Metastatic Colorectal Cancer: From Improved Survival to Potential Cure

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Key Words

Metastatic colorectal cancer · Resectability · Curative intent

Abstract

Context: The treatment of colorectal cancer has improved considerably in recent years, but it remains the second commonest cause of cancer deaths in men and women in the United States. Better therapies have resulted in prolonged median survival for patients with metastatic disease and a select number of patients can now be cured. **Evidence Acquisition:** We conducted a computerized search using PubMed and Google Scholar for reports published between January 1993 and August 2009 using mesh headings and key words relating to the treatment of colorectal cancer. If reports identified by these criteria referred to other papers not in the initial search, then these were also reviewed if relevant to metastatic colorectal cancer (MCRC). **Results:** Seven new chemotherapy agents have been licensed for the treatment of advanced colorectal cancer, with associated improved median survival from 5 months to 2 years. Complete responses are rare with systemic chemotherapy alone, but higher overall response rates to systemic and intrahepatic chemotherapies have enabled initially unresectable patients to undergo potentially curative surgical resection of

metastases. Improved surgical expertise together with the adjunctive use of radiofrequency ablation has further expanded the definition of resectability. Advances in the understanding of tumor biology have resulted in the development of clinically useful biomarkers and the emergence of active biological therapies. **Conclusions:** The multidisciplinary management of MCRC incorporating improved systemic and local therapies continues to improve median survival and enlarge the cohort of patients that can be approached with curative intent. Recent technological advances have facilitated a better understanding of tumor biology that promises continued advancements in patient care.

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Introduction

The management of patients with metastatic colorectal cancer (MCRC) has advanced in recent years, with many of the developments reflecting changes in general medical oncology practice, and a multidisciplinary approach is now the norm. Seven new drugs have been licensed, and predictive markers to guide treatment decisions are available. Improved surgical techniques and regional therapies such as hepatic arterial infusion

chemotherapy and radiofrequency ablation (RFA) have improved the outlook for patients with colorectal liver metastases (CLM). Median survival times are longer, and an increasing minority of select patients is actually cured. A better understanding of the biology of colorectal cancer initiated these improvements in patient management, and recent technological advances have provided the tools for further progress.

Methods

We conducted a computerized search using PubMed and Google Scholar for reports published between January 1993 and August 2009 using mesh headings and key words relating to the treatment of colorectal cancer. If reports identified by these criteria referred to other papers not in the initial search, then these were also reviewed if relevant to MCRC. The following search terms were used: MCRC, metastatic colon cancer, advanced colorectal cancer, advanced colon cancer, colorectal liver metastases, CLM, colorectal hepatic metastases, colorectal hepatic metastasis, chemotherapy, biologic therapy, systemic treatment, fluorouracil, irinotecan, oxaliplatin, cetuximab, panitumumab, bevacizumab, surgery, hepatic arterial infusion, radiofrequency ablation, biomarker, KRAS, UGT1A1, genetics, genome-wide association study. The references of all identified relevant studies were also searched for additional potentially relevant publications.

How Do Colon Cancer Cells Metastasize?

The ‘seed and soil’ hypothesis was proposed in 1889 to explain the pathogenesis of metastasis and stated that ‘seeds are carried in all directions; but they can only live and grow if they fall on congenial soil’ [1]. Mechanical factors play a role in MCRC; the mesenteric circulation and fenestrated capillaries of the liver facilitate hepatic metastasis [2, 3], but in the 1970s definitive proof of Paget’s ‘seed and soil’ hypothesis emerged when Hart and Fidler [4] and Fidler and Poste [5] demonstrated that while metastatic cells may reach a number of organs, metastases develop in a select few.

Metastasis appears to develop in three steps: the cells leave the primary site and disseminate (initiation), before invading new parenchyma (progression), and finally colonizing a distant organ (virulence) [6]. Many genetic and epigenetic events govern this process [6, 7]. The transition of a colorectal cancer from invasive carcinoma has been well described [8], and involves mutations in the Wnt pathway through APC gene inactivation or B-catenin activation [9], followed by KRAS activation [10], PI3K acti-

vation [11], TP53 inactivation [12], and loss of the transforming growth factor- β tumor suppressor pathway [13]. The remaining mutations required to establish a macro-metastasis are not well understood and may vary not just between malignancies, but also between individuals with the same primary tumor. The relatively quick metastasis of some colorectal tumors suggests that the required mutations may be obtained by certain cells early in their development, whereas other metastases take years to develop. Identification of markers for this differential biology would enable unique treatment of different tumors and personalized management for patients.

Systemic Treatment of MCRC

Fluorouracil and the Beginning of Progress

Targeted therapy is not a new concept in colorectal cancer. Fluoropyrimidines, whose target is thymidylate synthase, were introduced in 1957 at a time when median survival from MCRC was less than 6 months [14, 15]. More than 50 years later, 5-fluorouracil (5-FU) remains the cornerstone of systemic therapy, but median overall survival (OS) now exceeds 2 years with combination therapies (table 1). Bolus 5-FU in combination with leucovorin (LV), a folate that stabilizes the binding of the drug to thymidylate synthase [16], improves OS by approximately 5 months over best supportive care [17, 18], and infusion regimens have improved survival with an improved toxicity profile [19]. Two oral fluoropyrimidines, capecitabine and S-1, have been introduced, further ensuring that 5-FU remains an essential component of current regimens [20–24]. Genetic and epigenetic factors that contribute to the efficacy and toxicity of 5-FU have been identified [25–27]. Many molecular pathways involved in drug metabolism (e.g. dihydropyrimidine dehydrogenase – low levels increase toxicity), drug target (thymidylate synthase – high levels decrease response), and DNA repair pathways likely interact but do not predict outcome [28–32].

Irinotecan, Oxaliplatin and Combination Regimens

Combination regimens of infusion 5-FU with either oxaliplatin (FOLFOX) or irinotecan (e.g. FOLFIRI) form the backbone of current treatments for MCRC to which a biologic agent is often added. Irinotecan was confirmed as an active agent in MCRC when its combination with infusion 5-FU/LV produced significant improvements in response rate (RR) (35% vs. 22%, $p < 0.005$), time to progression (TTP) (6.7 vs. 4.4 months, $p < 0.001$), and OS

(17.4 vs. 14.1, $p = 0.031$), compared to 5-FU/LV alone [33]. Irinotecan is metabolized to its active metabolite, SN-38, by the UGT1A enzymes, and the UGT1A locus can be used to predict the risk of neutropenia with treatment [34–36]. The NCCTG/Intergroup trial N9741 established oxaliplatin as an active agent in MCRC, demonstrating superiority for infusion 5-FU/LV plus oxaliplatin (FOLFOX4) over IFL, a combination of irinotecan and bolus 5-FU/LV (RR: 45 vs. 31%, TTP: 8.7 vs. 6.9 months and median OS: 19.5 vs. 15 months) [37]. The combination of capecitabine and oxaliplatin (XELOX) has similar activity to FOLFOX4 (progression-free survival, PFS, 8.0 vs. 8.8 months, and OS 19.8 vs. 19.6 months, respectively) [38, 39].

Survival of patients with MCRC appears to be determined by exposure to all three active agents, and the sequence of treatment may be less important [40]. Further improvements in RR have been reported with the three-drug combination of 5-FU, oxaliplatin and irinotecan (FOLFIRI) compared with FOLFIRI (60% vs. 34%, $p < 0.0001$) which translated into improved PFS (9.8 vs. 6.9 months, $p = 0.0006$), OS (22.6 vs. 16.7 months, $p = 0.032$), and complete resection rates (R0) (36 vs. 12%; $p = 0.017$) [41]. However, toxicity is greater with the three-drug combination, and physician preference and desired outcome often decide treatment choice with data supporting sequential single-agent therapy in addition to combination therapy with FOLFIRI, FOLFOX, FOLFIRI and XELOX [42–46].

Patients with MCRC are typically treated for prolonged time periods, and schedule variations have been investigated to diminish toxicity and allow an optimal quality of life on treatment. Neuro- and hematologic toxicities most commonly limit treatment with oxaliplatin, while hematologic toxicity and diarrhea are the commonest treatment-limiting toxicities with irinotecan. Omission of oxaliplatin from FOLFOX for a period of twelve 2-week cycles reduces neurotoxicity without affecting efficacy [47], but 5-FU/LV must be maintained as a complete break from treatment can substantially compromise survival [48]. A ‘stop-and-go’ approach with FOLFIRI appears feasible based on the results of a randomized phase II study that demonstrated similar efficacy for a ‘2 months on – 2 months off’ regimen compared with continuous treatment [49].

The Addition of Biologics: The Benefits of Improved Understanding of Colorectal Cancer Biology

Three biological agents have been licensed for the treatment of colorectal cancer: bevacizumab, a human monoclonal antibody that targets vascular endothelial growth factor (VEGF); cetuximab, a chimeric human mouse monoclonal antibody against the epidermal growth factor receptor (EGFR), and panitumumab, a fully human antibody that targets the extracellular domain of EGFR.

Bevacizumab was approved after Goldberg et al. [37] and Hurwitz et al. [50] showed a survival benefit for the addition of bevacizumab to IFL. However, in a phase III study of 1,401 patients randomized to FOLFOX4 or XELOX with or without bevacizumab, PFS was extended in the bevacizumab population (9.4 vs. 8.0 months, $p = 0.0023$) [51], but median OS (21.9 vs. 19.9, $p = 0.0769$) and RR (47% vs. 49%, $p = 0.31$) were similar in both arms. Furthermore, the PFS benefit was limited to the XELOX arm (9.3 vs. 7.4 months, $p = 0.003$ but for FOLFOX: 9.4 vs. 8.6 months, $p = 0.19$). More patients discontinued treatment because of adverse events, including thromboembolic events and bowel perforations, in the bevacizumab containing arm (30% vs. 21%). While angiogenesis contributes to solid-tumor development [52, 53], it is unclear whether bevacizumab improves outcome with better chemotherapy regimens in the first-line setting. For patients with refractory disease, the addition of bevacizumab to FOLFOX improves RR (22.6% vs. 8.6%, $p < 0.001$), PFS (7.3 vs. 4.7 months, $p < 0.0001$), and OS (12.9 vs. 10.8, $p = 0.0011$) [54], and two observational studies support continuation of bevacizumab beyond progression [55, 56]. Physiological (hypertension [57]), genetic (VEGF genotype [58]) and circulating (VEGF [59–61], placental-derived growth factor [62] and VEGF receptors [63]) biomarkers have been retrospectively identified to guide patient selection but require validation in larger prospective studies before translation into the clinic [64].

The fact that approximately 80% of colorectal tumors stain positively for EGFR generated widespread interest in this pathway, resulting in two FDA-approved anti-EGFR agents. Cetuximab appears to restore sensitivity to irinotecan in refractory patients by increasing RR (23% vs. 11%, $p = 0.007$) and prolonging PFS (4.1 vs. 1.5 months, $p < 0.0001$) in combination with irinotecan compared to single agent cetuximab [65]. In the first-line setting, FOLFIRI plus cetuximab also improves RR (46.9% vs. 38.7%, $p = 0.005$) and PFS (8.9 vs. 8.0, $p = 0.036$) [66]. In the refractory setting, it improves RR (23 vs. 11%, $p = 0.007$) and time

to progression (4.1 vs. 1.5 months, $p < 0.0001$) [67]. Panitumumab plus best supportive care improves PFS over best supportive care alone in previously treated patients [68].

It was initially anticipated that the presumed targets of these agents (VEGF and EGFR) would serve as clinically useful biomarkers, in the same way that the HER2 status of a breast tumor can be used for treatment selection and prognostication [69, 70]. However, EGFR expression measured using immunohistochemistry is poorly predictive of response to cetuximab [67, 71–73], and more accurate measurement of EGFR status using fluorescent in situ hybridization and polymerase chain reaction does not provide clinically useful information. Patients whose tumors have a low EGFR gene copy number by fluorescent in situ hybridization are less likely to respond to anti-EGFR therapies, but high EGFR gene copy number is not associated with response to anti-EGFR therapy [74, 75]. Similarly, EGFR measured using polymerase chain reaction does not predict response to cetuximab, but does correlate with survival [76]. However, the mutation status of KRAS, a gene encoding the KRAS proto-oncogene downstream effector of EGFR, has been associated with poor prognosis and nonresponse to EGFR antagonists [77–80]. In fact, panitumumab was approved in Europe for patients with MCRC with wild-type KRAS (i.e. no mutation), after a phase III study demonstrated worse survival in patients with KRAS mutant tumors (hazard ratio, HR = 0.45, 95% confidence interval, CI, 0.34–0.59) [81], and two recent phase III studies confirm this association [82, 83]. Similarly, the benefit for cetuximab plus FOLFIRI was greater in KRAS wild-type tumors, with significant difference in PFS (HR = 0.68, $p = 0.017$) and RR (59% vs. 43%, $p = 0.0025$) [84].

The single-agent activity of these antibodies encouraged investigators to combine multiple biologics with chemotherapy regimens [85]. However, the combination of these biologics proved deleterious. In a large randomized phase IIIB study of FOLFOX4/FOLFIRI plus bevacizumab + or – panitumumab, there was an increased incidence of serious adverse events (56% vs. 37%), a reduced median PFS (9.0 vs. 10.5 months; HR = 1.29; 95% CI, 1.05–1.58) and OS (18.6 vs. not reached; HR = 1.44; 95% CI, 1.10–1.88), with two biologics versus one [86]. A study performed by the Dutch Colorectal Cancer Group randomized 716 patients to capecitabine, oxaliplatin, bevacizumab, + or – cetuximab and demonstrated a shorter PFS (9.8 vs. 10.7 months, $p = 0.019$) with the two antibodies versus one antibody [87]. Similarly, the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab resulted in inferior PFS, especially in patients with mutated

KRAS who received cetuximab [88], similar to previous reports [84, 89].

KRAS is therefore a biomarker with clinical utility and oncologists are now obliged to test KRAS mutational status prior to initiating therapy with cetuximab. However, KRAS does not predict response, i.e. only 30% of MCRC patients with KRAS wild-type tumors (nonmutated) respond to cetuximab, highlighting the limitations of a single biomarker, and other complementary predictors are needed. Pathways downstream of EGFR such as PI3K/PTEN/Akt or JAK/STAT have been investigated for biomarkers of EGFR antibody resistance [90], and BRAF status, EGFR amplification, and cytoplasmic expression of PTEN can be used to further stratify this population [91]. Additional targeted biological agents are in development for the treatment of MCRC that offer hope of further improvements in outcome for patients with MCRC [92].

Surgical Resection of Hepatic Metastases and Perioperative Systemic Therapy

Complete responses have been reported with systemic chemotherapy for patients with MCRC but long-term cure is rare with chemotherapy alone (table 1). Complete surgical resection of CLM is associated with 30–50% survival at 5 years [93–95]. Extrahepatic disease is typically considered a contradiction to hepatic resection but occasionally isolated extrahepatic metastases are resected and a 28% 5-year survival has been reported even in these patients [96].

Complete resection is essential since patients who undergo incomplete resection appear to have similar outcomes to patients who are not resected [97]. Unresectable CLM can be rendered resectable by preoperative chemotherapy, and in a study of 1,104 unresectable patients made resectable by chemotherapy survival rates were 33% at 5 years and 23% at 10 years, which is almost as good as for patients who are resectable at presentation [98]. Perioperative chemotherapy is also used for patients with resectable hepatic metastases to facilitate less radical surgery, and treat micrometastases. Some claim that response to chemotherapy predicts survival [99] although others report that patients who progress but remain candidates for surgical resection have the same outcome as responders [95], suggesting that close follow-up is required so as not to miss the resection window. Postoperative systemic chemotherapy appears beneficial after complete surgical resection [100–104]. Pooled analysis of two multicenter studies supports adjuvant systemic che-

Table 1. Clinical trials demonstrating progress in the systemic management of MCRC in the past 15 years

Clinical trial	Treatment	Median OS months	OS benefit months	p value	CR rate % ¹
Scheithauer et al., 1993 [17]	5-FU + LV BSC	11 5	6	0.006	0
Saltz et al., 2000 [156]	IFL bolus 5-FU	14.8 12.6	2.2	0.04	2.6 0.8
Kohne et al., 2005 [33]	inf. 5-FU/LV inf. 5-FU/LV + CPT-11	16.9 20.1	3.2	NS	3.7 2.8
Van Cutsem et al., 2001 [20]	bolus 5-FU/LV capecitabine	12.1 13.2	1.1	NS	0.7 0.3
De Gramont et al., 2000 [157]	inf./bolus 5-FU/LV inf./bolus 5-FU/LV + oxaliplatin	14.7 16.2	1.5	NS	0.5 1.4
Goldberg et al., 2004 [37]	IFL FOLFOX4	15 19.5	4.5	0.0001	NR
Tournigand et al., 2004 [45]	inf./bolus 5-FU/LV + CPT-11 FOLFOX6	21.5 20.6	0.9	NS	3 5
Hurwitz et al., 2004 [50]	IFL + placebo IFL + Bev	15.6 20.3	4.7	<0.001	2.2 3.7
Falcone et al., 2007 [41]	FOLFIRI FOLFOXIRI	16.7 22.6	5.9	0.032	5 7
Cassidy et al., 2008 [38]	FOLFOX4 XELOX	19.6 19.8	0.2	NS	NR
Saltz et al., 2008 [51]	FOLFOX/XELOX + placebo FOLFOX/XELOX + Bev	19.9 21.3	1.4	0.08	NR
Van Cutsem et al., 2009 [158]	FOLFIRI FOLFIRI + cetuximab	18.6 19.9	1.3	NS	0.3 0.5
Hecht et al., 2009 ² [159]	Chemo + Bev Chemo + Bev + PMAB	24.5 19.4	5.1	NR	0.4 0

CR = Complete response; BSC = best supportive care; inf. = infusion; Bev = bevacizumab; PMAB = panitumumab; NR = not reported; NS = not statistically significant.

¹ Complete response to chemotherapy alone.

² Trial closed prematurely due to inferior outcome in panitumumab arm.

motherapy over surgery alone, with a trend towards an improvement in median PFS ($p = 0.059$), and in a multivariate analysis adjuvant chemotherapy was significantly associated with a better OS ($p = 0.046$) [104–107]; nonetheless, level 1 evidence is lacking and clinical trials addressing this question are needed.

No biomarker reliably predicts outcome after treatment of CLM although a number of prognostic scoring systems have been developed that are useful for patient selection for resection and for stratification in clinical trials [107–111].

Hepatic Arterial Infusion Chemotherapy: Pushing the Boundary of Hepatic Resection

Direct infusion of the liver is possible as liver neoplasms are fed primarily by the hepatic artery whereas the portal vein supplies the normal liver [112]. Floxuridine (FUDR), a pyrimidine antimetabolite, is used in preference to 5-FU because of its short half-life and high rate of hepatic extraction (90%), leading to a 400-fold estimated increased exposure [113]. Direct infusion of chemotherapy into the hepatic artery exposes the tumor to higher

Fig. 1. OS for 218 patients on adjuvant HAI studies at Memorial Sloan-Kettering Cancer Center.

drug concentrations with minimal systemic toxicity. The development of a totally implantable pump facilitated the development of hepatic artery infusion (HAI) [114]. The approach has been criticized because of its associated hepatic toxicity, but hepatic toxicity, the major complication, can be minimized with close monitoring of patients, careful catheter placement resulting in less displacement and occlusion problems [115], and the addition of dexamethasone to FUDR which reduces the rates of biliary toxicity [116].

A recent meta-analysis reported a significantly better response rate for HAI chemotherapy (42.9% vs. 18.4%, $p < 0.0001$) compared with systemic 5-FU-based therapy [117], and a cooperative group study demonstrated improved OS favoring HAI (24.4 vs. 20 months, $p = 0.0039$) [118]. The former study concluded that fluoropyrimidine-based HAI should not be used alone in the first-line treatment of colorectal cancer [117], and HAI has more recently been combined with systemic therapy in a number of single-institution studies with impressive results. A median survival of 41 months was reported in one study that combined HAI with systemic oxaliplatin and irinotecan in 49 patients with unresectable liver metastases [119]. The RR in this study was 92%. Forty-nine percent of these patients were able to undergo resection though clearly unresectable at initiation of therapy [119, 120].

HAI can be administered in the postoperative setting with increased survival. In a randomized study of HAI + systemic therapy versus systemic 5-FU/LV alone, the 2-year survival (the endpoint of the study) was 86% versus 72% ($p = 0.03$) in HAI + systemic versus systemic

Fig. 2. Median OS and complete response (CRR) with systemic chemotherapy regimens for metastatic colorectal cancer. BSC = Best supportive care; Bev = bevacizumab; Cetux = cetuximab; CPT = irinotecan; Ox = oxaliplatin. * is the OS observed in a phase II study whereas other results in this figure are from phase III studies.

groups, respectively [121]. In a later report with a median follow-up of 10.3 years, the 10-year survival was 41.1% versus 27.7%, for the 2 groups, respectively [122]. Figure 1 illustrates the collective median survival from 4 studies at Memorial Sloan-Kettering Cancer Center evaluating HAI and systemic therapy after resection in 218 patients. With a median follow-up of 69 months the 5-year survival is close to 70% and 10-year survival approximately 50%. Close cooperation with surgeons to remove small recurrences and further chemotherapy if necessary can increase long-term survival. It appears that the hepatic parenchyma is particularly receptive to circulating colorectal cancer cells. It is unclear whether extrahepatic metastases are initiated at the same time as the liver lesions, or whether these hepatic metastases go on to seed extrahepatic sites, but cells may require additional mutations to survive in organs other than the liver. A hypothesis whereby the liver acts as 'gatekeeper' might explain the success of liver resection and HAI treatments, emphasizing the importance of further developing this modality using agents other than FUDR.

Radiofrequency Ablation (RFA) for the Treatment of Unresectable or Recurrent Hepatic Metastases

RFA offers an opportunity to eliminate residual metastases that are small in size or few in number when an R0 resection is not possible despite optimal systemic che-

motherapy and surgical expertise. RFA is a complementary option to surgery and chemotherapy for individuals with CLM and limited tumor burden (≤ 3 CLM, and lesion size ≤ 3 cm) or in patients with comorbidities, or poor hepatic reserve [123]. Despite its widespread use, there are no randomized data supporting RFA, and the clinical benefit of this treatment is unclear. A recent review of RFA by the American Society of Clinical Oncology concluded that 'there is a compelling need for more research to determine the efficacy and utility of RFA to increase local recurrence-free, progression-free, and disease-free survival as well as OS for patients with CLM' [124]. Two studies that attempted to investigate its benefit in a randomized phase III setting were closed early due to poor accrual; however, 13 clinical series and 8 comparative studies demonstrate long-term OS after RFA treatment [125–143]. The heterogeneous nature of these studies prevented a meaningful meta-analysis, but a recent systematic analysis of 1,578 patients with 3,655 RFA-treated CLM concluded that RFA can be a useful adjunct to both chemotherapy and surgery, resulting in a complete response or R0 resection, respectively, by eradication of residual lesions [123]. Studies comparing RFA with resection are often biased in favor of resection as hepatectomy likely removes undetected metastases and patients considered for RFA are usually more advanced. Nonetheless, long-term survival has been reported with 5-year survival up to 18% from the time of RFA [130]. The management of MCRC requires an individualized approach and RFA has a role to play in the coordinated, multidisciplinary care of patients.

The Success of and Future Hope for Personalized Therapy

The data presented here illustrate that with timely intervention coordinated by a multidisciplinary team, a greater number, albeit select minority, of patients with MCRC can be cured. The use of new, effective systemic and HAI chemotherapies with improved surgical techniques and RFA has expanded the definition of resectability. This success is in part due to the appropriate selection of patients for specific intervention using predominantly clinically criteria. Molecular characterization of patients and their disease may identify biomarkers to further refine treatment selection, resulting in a personalized approach for individual patients. A greater understanding of the biology of MCRC has also contributed to this progress, and ongoing developments continue to

provide insight into colorectal cancer pathogenesis that will hopefully result in further novel therapeutic approaches.

Recent advances including The HapMap project, The Human Genome project and the introduction of high-throughput genotyping have facilitated the scrutiny of DNA at a new level. Large genome-wide association studies (GWAS) have been performed, and to date 7 GWAS in colorectal cancer have identified 10 risk loci associated with a risk of developing colorectal cancer [144–150]. These genetic markers may direct screening and preventive therapy approaches, but may also identify unappreciated disease biology. No GWAS has yet investigated genetic variants associated with the development of MCRC, but it is possible that germ line markers exist that will serve the dual function of identifying individuals likely to develop metastases and elucidation of disease biology. Five of the 10 loci already reported are associated with the transforming growth factor- β signaling pathway, confirming the importance of this pathway in colorectal cancer carcinogenesis, and illustrating how this technology can improve our understanding of disease biology. Other genome-wide profiling studies have identified regulators of gene expression termed microRNAs that are deregulated in colorectal cancer. These small interfering RNAs may further enhance our understanding of colorectal cancer pathogenesis and provide clinically useful biomarkers and therapeutic targets [151–153]. Circulating tumor cells with metastatic potential have also been identified as prognostic markers in patients with colorectal cancer and are another biomarker under investigation [154]. These cells may contain molecular alterations that mirror cells within metastatic deposits and as such may reveal important somatic predictors of response to therapy [155]. To be clinically useful, molecular biomarkers will have to improve upon the predictive power of clinical characteristics presently used to guide treatment decisions, but recent advances suggest that molecular determinants may increasingly factor in the multidisciplinary management of patients with MCRC.

Conclusion

Advances in the systemic management of MCRC are reflected by the improved median survival times in recent phase III trials. Aggressive multidisciplinary management of CLM results in up to a 40% cure rate for a select minority of patients with MCRC. Improved RR with novel systemic regimens and targeted local ap-

proaches such as HAI have expanded the cohort of patients that can now be approached with curative intent. KRAS mutation testing identifies a group of patients that should not receive cetuximab, but biomarkers are needed which would enable selection of a subset of patients likely to respond. Recent technological developments have provided us with the tools to scrutinize DNA and RNA,

and have the potential to discover clinically useful biomarkers. This goal of personalized medicine may facilitate a more cost-effective and appropriate use of the large number of currently available therapies, and may also identify new biology for the further development of individualized treatment.

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