Hepatic resection, hepatic arterial infusion pump therapy, and genetic biomarkers in the management of hepatic metastases from colorectal cancer

John C. McAuliffe, Motaz Qadan, Michael I. D'Angelica

Hepatopancreatobiliary Surgery, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: MI. D'Angelica; (III) Provision of study materials or patients: MI. D'Angelica; (VI) Collection and assembly of data: MI D'Angelica; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Michael I. D'Angelica, MD, FACS. Enid A. Haupt Chair in Surgery, Attending, Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, USA. Email: dangelim@mskcc.org.

Abstract: The liver is the most common site of colorectal cancer metastasis. Fortunately, improvements have been made in the care of patients with colorectal liver metastasis (CRLM). Effective management of CRLM requires a multidisciplinary approach that is tailored to individuals in order to achieve long-term survival, and cure. Resection and systemic chemotherapy provides benefit in selected individuals. An adjunct to resection and/or systemic chemotherapy is the use of hepatic arterial infusion pump (HAIP) therapy. Many studies show HAIP provides benefit for select patients with CRLM. Added to the crucible of a multidisciplinary approach to managing CRLM is the ever growing understanding of tumor biology and genetic profiling. In this review, we discuss the outcomes of resection, systemic therapies and HAIP therapy for CRLM. We also discuss the impact of recent advances in genetic profiling and mutational analysis, namely mutation of KRAS and BRAF, for this disease.

Keywords: Colorectal liver metastasis (CRLM); resection; parenchymal-sparing; hepatic artery infusion pump (HAIP); KRAS; BRAF; FOLFOX

Introduction

About 132,700 new cases of colorectal cancer (CRC) are diagnosed each year in the United States. The liver is the most common site of metastatic disease, with up to 60% of patients ultimately developing liver metastases (CRLM) (1). Fortunately, significant improvements have been made for patients with metastatic colorectal cancer (mCRC).

Initial reports of hepatic resection for CRLM demonstrated an unexpected, prolonged long-term survival (2). Long-term follow up documented the curative potential of hepatic resection for limited CRLM in 15 to 25% of patients (3). Up until the 1990's, hepatic resections were fraught with significant blood loss, subsequent peri-operative complications, and a high mortality rate (4). Better understanding of hepatic anatomy, resection techniques, intraoperative anesthetic management, and postoperative care, have improved peri-operative outcomes. Currently, hepatic resection for CRLM is effective when performed at high volume specialty centers achieving a perioperative mortality rate of 1% (5,6). Parallel to this, evidence supports the use of hepatic artery infusion (HAI) of chemotherapy as an adjunct to managing CRLM. Likewise, our understanding of genetic aberration in CRLM emerges as important factor in treatment plans and prognosis.

In this review, we discuss surgical treatment and associated outcomes in the treatment of CRLM. In addition, the role and efficacy of HAI therapy are examined. Finally, we outline how genetic profiling and mutational

analysis can impact management of this disease in this era of molecular-based targeted therapies.

Surgical management of CRLM

Resection for CRLM has been well established over the last three decades. Patient selection with preoperative multidisciplinary review and improved perioperative management make resection a safe and effective treatment modality for patients with operable CRLM.

Patients' disease burden and future liver remnant are analyzed with cross-sectional imaging, volumetric studies, and evaluation of hepatic synthetic function. In general, patients with CRLM are considered resectable if their tumor burden can be removed with a negative margin while leaving a viable liver remnant that is able to drain bile and provide adequate synthetic function. Twenty percent of patients are estimated to have resectable disease at presentation (7).

Despite being technically resectable, outcomes are varied, and associated with a number of clinical and pathologic factors. Multivariate analysis of retrospective studies have shown that patient age, hepatic margin status, extrahepatic disease, number and size of tumors, CEA level, disease-free interval (DFI), and lymph node status of the primary tumor are associated with recurrence and survival after hepatic resection for CRLM (8,9). Many studies have combined these prognostic factors into clinical risk scores in attempts to improve prognostication. Stratifying patients into low and high-risk scores can predict survival following resection. In one example, a low-risk score was associated with a 60% 5-year survival while a high-risk score had an associated 14% 5-year survival. Despite effective stratification with clinical risk scores, patients with high-risk scores that undergo complete resection still have the potential for long-term survival and cure. These statistics underscore the need for better risk-stratification tools. The only factors that appear to make cure extremely unlikely, however, are a persistent positive hepatic margin and presence of extrahepatic disease (3,10). In summary, for patients with resectable liver-limited CRLM, the presence of adverse prognostic factors and high-risk scores do not preclude the potential for cure with complete resection and should not trump sound clinical judgment.

Hepatic parenchymal sparing techniques in lieu of extensive resections should now be routine in contemporary surgical management of CRLM and have been associated with significant improvements in perioperative outcomes (5,6).

House *et al.* published a retrospective study of 1,600 consecutive patients who underwent resection for CRLM to determine the outcomes in two separate eras [1985-1998, 1999-2004]. The incidence of hemi-hepatectomy and wedge resections decreased in the latter era. Segmental resections are being performed more frequently with improved perioperative outcomes, and without jeopardizing oncologic principles (11). Historically, mortality following hepatic resection was high but now the 90-day mortality related to resection for CRLM is less than 1% in experienced high volume centers (5).

Despite 5-year survival rates of 20-50% following complete resection, recurrence rates approach 70-80% with long-term follow up (12). The high recurrence rates provide the rationale for treating microscopic disease with adjuvant chemotherapy, in an attempt to improve outcomes. Early randomized trials demonstrated that the addition of adjuvant 5-FU chemotherapy as compared to resection alone was not associated with improved progression-free (PFS), or overall survival (OS) (13).

The EORTC intergroup 40983 randomized trial evaluated perioperative FOLFOX for patients with limited and resectable CRLM (14,15). Patients were randomized to receive perioperative FOLFOX or surgery alone. The initial publication on this trial documented a significant 7.3% absolute increase in PFS. However, with longer term follow up, OS was not statistically different between the two groups. This trial demonstrated that perioperative FOLFOX chemotherapy may improve early PFS but was not associated with improved survival. While this trial was not powered to detect small differences, it ruled out a major impact on OS. However, this patient cohort was heterogenous. It is clear that select patients in each treatment group had durable survival while others did not. This again adds mounting evidence for the need of improved predictive factors and that CRLM is a heterogenous disease process.

In summary, multidisciplinary management that incorporates both patient and tumor-related factors should be performed in order to individualize treatment plans. Hepatic resection for CRLM is the standard of care for patients who are able to undergo operation and with resectable disease, due to associated long-term survival and potential for cure. Of those undergoing a potentially curative resection, survival is approximately 50% at 5-year, and the cure rate ranges from 20-25%, which is superior to chemotherapy alone (3). Unfortunately, the benefit of neoadjuvant and adjuvant systemic chemotherapy is not

well understood in the context of curative surgery. The high recurrence rates after resection underscore the continued need for development of effective adjuvant therapies in patients undergoing resection of CRLM.

HAI pump therapy

Contemporary systemic therapies include 5-FU in combination with either oxaliplatin (FOLFOX), irinotecan (FOLFIRI) or both (FOLFOXIRI) (16-18). These provide response rates of 50% and median survivals of 16-24 months for untreated mCRC (17,19,20). Biologic agents targeting vascular endothelial growth factor (bevacizumab) or epidermal growth factor receptor (cetuximab) improve responses rates in select patients (21,22). Salvage with second and third line chemotherapeutic regimens once progression occurs provides diminutive benefit, with response rates no greater than 10% or 15% (23). These outcomes provide a benchmark with which to compare the efficacy of HAI chemotherapy.

HAI chemotherapy has been studied for decades (24,25). The therapy has not been universally embraced, perhaps because of the surgical training and expertise required for pump placement, the requirement for diligent and frequent follow-up, and the ability to recognize and manage complications. HAI chemotherapy requires establishment of a multi-disciplinary program consisting of a specialist surgeon, medical oncologist, interventional radiologist, gastroenterologist, nuclear medicine radiologist, technologists, and nursing staff.

The rationale for HAI therapy is based upon anatomic and pharmacologic principles. The hepatic arteries exclusively perfuse CRLM, while the portal vein and hepatic arteries jointly perfuse normal hepatocytes (26). The use of drugs that are extracted by the liver during first-pass metabolism results in high local concentrations of drug with minimal systemic exposure. Ensminger and colleagues showed that 94% to 99% of floxuridine (FUDR) is extracted by the liver during the first pass compared with 19% to 55% for 5-FU (27). In fact, mean tumor FUDR levels are increased 15-fold when the drug is injected via the hepatic artery (28). FUDR is therefore an ideal drug for HAI, providing a high hepatic concentration of drug with minimal systemic spill over and resultant toxicity. The development of an implantable infusion pump allowed for the safe administration of hepatic arterial chemotherapy in the outpatient setting (29).

Hepatic artery anatomy has a predilection for variation,

with one third of patients possessing aberrant anatomy (30). Currently, computed tomography (CT) angiography provides accurate determination of patient anatomy. A surgeon experienced with dissection of the porta hepatis is required for HAI pump placement. The gastroduodenal artery (GDA) is the preferred conduit for the pump catheter, since other conduits are associated with increased rates of pump-related complications (30).

Hepatic arterial chemotherapy in first-line treatment of unresectable colorectal liver metastases

One of the first randomized trials of HAI therapy for unresectable CRLM was conducted at MSKCC (31). This prospective randomized trial compared HAI therapy with systemic chemotherapy using FUDR in both groups. Of the 99 enrolled patients, 2 complete responses and 23 partial responses (53%) were observed in the group undergoing HAI therapy, compared to 10 partial responses (21%) in the systemic chemotherapy group (P=0.001). The crossover rate from systemic chemotherapy to HAI therapy was 60%, of whom 25% subsequently underwent a partial response. The median survival for the HAI therapy and systemic chemotherapy groups was 17 and 12 months, respectively (P=0.424), despite the high cross over of the patients from the systemic chemotherapy group to the HAI therapy group.

The Cancer and Leukemia Group B (CALGB) completed trial 9481, which compared systemic chemotherapy with 5-FU/LV to HAI therapy using FUDR, LV, and dexamethasone (32). One hundred thirty-four patients were randomized without crossover. Most patients (70%) had greater than 30% liver involvement and 78% had synchronous metastases. Ninety-seven percent of patients had not received any chemotherapy. Response rates were significantly higher in the HAI therapy-only group (47% vs. 24%; P=0.012), but time to progression was not significantly different (5.3 vs. 6.8 months; P=0.8). Time to hepatic progression was significantly improved in the HAI therapy arm (9.8 vs. 7.3 months; P=0.017), median OS was significantly better in the HAI therapy arm (24.4 vs. 20 months; P=0.0034). At 3- and 6-month follow-up, physical functioning, as measured with quality of life instruments, was improved in the HAI therapy group.

A total of 10 randomized phase III trials comparing HAI to systemic therapy have been completed. Most of these demonstrate a higher response rate with HAI therapy as compared to systemic chemotherapy in patients with unresectable CRLM. Whether improved response rates
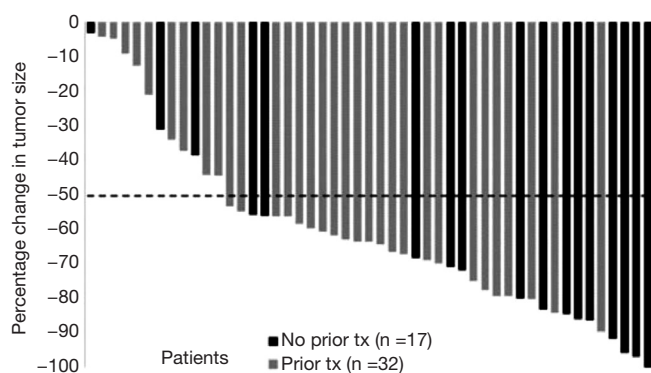
Figure 1 Waterfall plot of response to hepatic arterial infusion pump (HAIP) in phase II trial at MSKCC (40).

translate into prolonged survival is unknown, and most trials were underpowered to detect survival differences. In addition, many of these studies allowed crossover to the HAI therapy. Many trials also used HAI with 5-FU, which is considered less effective than FUDR. Some trials included patients with extrahepatic disease, for which HAI alone is ineffective. Lastly, many trials utilized ports with high failure rates and inability to deliver therapy.

Two meta-analyses of the original seven trials were conducted and included more than 600 patients. The first confirmed the increased response rates seen with HAI therapy over systemic chemotherapy (41% *vs.* 14%) (33). A second meta-analysis published the same year found an absolute survival difference of 12.5% at 1 year (P=0.002) and 7.5% at 2 years (P=0.026) in favor of HAI therapy (34).

Combined hepatic arterial and systemic chemotherapy for treatment of unresectable colorectal liver metastases

Extrahepatic disease progression develops in 40% to 70% of patients who undergo HAI therapy for unresectable CRLM. Since HAI with FUDR results in minimal systemic exposure, combining HAI with FUDR and systemic chemotherapy was the next logical therapeutic strategy. Safi *et al.* studied whether intra-arterial FUDR alone or a combination of intra-arterial FUDR and IV FUDR given concurrently would improve survival (35). Response rates were 60% in both groups. However, the incidence of extrahepatic disease progression was significantly lower in patients who received combined systemic and hepatic therapy.

In a MSKCC phase I study, 36 patients with unresectable CRLM received HAI FUDR and systemic oxaliplatin plus irinotecan or oxaliplatin plus 5-FU/LV. Eighty-nine percent of patients were previously treated and 69% had previously received irinotecan. Both regimens were well tolerated, and response rates for the two groups were 90% and 88% (36). In a non-randomized study analyzing HAI therapy with FUDR and systemic irinotecan after cytoreduction of unresectable hepatic mCRC, 71 patients received therapy and were compared with a historic control group that received cytoreduction alone. Time to progression was 19 *vs.* 10 months, and median survival was 30.6 *vs.* 20 months for the HAI therapy *vs.* control groups, respectively (37). Similarly, a Japanese group examined HAI therapy with 5-FU and systemic irinotecan in previously treated patients and demonstrated response rates of 76.5%, with median OS of 20 months (38). Therefore, as compared systemic therapy alone, HAI therapy combined with modern systemic chemotherapy is associated with higher response rates.

Utilizing chemotherapy to convert unresectable patients to complete resection is an achievable goal of chemotherapy. Adam *et al.* presented their French experience of patients with unresectable CRLM. Of 1,104 patients considered unresectable at presentation, 12.5% were converted to surgical candidates with contemporary systemic cytotoxic chemotherapy (39). The patients who underwent resection realized a 3-year OS of 52%; a number far greater than the benchmark of 2 years for systemic therapy without resection. Importantly, most recurrences were extrahepatic providing the rationale for continued systemic chemotherapy. In a recent prospective phase II trial of HAI therapy and modern systemic chemotherapy combined with bevacizumab for patients with unresectable CRLM, 49 patients underwent evaluation of the conversion rate from unresectable liver metastases to complete resection as the primary outcome (40). Sixty-five percent of patients had received previous systemic chemotherapy. The median number of metastases was 14. The overall response rate was 76%. Importantly as depicted in a waterfall plot, most patients had a greater than 50% reduction in tumor volume (*Figure 1*). Such a dramatic improvement in tumor burden allows for resection to be considered. Twenty-three patients (47%) achieved conversion to resection at a median of 6 months from treatment initiation. Median OS and PFS were 38 and 18 months, respectively, with resection being the only factor associated with prolonged OS and PFS on multivariate analysis (3-year OS of 80% when resected compared with 26% in unresectable patients). Ten patients had no evidence of disease at the time of publication with a median follow up of 39 months. Importantly, a high

biliary toxicity rate was found in the first 24 patients whose treatment included bevacizumab, but without any positive impact on outcome. As a result, bevacizumab is no longer used in HAI therapy combinations (41).

Moreover, Elias *et al.* presented their French experience of 87 patients with isolated CRLM between 1999 and 2003 who were treated with both HAI of oxaliplatin and systemic 5-FU. Importantly, 79% of patient had received prior contemporary systemic chemotherapy. Twenty-six percent of the cohort were converted to resectability and realized median OS of 42 months (42). Therefore, in two separate studies, HAI therapy converts unresectable patients to surgical candidates which confers long-term survival.

Adjuvant hepatic arterial chemotherapy following liver resection

Following resection of CRLM, at least 60% to 70% of patients recur at a median of 16 months (12). Patterns of recurrence are important to consider when devising adjuvant treatment strategies. At least half of all recurrences involve the liver, and, in one study, 64% of patients had their first site of recurrence in the liver (12). This provides rationale for targeting the liver as an adjunct to adjuvant systemic therapies.

There are four randomized trials evaluating adjuvant HAI chemotherapy following hepatic resection of CRLM. In an MSKCC study, 156 patients with resected hepatic metastases were randomized to either 6 months of systemic 5-FU/LV or systemic 5-FU/LV plus HAI therapy with FUDR (43). Randomization was performed intraoperatively after complete resection. Patients were stratified based on the number of metastases and prior treatment history. The primary endpoint was 2-year survival and was 86% in the combined-therapy group *vs.* 72% for those who received systemic chemotherapy alone (P=0.03), with median survival of 72.2 and 59.3 months, respectively. In an updated analysis, with a median follow-up of 10 years, OS was 41% in the HAI group versus 27% in the systemic chemotherapy only group (P=0.10) (8,44). Overall PFS was significantly greater in the combined-therapy group (31.3 *vs.* 17.2 months; P=0.02). The median hepatic PFS was not yet reached in the combined-therapy group, whereas it was 32.5 months in the monotherapy group (P<0.01).

In a German multi-institutional study, 226 patients were randomized to resection alone without systemic therapy or resection plus 6 months of HAI therapy with 5-FU/LV given as a 5-day continuous infusion every 28 days (20).

The study was terminated early, due to an interim analysis suggesting a low chance of survival benefit with HIA therapy. The impact of HAI therapy in this study is difficult to assess because only 74% of patients assigned to HAI therapy received this treatment, and only 30% completed it. There was no difference in time to progression, time to hepatic progression, and median OS in an intention-to-treat analysis. When patients were analyzed "as treated", time to hepatic progression (45 *vs.* 23 months) and time to progression or death (20 *vs.* 12.6 months) was improved in the HAI therapy arm. Despite this trial's shortcomings, when analyzed appropriately it was still a positive trial showing HAI efficacy.

The intergroup study randomized 109 patients to resection alone without systemic therapy, or resection followed by 4 cycles of HAI therapy with FUDR and infusional systemic 5-FU, followed by systemic 5-FU (45). The endpoint was disease-free survival (DFS). The 4-year (DFS) (46% *vs.* 25%; P=0.04) and 4-year hepatic DFS (67% *vs.* 43%; P=0.03) favored HAI therapy but no difference was reported in median or 4-year OS between the groups when analyzed on an intention-to-treat basis.

Finally, a study conducted in Greece on 122 patients used mitomycin C, 5-FU, and interleukin (IL)-2 by both HAI therapy and the IV route *vs.* the IV route alone. The 2-year survival, 5-year survival, DFS, and hepatic DFS were all significantly longer for the HAI therapy plus systemic chemotherapy group (46).

The potential benefit of combination HAI FUDR therapy when combined with modern systemic chemotherapy in the adjuvant setting is unknown since no randomized trials addressing this have been performed. In a retrospective analysis, House and colleagues retrospectively compared 125 patients who underwent HAI therapy with FUDR with 125 consecutive similar patients who received modern systemic therapy alone, and noted an associated prolonged OS, hepatic recurrence-free survival (RFS), and disease-specific survival (DSS) with adjuvant combination HAI and systemic therapy; 75%, 48%, and 79%, *vs.* 55%, 25%, and 55%, respectively (P<0.01) (47). Therefore, despite contemporary cytotoxic chemotherapy, HAI FUDR continues to provide better outcomes for those with CRLM.

To further illustrate this point, a phase I trial combining adjuvant HAI FUDR with escalating doses of oxaliplatin and 5-FU was performed. Safety and feasibility were established and the 4-year OS and PFS were a very promising 88% and 50%. In a randomized phase II

trial of patients treated with HAI FUDR and modern systemic chemotherapy (depending on prior treatment) randomized to receive bevacizumab or not, the 4-year OS was 85% (32,48).

In another study from France, 98 patients underwent curative resection of CRLM. Forty-four patients received combined HAI of oxaliplatin with systemic 5-FU. Fifty-four patients received contemporary systemic therapy alone. Three-year disease free survival was 33% compared to 5% (P=0.0001) for those treated with HAI oxaliplatin versus systemic alone. Additionally, OS showed a trend for improvement for those treated with HAI oxaliplatin (49).

A new review comparing patients treated with adjuvant HAI and systemic therapy after liver resection prior to 2003 or after 2003 show a 5-year survival of 56% and 80% for those treated before or after 2003, respectively (50).

In summation, these data show combination HAI and systemic chemotherapy therapy provide improved benefit compared to each alone. The findings provide the rationale for a randomized trial comparing adjuvant HAI therapy plus systemic chemotherapy versus modern systemic chemotherapy alone in the treatment of resected CRLM.

Genetic profiling and prognosis for colorectal liver metastases

Cancer is frequently associated with genetic aberrations. These aberrations lead to over or under production of proteins, which, in turn, lead to cellular transformation and autonomous growth potential. KRAS and BRAF mutations have emerged as important genetic aberrations affecting the management CRLM.

About 20% to 40% of CRC harbor mutations in KRAS (51-53). These mutations are conserved through all stages of a patient's metastatic disease. This suggests that KRAS mutation may be a driving genetic alteration. KRAS mutations may also be prognostic (54). At MSKCC, a retrospective study was performed to determine the impact of KRAS mutation on DSS following hepatic resection for CRLM. KRAS mutation was independently associated with a worse DSS compared to wild-type tumors (2.6 vs. 4.8 years) (51). KRAS mutations were also associated with a short DFI and higher numbers of hepatic tumors. In a MD Anderson Cancer Center (MDACC) analysis, all patients undergoing hepatic resection for CRLM received preoperative contemporary cytotoxic chemotherapy and bevacizumab (53). Tumors harboring wild-type KRAS had fewer than 50% viable cells 58% of the time, compared

to 38% of the time in mutated KRAS tumors. Hepatic and pulmonary recurrence rates were decreased for wild-type KRAS patients compared to mutated KRAS patients. These differences were associated with a prolonged OS for patients with wild-type KRAS tumors (81% compared to 52% at 3 years). In the Johns Hopkins experience, patients harboring mutated KRAS CRLM had a median RFS of 11 months compared 18 months for those with wild-type KRAS patients following curative resection of CRLM (52).

In another study, 169 patients with resected CRLM received adjuvant HAI therapy and systemic chemotherapy, of whom 118 were wild-type KRAS, and 51 had KRAS mutated tumors (55). The 3-year RFS for patients with wild-type KRAS tumors was 46%, compared with 30% for patients with mutated KRAS tumors (P=0.005). The 3-year OS was 95% vs. 81%, respectively. Interestingly, KRAS was an independent predictor of RFS (HR 1.9) on multivariate analysis. In summary, these data suggest that KRAS mutation is associated with an aggressive disease biology and worse outcome after resection of CRLM.

As stated, KRAS mutation is a poor prognostic factor for CRC. Additionally, KRAS mutation predicts a poorer outcome with systemic cytotoxic chemotherapy as illustrated in the MDACC and Johns Hopkins data. In the MSKCC experience, this holds true as well (Table 1). However, multimodality treatment for select patients utilizing resection, HAI, and systemic therapy appears to mitigate these poor outcomes. In an updated review of MSKCC experience, patients with CRLM and wild-type KRAS have a 3-year survival of 97% when treated with HAI FUDR and systemic therapy. Those with KRAS mutation realize a 3-year survival of 89% with HAI FUDR and systemic therapy. Both of these survivals are compelling evidence that HAI is providing benefit to those with CRLM above and beyond that provided by systemic therapies alone despite KRAS mutation status.

BRAF is a serine/threonine-protein kinase downstream in the signaling cascade from ras produced by the proto-oncogene BRAF. The gene is mutated in multiple tumors including CRC. In general, BRAF mutations portend worse outcome for patients with CRC. In a population-based analysis, OS for patients with mCRC harboring BRAF mutations was 8 months compared to 17 months for wild-type patients and was independently associated with worse outcome (HR 10.6, P <0.001) (56). In the context of metastasectomy for mCRC, the MSKCC experience was analyzed (57). Only 41% of patients with mutated BRAF had isolated liver disease as compared to 63% of those with

Table 1 Differential survival of CRLM treated at three institutions

Study	Pts (n)	Median FU (month)	3-Year RFS (%)		3-Year OS (%)	
			KRAS WT	KRAS MUT	KRAS WT	KRAS MUT
MSKCC (50)	148	80	50	32	97	89
Johns Hopkins (52)	202	18	34	28	70	60
MDACC (53)	193	33	34	14	81	52

Pts, patients; CRLM, colorectal liver metastasis; RFS, recurrence-free survival; OS, overall survival.

wild-type BRAF. Metastases were more likely to be in the peritoneum (26%) or lung (12%) for BRAF mutants. Even in the context of curative metastasectomy, OS was 61% at 2 years for patients with BRAF mutations compared to 86% for wild-type. Despite resections with curative intent, BRAF mutation appears to be a poor prognostic factor.

Micro-array technology to assess mRNA expression in tumors has allowed investigators to study the prognostic impact of genetic expression signatures. Using high throughput RNA and genetic analysis methods, MSKCC has been able to improve accuracy of predicting 3-year outcomes following resection of CRLM by developing an expression molecular risk score (58). This molecular risk score was more prognostic of outcome compared to previously validated clinical risk scores. These results remain in their infancy and require external validation but provide the promise of improving our knowledge of CRLM management.

Conclusions

During the last three decades, there has been progressive improvement in the management of CRLM. Hepatic resection is performed with low risk at high-volume specialized centers, and has been established as the standard of care for resectable disease with associated prolonged survival and potential for cure. Likewise, systemic therapies have improved, with the advent of novel cytotoxic systemic chemotherapeutic agents. Furthermore, targeted therapies are now applied to contemporary drug regimens and have modestly improved outcomes in patients with mCRC. HAI chemotherapy has also evolved, and provides a unique and effective therapy both in the unresectable setting and as an adjuvant therapy following resection seemingly beyond that of systemic therapies alone. Multidisciplinary care for each patient with CRLM is crucial to orchestrate the multiple management strategies to extent survival. Combining clinical features with molecular profiling may provide

superior prognostication for patients with CRLM. The promise of individualized therapy, tailored according to specific genetic mutations and disease patterns, is now being realized and continues to evolve.

Acknowledgements

Footnote

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

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