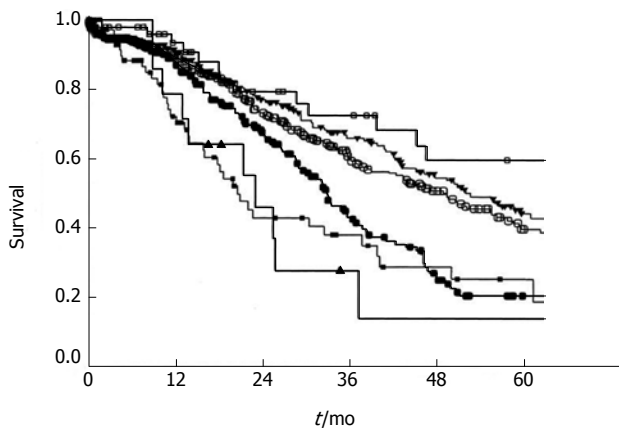


Figure 1 Survival after hepatic resection stratified by the clinical risk score. Open box: score 0 ($n = 52$); filled triangle: score 1 ($n = 262$); open circle: score 2 ($n = 350$); filled circle: score 3 ($n = 243$); filled box: score 4 ($n = 80$); open triangle: score 5 ($n = 14$). $P < 0.0001$ (from Fong *et al*^[6]). Used with permission.

the first nomogram for predicting disease-specific survival for the individual patient^[75]. The nomogram appears to better represent characteristics of individual patients, for instance incorporating the true preoperative CEA value rather than applying an arbitrary cutoff value^[76].

The ultimate clinical value of these prognostic scoring systems remains debatable. In a study by Nathan *et al*^[77], the authors reported a c-statistic of only 0.5 to 0.6 for many of the scoring systems. The authors postulated that the moderate-to-poor accuracy of the staging systems was related to the inability to account for neoadjuvant treatments, varying R0 resection rates, as well as differences in establishing categorical cutoff values for continuous data fields (*e.g.*, CEA level > 200 ng/mL, and size of the largest metastasis > 5 cm, *etc.*). Moreover, despite some external validation, these scores are based on single-institution cohorts and have not been modified based on newer developments in treatments. Lastly, the variations observed in the OS of patients with similar prognostic scores suggest that other factors may play a role in determining survival after resection of CRLM, most intriguingly patient-specific biological and molecular factors^[78].

BIOLOGICAL, PATHOLOGICAL, AND MOLECULAR MARKERS

Recently, attention has turned to the use of biological and molecular markers as a more accurate means to predict long-term outcomes. Patient and tumor specific markers may provide more accurate predictions of survival after hepatic resection for colorectal metastasis (Table 3).

Tumor response to preoperative chemotherapy on imaging

Preoperative chemotherapy is increasingly being used, especially among patients with advanced CRLM. Preoperative “conversion” chemotherapy has allowed many previously unresectable patients to be treated and converted/down-

sized so that surgery becomes possible^[79,80]. In some centers, neoadjuvant therapy for patients with resectable disease is also frequently being used^[32,79]. The use of preoperative systemic chemotherapy provides the opportunity to assess response. Response to chemotherapy has been shown to improve 5-year survival from 35% to 85% in one study when compared with patients who did not receive chemotherapy^[38]. Adam *et al*^[32] reported a 30% increase in 5-year survival among patients who underwent hepatectomy after an objective tumor response *vs* patients who had tumor progression while receiving neoadjuvant chemotherapy. Similarly, recurrence-free survival (RFS) has been shown to be influenced by tumor response. In a study by Gruenberger *et al*^[39], patients who had a response to chemotherapy had a RFS of 24.7 mo *vs* only 3 mo for patients with progressive disease.

Most commonly, response to chemotherapy can be assessed by standard cross-sectional imaging using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. RECIST allows for the assessment of changes in the standard cross-sectional diameter of lesions. Oxaliplatin- and irinotecan-based cytotoxic chemotherapeutic regimens may result in radiographic “shrinkage” of tumors. In contrast, the use of biologic or targeted agents, such as bevacizumab, can sometimes be difficult to assess using RECIST criteria on cross-sectional imaging. For example, in a phase III study examining the addition of bevacizumab to oxaliplatin-based chemotherapy for metastatic colorectal cancer, the investigators noted an improved progression-free survival without affecting RECIST-defined response rates^[81]. In a separate study, Chun *et al*^[82] reported that morphological changes in CRLM lesions - rather than RECIST changes - were prognostic with regard to long-term outcomes.

Tumor response to preoperative chemotherapy on pathology

In addition to assessment on preoperative imaging, tumor response can be assessed on pathological examination after extirpation of the tumor. Andreou *et al*^[61] reported on the effect of pathological response to neoadjuvant chemotherapy in achieving negative margins. Patients with a minor pathologic response to preoperative chemotherapy ($\geq 50\%$ residual viable tumor cells) had significantly worse OS (5-year OS rate 46% after R0 resection *vs* 0% after R1 resection). In a study by Adam *et al*^[83], complete pathological response (CPR) was similarly correlated with an increase in overall 5-year survival from 45% to 76%. This finding was subsequently confirmed by correlating pathologic response, considered as mean of the percentage of cancer cells remaining within each tumor, with 5-year overall survival. In a separate study, Blazer *et al*^[84] reported on 305 patients who underwent preoperative irinotecan- or oxaliplatin-based chemotherapy, followed by resection of CRLM. In this group of patients, 9% had a complete response (no residual cancer cells), 36% a major response (1% to 49% residual cancer cells), and 55% a minor response ($\geq 50\%$ residual cancer cells). The residual tumor was assessed semiquantitatively, estimating the proportion of residual

Table 3 Studies of prognostic biomarkers

Study	No. of patients	Positive case (%)	Biomarker	Correlation with survival
Nash <i>et al</i> ^[110]	188	27	KRAS	Independent predictor of poor survival (HR = 1.9)
Nash <i>et al</i> ^[110]	188	62	Ki-67	Independent predictors of poor survival (HR = 2.6)
Teng <i>et al</i> ^[113]	292	2.1	BRAF	Independent prognostic biomarker after metastasectomy (HR = 6.245, $P < 0.003$)
Smith <i>et al</i> ^[26]	66	36	Ki-67	
Smith <i>et al</i> ^[26]	66	35	hTERT	Htert correlate with survival ($P = 0.0001$)
Dòmont <i>et al</i> ^[25]	201	43	hTERT	Independent predictor of poor survival (RR = 2.03, $P < 0.0001$)
Gonen <i>et al</i> ^[123]	156	Not reported	TS	Independent predictor of poor survival (RR = 4.22, $P < 0.01$)
Costa <i>et al</i> ^[137]	104	Not reported	TLI	High TLI independently Predicted decreased DFS ($P = 0.035$)
Nitti <i>et al</i> ^[128]	69	64	p53	Independent predictor of poor survival (RR = 2.53, $P = 0.008$)
Mehta <i>et al</i> ^[144]	50	30	FGA	A high FGA is an independent predictor of survival ($P = 0.01$)
Shimomura <i>et al</i> ^[136]	64	31	HIF-1 α	High HIF-1 α is an independent risk factor for recurrence

hTERT: Human telomerase reverse transcriptase; TS: Thymidylate synthase; TLI: Thymidylate labeling index; DFS: Disease free survival; FGA: Fraction of genome altered; HIF-1 α : Hypoxia inducible factor-1 α .

cancer cells in relation to the tumor area, comprehensive of areas of chemotherapy-related tissue injury, tumor necrosis, fibro-collagenous proliferation, and other reparative changes. Survival was strongly correlated with pathologic response: 5-years survival was 75%, 56%, and 33% for patients with a complete response, major response, or minor response respectively^[84].

A semi-quantitative analysis of the proportion of viable cancer cells, however, is limited due to the difficulty in determining the baseline percentage of tumor cell before preoperative chemotherapy. Therefore, it could be that this type of pathological response would have a better prognostic role than a predictive one based on response to chemotherapy^[82,84]. Interestingly Tanaka *et al*^[85] found that a complete pathological response in all the metastases is not necessary to obtain a correlation with OS. The authors showed that patients with multiple metastases and complete response in some of those tumors still experienced a higher OS and DFS compared with pathologic non-responders. The “best” OS was, however, noted among those patients in whom all CRLM lesions showed a complete response^[85].

Tumor regression grading, as well as tumor thickness at the tumor-normal interface, have been proposed as prognostic histopathological factors^[83-90]. Based on the tumor regression scheme proposed for esophageal carcinoma, Rubbia-Brandt *et al*^[90] described a pathological grading system for CRLM^[90]. In this schema, tumor regression was characterized by fibrosis overgrowing on tumor cells, decreased necrosis, and the presence or absence of tumor glands at the periphery of liver metastases. Based on this, a tumor regression grade (TRG) score, ranging from 1 to 5, was proposed and subsequently shown to correlate with DFS^[91]. Maru *et al*^[89] recently introduced the idea of using tumor thickness measured at the tumor-normal interface as a new prognostic factor for therapy response and survival. Greater tumor thickness predicted shorter recurrence-free survival: 70% for patients with a tumor

thickness of < 0.5 mm, 51% for patients with a tumor thickness between 0.5 mm and 5 mm, and 35% for patients with a tumor thickness of ≥ 5 mm^[89].

Other factors noted on pathology beyond response to preoperative therapy may impact prognosis. Rudolf Virchow hypothesized in 1863 that the origin of cancer was at sites of chronic inflammation. Today, the causal relationship between inflammation, innate immunity and cancer is widely acknowledged. Nonetheless, many of the molecular and cellular mechanisms mediating this relationship still remain unresolved^[92,93]. Okano *et al*^[94] reported that patients with dense tumor infiltrating lymphocytes (TIL) surrounding metastatic liver survived longer than patients with weak TILs after hepatic resection. Canna *et al*^[95] recently examined the relationship between local and systemic inflammatory responses and outcomes in patients undergoing resection of colorectal cancer. A low tumor CD4+ T-lymphocyte infiltrate was associated with an elevated circulating C-reactive protein (CRP) and both were associated with a poor outcome. Furthermore CRP was superior to tumor T-lymphocytic infiltration in predicting cancer specific survival^[95]. There is increasing evidence that a host's inflammatory response to tumor (IRT) is associated with recurrence and lower survival in patients undergoing potentially curative resection for colorectal cancer^[96,97]. Similar studies have shown worse OS and DFS in patients with an elevated preoperative CRP > 10 mg/L and neutrophil to lymphocyte ratio (NLR) $> 5:1$ ^[93,95-100]. NLR $> 5:1$ has been shown to be an independent predictor of recurrence and worse survival in patients undergoing resection for CRLM^[101].

MOLECULAR MARKERS OF PROGNOSIS

KRAS, BRAF

KRAS, along with HRAS and NRAS, belongs to a family of GTPases. When activated, KRAS can induce a cascade of mitogen-activated protein kinases (MAPKs) that

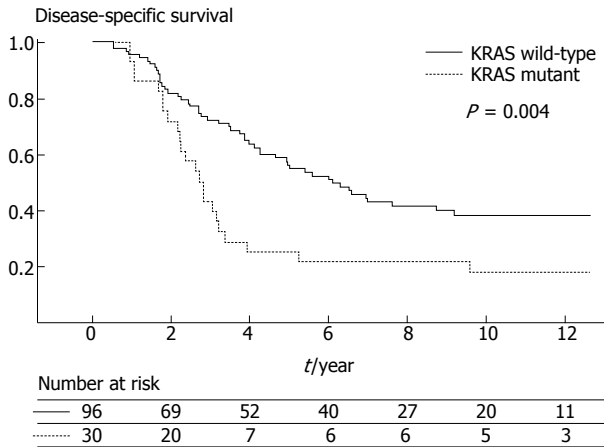


Figure 2 Disease specific survival after liver resection stratified by KRAS mutation (from Nash *et al*^[110]). Used with permission.

transfers signals from the cell membrane *via* the cytoplasm into the nucleus. The ras gene products activate proteins in the Raf family, which consists of the ARAF, BRAF and RAF-1 members^[102]. Mutations of the *KRAS* gene predicts resistance to epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies, and acquired resistance to anti-EGFR therapies may be due to the late switch in KRAS mutational status^[103,104]. The reported prevalence of KRAS mutations in liver metastases varies from 15% to 44%. While several studies have reported no statistically significant association between KRAS mutation and metastatic progression, proliferative index, or survival has been reported^[105-109], Nash *et al*^[110] did report a prevalence of 27% KRAS mutation in liver metastasis and noted an independent association between KRAS mutation and worse survival after liver resection (Figure 2). In a separate study, Karagkounis *et al*^[111] reported KRAS and BRAF analysis performed on 202 patients undergoing surgery for CRLM at the Johns Hopkins Hospital. In this study, the authors noted that KRAS mutations were found in approximately one third of patients, while BRAF mutations were found in only 2% of patients undergoing surgery for CRLM. KRAS status was an independent predictor of overall and recurrence-free survival (Figure 3); the low incidence of BRAF mutation limited assessment of its prognostic impact^[111]. Other studies, however, have noted BRAF mutation to be an independent prognostic factor of worse survival following resection of CRLM, as well as a poor prognostic factor for colon cancer patients of various stages^[102,112-114]. KRAS status may not only predict overall recurrence, but perhaps also the pattern of recurrence. Vauthey *et al*^[115] recently reported that RAS mutation was predictive of early lung recurrence after curative resection of CRLM.

As the MAP kinase signaling pathway is involved in the inflammatory cascade, Huang *et al*^[112] described the role of the activated MAP kinase pathway and CRP in liver metastases. This study demonstrated the significance of both specific C reactive protein (CRP) single nucleotide polymorphisms (SNP) and mutations in *KRAS*/BRAF

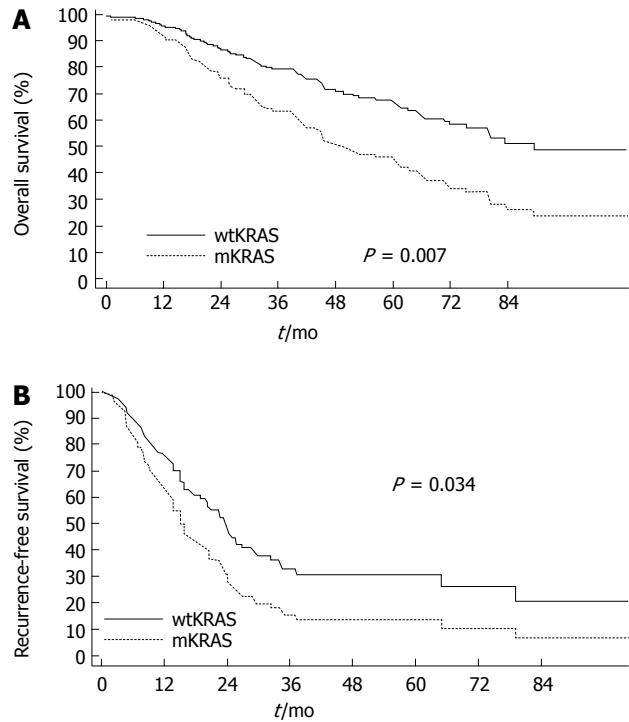


Figure 3 Overall (A) and disease-free (B) survival after hepatic surgery for colorectal liver metastasis depicted by KRAS mutation status (multivariate Cox model) (wtKRAS, wild type KRAS; mKRAS, mutated KRAS) (from Karagkounis *et al*^[111]). Used with permission.

in liver metastases with respect prognosis after resection of CRLM^[116]. CRP SNP rs7553007 and *KRAS* mutations were found to be independent prognostic factors for CRC patients with synchronous liver metastasis^[112].

hTERT

Telomerase is a ribonucleoprotein enzyme responsible for the replication of telomeres, preventing cell senescence and death. Telomerase has two core functional components: the catalytic subunit of hTERT (with telomere-specific reverse transcriptase activity) and a telomerase RNA template. hTERT is the rate-limiting component of telomerase complex and its expression correlates with telomerase activity^[117]. Despite the growing evidence that hTERT is predictive of response to neoadjuvant chemotherapy among patients with rectal cancer, the prognostic role of hTERT among patients with resected CRLM has not been well studied^[114,115]. Fong *et al*^[9] and Smith *et al*^[26] did compare the prognostic value of the Fong clinical scoring system *vs* markers of cell proliferation, such as hTERT. In this study, the authors noted that hTERT correlated better with survival than predictions based on the clinical risk score^[9,26]. The independent prognostic value of hTERT has subsequently been validated as predictor of worse overall survival among patients with surgically resected CRLM^[25,118,119].

Thymidylate synthase

Thymidylate synthase (TS), the target enzyme of fluoro-

uracil (FU)-based chemotherapy, is commonly reported to correlate with response to systemic therapy and survival^[120-123]. A few small studies have suggested that TS gene overexpression might be associated with poor prognosis in patients undergoing resection of CRLM^[120-122]. A separate study by Gonen *et al.*^[123] confirmed that TS was an independent poor prognostic factor for OS and progression-free survival in a multivariate analysis using data from a large cohort of patients with resected CRLM. Interestingly, this same group also analyzed tumor mRNA and confirmed that tumor TS expression was associated with lower RFS and disease specific survival^[123]. Other authors have also noted that TS seems to correlate with the clinic risk score in patients who undergo resection for CRLM^[124].

p53

p53 is a tumor suppressor gene with a central role in controlling the cell cycle and apoptosis through regulation of Bax activity. p53 mutation correlates with the development of CRLM, as well as increased metastatic burden^[125]. While such findings have raised interest in the potential of p53 as a predictive biomarker, data on the prognostic role of p53 in patients with resected CRLM has yielded mixed and inconclusive results^[126]. Bellucco *et al.*^[127] showed a lower median survival among patients with p53-positive tumors with synchronous unresectable CRLM treated by hepatic artery infusional chemotherapy. These data were later confirmed in patients undergoing curative hepatic resection for CRLM, as p53 protein status was the single best predictor of survival (median survival: p53 wild type, 93 mo *vs* p53 mutated 27 mo)^[128]. Similarly, 3- and 5-year survival were better among patients with p53 wild type CRLM^[128]. Tanaka *et al.*^[129] also showed that mutated p53 remained an independent prognostic factor for worse survival after hepatectomy based on a multivariate analysis. In contrast, Yang *et al.*^[130] reported a separate study in which patients with p53 mutated CRLM actually had a better long-term survival after liver resection compared with patients who had wild type p53 tumors. Thus, the results of p53 on prognosis are conflicting and the actual role of p53 in defining long-term outcome remains to be determined.

Ki-67

Ki-67 is a proliferation marker, present in the nucleus during cellular proliferation. Due to its correlation cellular proliferation, Ki-67 has been identified as a possible predictive factor of outcome after liver resection of CRLM. Weber *et al.*^[29] conducted a large single-institutional study showing that Ki-67 labeling index was a reliable prognostic factor of survival among patients with resected CRLM. The prognostic impact of Ki-67 was subsequently confirmed on a meta-analysis that identified Ki-67 overexpression as a strong predictor of survival^[131]. In a comparison between the Fong clinical scoring system^[9] and the expression of Ki-67 as prognostic factors, Smith *et al.*^[26] concluded that both Ki-67 correlated better with survival than the clinical score.

Hypoxia inducible factor-1 α

Hypoxia inducible factor-1 α (HIF-1 α) is a transcription factor involved in crucial aspects of cancer biology, including angiogenesis, cell survival, glucose metabolism and invasion^[132]. Recent studies have shown that inflammation induces HIF-1 α activity^[132-135]. Moreover, constitutive activation of Ras-MAPK pathway and the PI3K-AKT pathway, or loss of function of tumor suppressor protein, as p53, regulate HIF-1 α activity. Recently Shimomura *et al.*^[136] evaluated the clinical significance of HIF-1 α expression in CRLM. The authors concluded that overexpression of HIF-1 α is an independent risk factor for cancer recurrence after curative resection for CRLM^[136]. With new confirmatory studies, HIF-1 α may prove to be an important prognostic factor for survival after CRLM resection.

Miscellaneous Markers (p21, H-thymidine labeling index and markers of angiogenesis)

Studies have been unable to correlate prognosis between p21, a cyclin-dependent-kinase inhibitor and a key effector of p53 anti-proliferative activity, and OS in patients with CRLM^[126]. Similarly, only one study has analyzed the relation between 3H-thymidine labeling index (TLI) and clinical outcome^[137]. In this study, the authors did find that TLI correlated relapse at 4 years following surgery^[137]. There is insufficient data to evaluate the prognostic value of markers of angiogenesis and thrombospondin-7.

Circulating tumor cells and circulating tumor DNA

Circulating tumor cells (CTC) and disseminated tumor cells (DTC) may serve as prognostic factors for tumor relapse after potentially curative resection of CRLM. Some investigators have suggested that intraoperative manipulation of the tumor may increase CTC and DTC, spreading malignant cells and causing an increase in intrahepatic or extrahepatic tumor recurrences^[138]. The data on this hypothesis are scarce and there is no consensus regarding the matter. While most studies analyzing CTC and DTC have largely focused on their prognostic value in the setting of primary colorectal cancer, a few studies have examined their role in the setting of CRLM. Vogelaar *et al.*^[139] demonstrated that patients free of DTC in their bone marrow assessed by RT-PCR had a significantly better DFS and OS after resection of CRLM. A recent meta-analysis investigated the association between outcomes in patients with resected CRLM and tumor cells in the blood or bone marrow^[140]. Specifically, in a cohort of 1329 patients (16 studies), the authors reported strong evidence suggesting that CTC correlated with worse OS and DFS. Of note, patients with detectable CTC had a 2 fold risk of progression or recurrence and a 2.5 fold increased risk of death compared with patients who had no CTC detected^[140].

Another developing field of cancer research is the detection of tumor-derived circulating mutant DNA. Circulating tumor DNA (ctDNA) represents a small part of the circulating DNA, making detection challenging. Recently Diehl *et al.*^[141] proposed a multistep approach to quantify ctDNA in patients with metastatic colorectal cancer un-

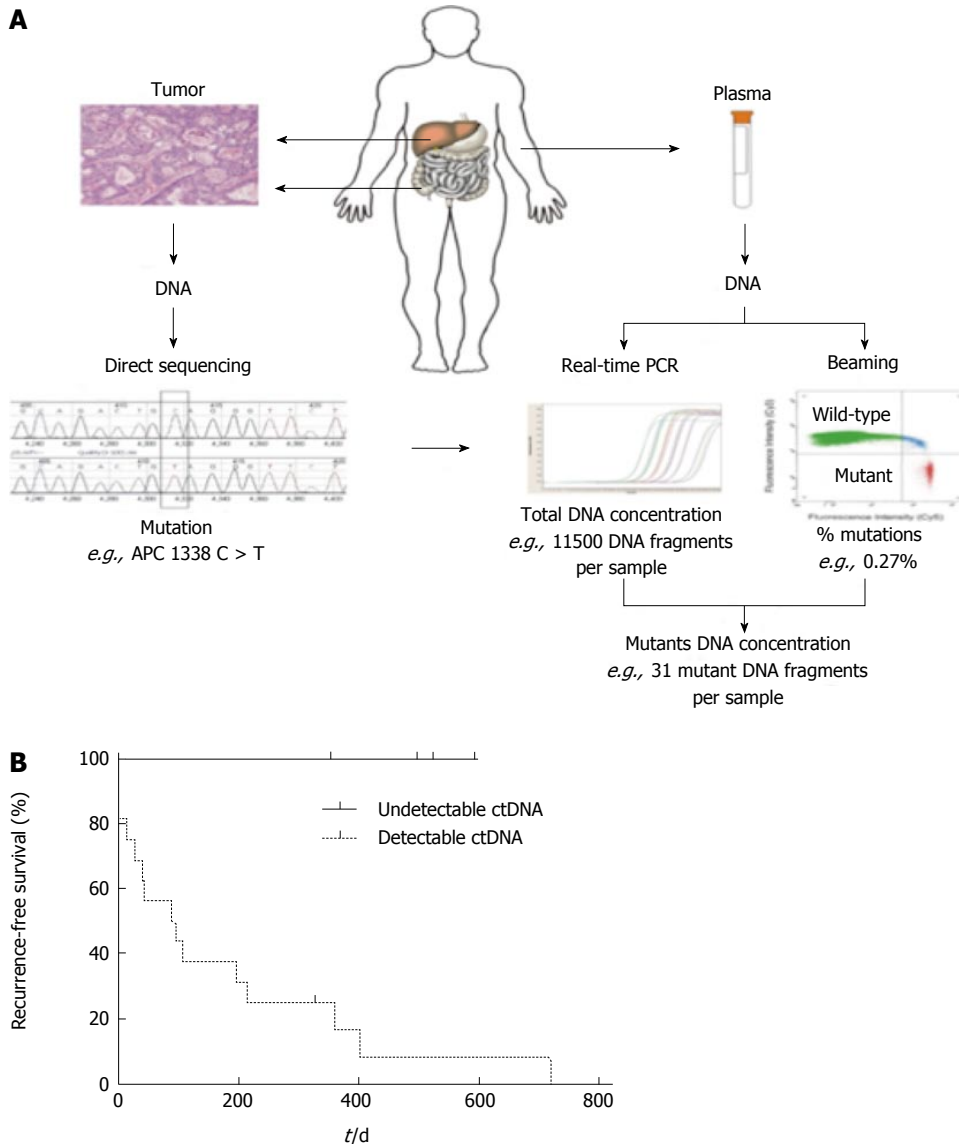


Figure 4 Patients with detectable ctDNA following resection of colorectal liver metastasis, recurrence was universal. A: Depiction of process by which ctDNA is detected and amplified from the specimen and plasma of patients; B: Representative flow cytometric data of ctDNA of one subject who underwent resection of colorectal liver metastasis. Note that the notable difference in recurrence-free survival in subjects with detectable vs undetectable ctDNA (from Diehl *et al*^[141]). Used with permission. PCR: Polymerase chain reaction.

dergoing surgery and receiving chemotherapy. Using this beaming technique, the authors were able to detect ctDNA in a subset of patients following resection of CRLM. Among those patients with detectable ctDNA following resection of CRLM, recurrence was universal (Figure 4). In addition, the investigators noted a significant difference in DFS among patients with and without detectable ctDNA. Although preliminary in nature, these results suggest that ctDNA might be a promising prognostic factor of outcome following resection of CRLM.

Genetic integrity

The development and progression of colorectal cancer is a multistep process leading to the accumulation of genomic alterations that occur over the lifetime of a tumor^[142] (Figure 5). The loss of genomic integrity, in terms

of gross chromosomal aberrations and abnormalities of nuclear DNA content (aneuploidy), has been examined in relation to long-term outcome. In the early 1990's, Cady *et al*^[143] found that aneuploidy was an independent prognostic factor, negatively impacting DFS. More recently, Metha *et al*^[144] used an array-based comparative genomic hybridization to investigate the association of DNA copy number alterations with survival in patients with CRLM resected with curative intent. The total fraction of genome altered (FGA) in the metastases was noted to be an independent predictor of survival in patients with resected hepatic colorectal cancer metastases. In addition, the authors described a direct proportionality between level of FGA and probability of survival^[144]. Although genetic instability seems to be correlated with tumor aggressiveness in primary colorectal cancer, it is not clear yet if it has a

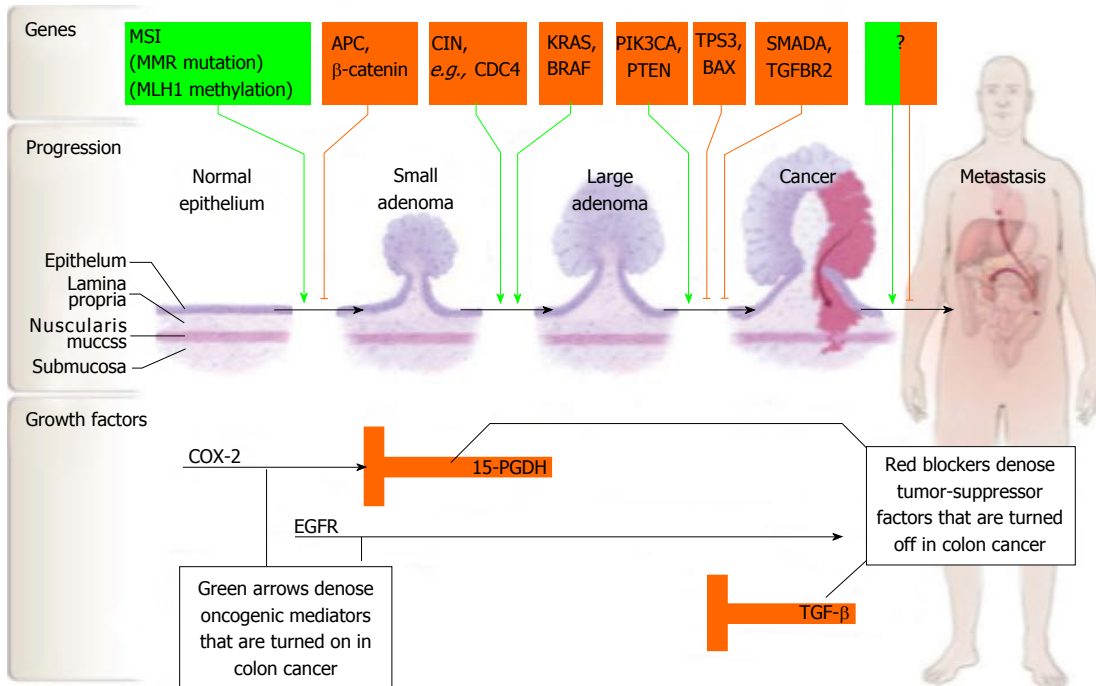


Figure 5 Carcinogenesis of colorectal cancer (from Markowitz *et al*^[145]). Used with permission. EGFR: Epidermal growth factor receptor; TGF: Transforming growth factor; COX-2: Cyclooxygenase-2.

prognostic value in following resection of CRLM^[126].

CONCLUSION

Survival following resection of CRLM varies and is dependent on clinical, tumor, and molecular factors. Accurate predictors of prognosis are important for patients, as well as providers. While some preoperative clinicopathologic factors are associated with outcome, the emergence of biologic and molecular markers may allow for a more individualized approach to prognosis. Factors such as KRAS, BRAF, TS, hTERT, Ki-67 can help predict long-term prognosis following CRLM. In addition, more recent data on CTC and ctDNA holds for a more sensitive and powerful metric of prognosis near the time of surgery for CRLM. With more accurate markers of prognosis in the future, a greater emphasis on patient-specific treatments and prognostic information will hopefully continue to emerge.

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