Accomplishments in 2008 in the Management of Curable Metastatic Colorectal Cancer

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SUMMARY

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I. OVERVIEW OF THE DISEASE

I-A. Incidence

Colorectal cancer (CRC) is the fourth most common cancer diagnosed worldwide (about 1.2 million new cases per year)[1] and accounts for the second highest number of cancer-related deaths.[2] Approximately 35% of patients have stage IV disease at presentation and 20% to 50% with stage II or III disease progress to stage IV.[3]

I-B. Prognosis

New therapies and improved surgical techniques have continued to reduce the death rate of all patients with colorectal cancer by almost 1.8% per year. The overall 5-year survival rate for stage IV disease remains approximately 10%.[4] In the natural course of the disease, up to 50% of patients develop metastases to the liver, which is the most common site of metastasis.[5] Approximately 20% to 25% of CRC patients have liver metastases at presentation (ie, synchronous liver metastases); the presence or absence of liver metastases primarily determines survival.[6] Even in patients with an isolated liver metastasis, the progression of the liver disease, rather than of the primary CRC, determines overall life expectancy.[7] If left untreated, survival in patients with colorectal liver metastases (CRLM) is measured in months.[7–9]

Peritoneal carcinomatosis (PC) may occur from transmural spread of the primary malignancy or from perforation at diagnosis and is associated with a poor prognosis.[10] Pulmonary metastasis from CRC (CRPM) is also common but less studied. Surgical resection of CRPM has increased in recent years, showing long-term benefit in selected patients, similar to that seen with liver resection for CRLM.[11] Although cerebral metastases are uncommon, CRC is responsible for approximately 3% of brain metastases, which generally occur at a later disease stage.[12]

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II. CURRENT THERAPY STANDARDS

II-A. Colorectal Liver Metastases (CRLM)

The main therapeutic modalities for CRLM consist of surgical resection, chemotherapy, and radiofrequency ablation (RFA); however, hepatic resection is currently the only potentially curative treatment.[13]

II-A. 1. Resectable Tumors

At the time of presentation, only 15% to 20% of patients with CRLM are candidates for resection with curative intent.[14] Resectability is mainly defined by the ability to perform a curative hepatectomy, resecting all lesions while leaving at least 30% of nontumoral liver parenchyma.[15] Five-year survival rates of 35% to 55% have been reported among patients undergoing hepatic resection.[3,16]

II-A. 2. Strategies to Convert Nonresectable Liver Metastases to Resectable Status

Preoperative or conversion chemotherapy has become the primary treatment approach for nonresectable CRLM.[17] This therapy helps to downstage liver disease, allowing more patients to undergo curative hepatectomy with a ≥ 30% nontumoral liver parenchyma remnant. The chemotherapy regimens used include fluorouracil, leucovorin, oxaliplatin, irinotecan, and monoclonal biologic agents (cetuximab/bevacizumab). Modern chemotherapy allows 12.5% of patients with initially unresectable CRLM to be rescued by liver surgery. Current data suggest that the perioperative combination of a monoclonal biologic agent with cytotoxic chemotherapy regimens can significantly increase progression-free survival in resected mCRC patients.[18] Despite a high recurrence rate and the requirement for repeat hepatectomies and extrahepatic resections, 5-year survival rate of 33% has been reported, approaching that of patients diagnosed with operable disease.[15] However, hepatectomy is contraindicated in patients with potentially resectable CRLM receiving neoadjuvant chemotherapy whose tumors progress before surgery, due to the poor reported outcome, even after potentially curative hepatectomy.[19]

Preoperative portal vein embolization (PVE), first described by Kinoshita[20] and then used by Makuuchi[21] in the setting of hepatic resection of hilar cholangiocarcinomas, is an effective means of inducing hypertrophy of the future liver remnant (FLR), thus allowing safe hepatic resection. The underlying principle involves blocking portal venous flow to the side of the liver ipsilateral to the lesion in order to induce hypertrophy of the contralateral side and increase the volume of the FLR. In patients with an otherwise normal liver, current guidelines recommend preoperative PVE when the ratio of the remnant liver volume is < 30%. Patients submitted to prolonged chemotherapy with a high risk of induced hepatic lesions should benefit from this method when this ratio is less than 40%. The optimal time interval necessary to induce maximum hypertrophy after PVE has not been established, although some Japanese teams perform resection as early as 2 weeks after PVE. The majority of groups, however, use a 4–6 week interval between PVE and surgery. Long-term survival has been comparable to that after resection without PVE.[22]

RFA has been applied mainly as a complementary procedure to surgery, allowing more effective disease clearance in selected patients with otherwise unresectable tumors. Adding RFA to hepatic resection has been reported to be well tolerated; perioperative morbidity and mortality have been comparable to that after resection alone. For patients with metastases considered unresectable, RFA combined with hepatic resection can achieve a median survival up to 37 months. Results from the European Organisation for Research and Treatment of Cancer (EORTC) CLOCC trial have also demonstrated that RFA is superior to chemotherapy alone in treating patients with colorectal metastases that could not be managed by resection alone.[23] In patients with extensive bilobar disease, recurrence rates are high, but long-term survival is encouraging and may be improved with aggressive postoperative chemotherapy.[24]

In some patients with multiple hepatic CRLM, a complete metastatic clearance cannot be achieved by a single hepatectomy, even when downstaged by chemotherapy, after portal embolization, or combined with a locally destructive technique (RFA or cryotherapy). In two-stage hepatectomy, the tumor clearance of one hemiliver is obtained first (as a noncurative intervention) and the remaining tumor lesions of the contralateral hemiliver are resected in a second operation, after a period of liver regeneration.[25] This approach has yielded good outcomes in patients with multiple, bilateral CRLM.[26]

II-A. 3. Synchronous Colorectal Liver Metastases

Treatment strategies for patients with synchronous CRLM are still unclear. Synchronous metastases usually indicate a more disseminated disease status and are associated with shorter disease-free survival than metachronous metastasis.[27] The timing of surgery for primary CRC and CRLM as well as that of chemotherapy is controversial. To date, studies comparing simultaneous vs. staged resection have shown that simultaneous resection may be safe but no survival advantage has been demonstrated. Comparison is difficult because simultaneous resection is often restricted to patients with more limited hepatic disease. Caution should be exerted particularly before performing simultaneous colorectal and major hepatic resections due to increased morbidity and mortality rates.[28,29] On the other hand, several studies have reported comparable morbidity and mortality for patients undergoing simultaneous resection vs. staged resection of the colon and liver tumors.[30–32] However, in most of these studies, the patients submitted to simultaneous procedures had limited liver resection and were a more select group compared with those undergoing staged surgery by the same teams. In practice, the decision to perform simultaneous resection is on an individual basis, and it is recommended that colorectal and major liver resections (> 3 segments) should not be performed at the same time. One-stage procedures (combined limited liver and colorectal resection) should be reserved for experienced teams sharing both colorectal and liver surgery expertises.

II-A. 4. Predictors of Survival After Resection of CRLM

Several factors have been found to influence patient prognosis after major liver surgery for metastatic disease: The tumor-free margin of the resected specimen, number of metastases, disease-

free survival, primary tumor stage, and parameters describing the tumor/host biology (tumor markers, neutrophil counts) are consistent findings in different analyses.

- Currently, a resection margin of >1 cm is considered optimal, and is an independent predictor of survival after CRLM resection. However, subcentimeter resections have also been associated with favorable outcome and should not preclude resection.[33,34] In addition, a recent study demonstrated that patients undergoing R1 vs. R0 resection had similar overall and disease-free survival rates (61% vs. 57%, and 28% vs. 17%, respectively). Recurrence rate was higher in the R1 group, but recurrences were intrahepatic rather than localized at the surgical margin.[35] Therefore, R1 resection should not be considered an absolute contraindication to liver resection, provided a complete intraoperative macroscopic resection is achieved.
- Although there is no fixed limit on the number of liver metastases that can be resected as long as all are resectable, the number of liver metastases is one of the most important predictors for recurrence.[36] The number of metastases that may be resected has increased over the past years; however, more than 8–10 metastases are associated with a very high recurrence rate resulting in significantly decreased survival (1- and 3-year survival rates of 80% and 35%, respectively).[37]
- The primary tumor stage[38] and location[14] were found to be associated with prognosis of patients with CRLM.
- An elevated neutrophil-lymphocyte ratio (NLR) was found to be a prognostic indicator in primary CRC and to increase risk of both recurrence and death in patients undergoing surgery for CRLM.[39]
- An interesting report by DeOliveira et al states that presence of hypoechoic lesions on intraoperative ultrasonography is associated with poor patient survival.[40]
- Emphasis is now being given to molecular tumor biomarkers[41] and tumor immunity,[42] considered by investigators to be more powerful than many traditional clinicopathologic factors at predicting survival after resection of CRLM. However, further evaluation of these parameters is required before they are introduced for prognostication purposes.

II-B. Peritoneal Carcinomatosis From Colorectal Cancer

Peritoneal carcinomatosis (PC) is a common manifestation of CRC and has traditionally been regarded as a terminal disease with short patient survival. However, treatment with chemotherapy has improved patient prognosis.

In the past decade, a local-regional therapeutic approach combining cytoreductive surgery with perioperative intraperitoneal chemotherapy (hyperthermic intraperitoneal chemotherapy [HIPEC] and/or immediate postoperative intraperitoneal chemotherapy) has evolved, and promising survival results have been reported, even though presence of PC has traditionally been considered an absolute contraindication to liver resection.[43] In a retrospective multicenter study involving 506 patients, median survival was 32.4 months in highly selected patients who completed cytoreductive surgery, vs. 8.4 months in those who did not complete cytoreductive surgery.[44] In a recent study, median survival was 24 months in patients with isolated, resectable PC treated with modern chemotherapy, but only surgical cytoreduction plus HIPEC was able to prolong median survival up to 63 months, with a 5-year survival rate of 51%.[45]

II-C. Colorectal Pulmonary Metastases (CRPM)

Patients with only pulmonary metastases as a site of extrahepatic disease have a particularly good outcome after complete metastasectomy of both liver and lung disease. Five-year survival rates have ranged from 22% to 50% in patients with metastases limited to the lungs.[46] Chemotherapy is generally used in conjunction with resection.

II-D. Colorectal Liver Metastases With Extrahepatic Disease

After reasonable success of multimodality treatment for isolated liver and pulmonary metastases, interest is emerging for the treatment of more complex multi-organ metastases. Surgical resection of both hepatic and pulmonary colorectal metastases has been associated with prolonged survival in selected patients.[47,48] Patients with simultaneous hepatic and extrahepatic disease do, however, need to be well selected for surgery. Elias et al stated that extrahepatic disease, when resectable, is no longer a contraindication to hepatectomy.[49] More important, the total number of metastases, whatever their location, has a stronger prognostic effect than the site of the metastases. However, further validation of this concept is needed.

III. ACCOMPLISHMENTS (OR LACK OF ACCOMPLISHMENTS) DURING THE YEAR

III-A. Therapy

Management of advanced CRC and of metastases from CRC has evolved dramatically in the past decade. What was once considered stage IV (incurable) disease has now become possibly curable, based on advances in surgical techniques, chemotherapy, and perioperative care. Research findings that were reported during the past year are summarized below.

III-A. 1. New Staging System

The recent advances in management of advanced colorectal cancer are not reflected in the current staging systems. By redefining resectability, and with the use of modern chemotherapy, nearly 10% of initially unresectable patients are now alive 5 years after diagnosis. However, current systems categorize all disease spread beyond the lymph node basin of the primary tumor as unstratified stage IV. If untreated, such patients have poor survival, whereas data suggest that if it is possible to resect liver disease, survival can be significantly improved.[50] In addition, there is no strong consensus on what constitutes resectable liver disease, and selection criteria to identify resectable patients may vary. Therefore, a new staging system that would reflect the current strategies and prognoses for patients with metastatic disease is urgently needed.

III-A. 2. Systemic Chemotherapy in Resectable Liver Metastases

- Adjuvant systemic chemotherapy following liver resection was previously investigated by different groups. Even the two largest studies of the Fédération Francophone de Cancérologie Digestive (FFCD) and the EORTC did not reach their recruitment aims.

Results of these trials were combined in a metanalysis by Mitry et al,[51] which showed a strong trend toward better disease-free survival with adjuvant 5-FU treatment (HR 0.76, $P = 5.8$), and a trend toward favorable overall survival (HR 0.76, $P = 9.8$).

- The EORTC Intergroup randomized phase III 40983 study examined perioperative FOLFOX4 (5-fluorouracil [5-FU], leucovorin, oxaliplatin) chemotherapy for patients with potentially resectable CRLM. Final results were published in 2008.[52] A total of 364 patients with up to four CRLM were randomized between perioperative FOLFOX4 (oxaliplatin 85 mg/m² and LV5FU2), six cycles before and six cycles after surgery (CT), vs. surgery alone (S). Eleven of 182 patients were ineligible in each arm, mostly due to more advanced disease; 31 and 30 patients in the CT and S arms, respectively, could not undergo resection. At a median follow-up of 3.9 years, progression-free survival (PFS) was significantly better with CT in the group of resected patients (Table 1), although the trial was formally not positive in the intention-to-treat (ITT) analysis (HR 0.79, $P = .058$).
- In addition, data from United States and Europe show better survival in patients receiving adjuvant chemotherapy after resection of CRC liver metastases.[53] Despite the lack of a statistically positive trial by ITT analysis or metanalysis, use of adjuvant or neoadjuvant systemic treatment is widely recognized as standard of care in cases of liver resection, and was the focus of single-center studies with XELOX/FOLFOX[54] and XELOX plus bevacizumab.[55]
- A recent randomized phase III trial found no significant advantage for adding irinotecan to adjuvant treatment after R0 resection of liver metastases: 2-year disease-free survival rates were 51% and 46% for FOLFIRI and 5-FU/LV, respectively (HR 0.89, CI 0.66–1.19, $P = .43$); and 3-year overall survival rates were 73% and 72%, respectively.[56] These results are similar to those from other studies investigating irinotecan in adjuvant treatment of stage III disease.[57–59]

cetuximab vs. 1.7% with FOLFIRI alone [includes both *K-ras* wt and mutant tumor status]).[60] Similar results have been obtained in the OPUS trial (FOLFOX ± cetuximab vs. standard chemotherapy alone). The response rate in patients with *K-ras* wild-type tumors was 61% with the addition of cetuximab vs. 37% with standard chemotherapy.[61] Another randomized phase II multicenter study (the CELIM study) of cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI in the neoadjuvant setting of nonresectable metastatic CRC confined to liver, found response rates of 68% and 57% in the FOLFOX6 and FOLFIRI arms, respectively. In a combined analysis of both arms, response rate was 70% in patients with wild-type *K-ras* tumors. R0 resections were performed in 34% of patients.[62] *(For more information on these and other studies of treatments for metastatic CRC, see the paper by Goldberg et al, covering Accomplishments in 2008 in the Treatment of Advanced Metastatic Colorectal Cancer, this issue, page S23.)*[63]

- Studies have begun to examine combinations of triple cytotoxic chemotherapy plus antibody treatment with bevacizumab or cetuximab. Randomized trials have demonstrated that combining a biologic agent with an oxaliplatin- or irinotecan-based doublet can improve efficacy and also the rate of secondary resection of metastases.[64] The combination of cetuximab with a chronomodulated FOLFOXIRI regimen resulted in an 85% response rate and a 75% resection rate. However, dose reduction was necessary because of unacceptable rates of diarrhea, and a less conservative definition of non-resectability was used.[65] Further studies are needed to show an advantage over FOLFOXIRI or chemotherapy plus cetuximab.
- Results have been obtained with new agents. First-line therapy with sunitinib (multitargeted tyrosine kinase inhibitor) and FOLFIRI produced tumor regressions in non-resectable patients.[66] A recent press release addressing a phase III trial of sunitinib + FOLFIRI vs. FOLFIRI alone noted that the trial did not meet the primary PFS end point. Full presentation of the data is pending.[67]
- Two groups reported that pathologic complete remission (pCR) after neoadjuvant therapy has a major influence on survival after resection of liver metastases.[68,69] "Risk factors" for this pCR are age, size of metastases, tumor markers, and clinical response.[68] However, pCR is a rare event (4%–9%).[68,69] Therefore, a longer duration of preoperative treatment to achieve pCR instead of proceeding to resection is currently not justified; these findings also undermine the importance of intensifying multidisciplinary treatment approaches for these patients.
- Rescue chemotherapy for CRLM previously refractory to conventional systemic therapy:

Table 1. EORTC phase III 40983 study of perioperative FOLFOX4: Progression-free survival.

	No. pts CT	No. pts Surgery	% Absolute Difference in 3-yr PFS	HR (CI)	*P* Value
All patients	182	182	+7.2% (28.1% to 35.4%)	0.79 (0.62–1.02)	$P = .058$
All eligible	171	171	+8.1% (28.1% to 36.2%)	0.77 (0.60–1.00)	$P = .041$
All resected	151	152	+9.2% (33.2% to 42.4%)	0.73 (0.55–0.97)	$P = .025$

Abbreviations: CI = confidence interval; CT = perioperative chemotherapy; EORTC = European Organisation for the Research and Treatment of Cancer; FOLFOX4 = 5-fluorouracil, leucovorin, oxaliplatin; HR = hazard ratio; PFS = progression-free survival.
Data from Nordlinger et al.[52]

III-A. 3. Systemic Chemotherapy in Nonresectable Liver Metastases

The efficacy of FOLFOX and FOLFIRI has been demonstrated in large single-center series. These regimens are considered effective in facilitating hepatic resection in selected, initially nonresectable patients. Increasingly, however, the trend is to use a combination of three chemotherapy agents (all cytotoxic agents or two cytotoxic agents and one biologic agent):

- In the phase III CRYSTAL trial, which included 1,217 patients, combined use of cetuximab with FOLFIRI (5-fluorouracil, irinotecan, leucovorin) improved response rates (59% vs. 43%, $P = .004$) and PFS (HR 0.68, CI 0.50–0.94, $P = .02$) in patients with *K-ras* wild-type (wt) tumors; and increased R0 resection rates of patients with initially unresectable metastatic CRC (4.8% with FOLFIRI +

Table 2. Principal trials in patients with colorectal metastases.

Trial ID	Phase	Status	Trial Description
Phase III Trials			
USCTU-4351 (NCT00482222)	III	Active	Neoadjuvant and adjuvant combination chemotherapy with vs. without cetuximab
GERCOR-C02-1 (NCT00268398)	III	Active	Adjuvant FOLFOX4 vs. FOLFOX7 and FOLFIRI
HEPATICA (NCT00394992)	III	Active	Adjuvant XELOX + bevacizumab vs. XELOX alone
Sir-Spheres1 (NCT00199173)	III	Active	Hepatic intra-arterial injection of yttrium-90 microspheres vs. infusional IV 5-FU in patients refractory to standard IV chemotherapy
Adjuvant, Perioperative, or Neoadjuvant Trials			
FRE-IGR-CHOICE (NCT00544349)	II	Active	LV5FU2 simplified + cetuximab with intra-arterial hepatic oxaliplatin for potentially resectable metastases
EORTC-40051 (NCT00438737)	II	Active	Adjuvant FOLFOX + cetuximab vs. FOLFOX + cetuximab + bevacizumab
DUMC-5883-04-6RO (NCT00103142)	II	Active	Active immunotherapy with PANVAC or autologous, cultured dendritic cells infected with PANVAC after complete resection
CHUV-CH-OCFL (NCT00513266)	II	Active	Oxaliplatin-CPT-11-5-FU-leucovorin + bevacizumab and cetuximab (OCFL-BC) for potentially resectable liver and/or lung metastases
ACO-ASSO-LM1 (NCT00444041)	II	Active	Perioperative XELOX and bevacizumab for potentially resectable liver metastases
RMNHS-RMH-CCR-BOXER (NCT00450346)	II	Active	Neoadjuvant XELOX + bevacizumab
MSKCC 04-086 (NCT00200200)	II	Active	Hepatic arterial infusion with FUDR + DXM together with systemic chemotherapy ± bevacizumab in patients with resected liver metastases
OPTILIV 07 Eudract 2007-004632-24 (NCT00852228)	II	Active	Intravenous cetuximab and hepatic artery infusion of three-drug chemotherapy in patients with liver only metastases from colorectal cancer
EMR 62 202-505 (NCT00778830)	II	Approved but not yet active	Evaluation of safety and efficacy of FOLFIRI plus cetuximab or FOLFOX plus cetuximab as first-line therapy in subjects with KRAS wild-type metastatic colorectal cancer (APEC-Study)
MK0646-004, (NCT00614393)	III/II	Active	Study of MK0646 in combination with cetuximab and irinotecan in metastatic colorectal cancer
LSO-OL006 (NCT00440310)	III	Active	Phase III Trial of Litx™ plus chemotherapy vs. chemotherapy only treating colorectal cancer patients with recurrent liver metastases
Trials for Initially Unresectable Metastases			
CCCGHS-CHEMO-SIRT (NCT00408551)	II	Active	Chemotherapy with selective internal radiation treatment using Y-90 microspheres for unresected liver metastases
CELIM (NCT00153998)	II	Active	FOLFOX + cetuximab vs. FOLFIRI + cetuximab for unresectable liver metastases
CHUG-ERBIFORT (NCT00557102)	II	Active	FOLFIRI and cetuximab for unresected liver or lung metastases
NCI-04-C-0229 (NCT00089401)	II	Active	Isolated hepatic perfusion with melphalan for unresectable liver metastases
MSKCC-06075 (NCT00492999)	II	Active	Hepatic arterial infusion with FUDR and DXM in combination with best systemic chemotherapy plus bevacizumab
STX0206 (NCT00724503)	III/II	Active	FOLFOX Plus SIR-Spheres microspheres vs. FOLFOX alone in patients with liver mets from primary colorectal cancer
EU-20565,GERCOR-OPTIMOX3-TARCEVA, ROCHE-GERCOR-C04-2, GERCOR-DREAM C04-2 (NCT00265824)	III	Active	Combination chemotherapy and bevacizumab with or without erlotinib in treating patients with metastatic colorectal cancer that cannot be removed by surgery

(Continued on next page)

Table 2 (cont'd). Principal trials in patients with colorectal metastases.

Trial ID	Phase	Status	Trial Description
Trials for Initially Unresectable Metastases (cont'd)			
D8480C00051 EUDRACT No 2006-001194-14, HORIZON II (NCT00399035)	III	Active	Cediranib (AZD2171) in addition to chemotherapy in patients with untreated metastatic colorectal cancer
CTRU-PICCOLO-MO-05-7289 (NCT00389870)	III	Active	Irinotecan with or without panitumumab or cyclosporine in treating patients with advanced or metastatic colorectal cancer that did not respond to fluorouracil

Abbreviations: CELIM = Cetuximab in Neoadjuvant Treatment of Nonresectable Colorectal Liver Metastases; CPT-11 = irinotecan; DXM = dexamethasone; EORTC = European Organisation for the Research and Treatment of Cancer; FOLFIRI = 5-fluorouracil, irinotecan, leucovorin; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; FUDR = floxuridine; GERCOR = French Oncology Research Group; IV = intravenous; LV5FU2 = 5-fluorouracil + leucovorin; MSKCC = Memorial Sloan-Kettering Cancer Center; XELOX = capecitabine + oxaliplatin.

– A retrospective study evaluated 151 patients with CRLM refractory to first-line conventional chemotherapy, who then received combination therapy with cetuximab.[48] Of 151 patients, 25 (16%) underwent surgery after a median of six cycles of combination therapy with cetuximab. After a median follow-up of 16 months, 23 of the 25 patients (92%) were alive, and 10 (40%) were disease-free. Median OS and PFS durations from initiation of cetuximab therapy were 20 and 13 months, respectively.
– Similarly, in a single-arm study, tritherapy with fluorouracil/leucovorin, irinotecan, and oxaliplatin in patients with initially unresectable CRLM, 82% of patients were able to have R0 resection. Complete clinical remission rate postsurgery was 79% and 2-year survival rate was 83% following triple cytotoxic chemotherapy.[70]

III-A. 4. Selective Internal Radiation Therapy (SIRT)

Selective internal radiotherapy (SIRT) using yttrium-90–labeled resin microspheres is increasingly being used for the radioembolization of unresectable CRLM. Combining this modality with other treatments such as chemotherapy or RFA has been reported to produce promising results. In selected patients, radioembolization can downstage liver metastases such that subsequent RFA can be performed, thereby increasing the number of patients with a "complete response" after minimally invasive therapy.[71] Encouraging results, comparable with those obtained with a second or subsequent line of chemotherapy, have been reported in heavily pretreated patients with CRLM.[72] However, whether this treatment modality has a role in the management of patients with CRLM needs to be explored further in prospective trials.

III-A. 5. Selection of Patients for Liver Resection

Studies have investigated the contribution of positron emission tomography (PET) for patient selection for liver resection. The previous, nonrandomized experience from different centers showed that patient selection could be markedly improved by using PET. Wiering and colleagues randomized 150 patients to be staged with conventional computed tomography scan (CT) or with additional PET.[73] In the PET group, 7% of the patients did not undergo surgery because of the PET findings. The rate of futile laparotomies (no R0 resection or recurrence within the first 6 months after laparotomy) was significantly lower in the PET group than in the conventional staging group (28% vs. 45%, $P = .042$).

III-A. 6. Radiofrequency Ablation

The contribution of RFA in the treatment of CRLM has been unclear for a long time. At the 2008 ASCO meeting, Ruers and coworkers presented the EORTC CLOCC trial, which compared chemotherapy with chemotherapy plus open RFA in 119 patients.[23] Results showed a significant PFS benefit for patients in the RFA group (60% vs. 40 % after 1 year, $P = .027$) and a promising local control rate (local recurrence in 6.5% of RFA lesions).

III-B. Biomarkers

For information on data reported in 2008 regarding biomarkers in CRC, the reader is referred to the paper by Tejpar and Odze, covering Accomplishments in 2008 in Biomarkers for Gastrointestinal Cancers, this issue, page S73.[74]

IV. WHAT NEEDS TO BE DONE?

IV-A. Optimizing Patient Care

Most patients with colorectal metastases still present to general surgeons and oncologists who are not specialists in their management. Because the treatment strategy frequently depends on the response to earlier therapies, and proper treatment of metastases at an early stage is associated with better outcome, certain procedures and systems are needed to provide optimal care for patients with metastatic CRC. These include regular surveillance and a multidisciplinary team (MDT) approach; computer programs such as Oncosurge[75] are also a step in this direction. Oncosurge helps to determine resectability of individual patients and define optimal treatment strategies. It can also be used for medical education.

V. FUTURE DIRECTIONS

V-A. Comments on Research

Surgical resection with intent to cure is a standard approach for selected patients with CRLM. However, optimal therapy for nonresectable CRLM, synchronous CRLM, metastases to organs other than liver, the role of RFA and/or chemotherapy as curative measures, and many other issues remain unanswered. Given the potential for remission and sometimes cure that can be achieved with surgery, the resectability of metastases, mainly hepatic, is emerging as a new end point in the treatment of patients with metastatic

CRC. Whether potent chemotherapy regimens, including triplets or doublets with biologics, in patients with marginally unresectable metastases is a valid strategy for improving long-term outcome as compared with conventional chemotherapy remains an open question. Table 2 lists current key trials evaluating treatments for patients with metastatic colorectal cancer.

V-B. Obstacles to Overcome

- The number of patients with metastatic CRC who can be offered treatment with the intent to cure is low. Therefore, it is not feasible to conduct prospective randomized trials to answer the many remaining questions in management of this patient cohort. The majority of new studies involve retrospective analyses of data from high-volume centers. A prospective worldwide registry has been established (www.livermetsurvey.org) to determine the patterns of care and outcomes of patients with CRC liver metastases.
- Several imperative questions remain to be answered. For example, whether first-line chemotherapy (combined triple or double agents with targeted biologic agents) should be given only to patients with potentially resectable metastases or to all metastatic patients is yet to be clearly defined. Similarly, the optimal treatment strategy and treatment timing for patients with synchronous colorectal metastases (chemotherapy or surgery first; one- or two-stage surgery, and which site first) all remain to be answered by future studies.
- Universally accepted definitions and staging systems to improve the patient work-up and to allow comparisons of results from different studies are long overdue. Further evaluation of new proposals such as the "grid staging system" should also be addressed by future studies.[76]

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Disclosures of Potential Conflicts of Interest

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Dr. Adam and Dr. Hoti have indicated no potential conflicts of interest.