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Ongoing Adjuvant/Neoadjuvant Trials in Resectable Metastatic Colorectal Cancer

Daniel Krell[1,2] · **Rob Glynne-Jones**[2,3]

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Abstract The treatment of patients with colorectal cancer with colorectal liver metastases remains an exciting challenge for the multidisciplinary team. The role and choice of induction chemotherapy, the timing of surgery in resectable disease and the prioritisation of resection of the primary or the metastases are all still controversial. A true multidisciplinary approach and individualisation of treatment strategies are recommended.

Keywords Colorectal cancer · Neoadjuvant chemotherapy · Biological agents · Colorectal liver metastases · Liver first procedure · Timing of surgery

Introduction

Colorectal cancer (CRC) is a common cancer, which often metastasises to the liver. Approximately 20–30 % of patients will have liver metastases at the time of diagnosis, and subsequently, up to 50 % of patients with CRC will develop colorectal liver metastases (CRLM) [1]. For CRLM, liver resection has become a potentially curative strategy, in which the safety has been improved by the use of preoperative portal vein embolization to enhance the hypertrophy of the future liver remnant, keeping a low central venous pressure to decrease bleeding, and intraoperative ultrasound to define the location of intra-parenchymal tumours and vascular structures. However, only about 20 % of patients present with metastases confined to the liver that are initially resectable [2], and strategies to downsize and downstage the metastases are usually required to facilitate their removal. Successful surgical R0 resection confers a 5-year overall survival (OS) of 35–40 % and a 10-year OS rate of 25 % [3, 4], but further disease progression is likely to occur in 75 % of patients [5], mostly in the liver or lungs, within the 2 years of surgery, raising the question of whether adjuvant therapy should be used in this setting [6]. Several early studies have suggested a benefit from this approach [7–9].

Even with an R1 resection, the effectiveness of current chemotherapy may achieve similar outcomes [10•]. This survival rate after liver resection compares with a 75 % 5-year OS rate in patients with stage III disease following removal of the primary tumour following adjuvant chemotherapy and <10 % in unselected patients with stage IV disease treated with chemotherapy alone [11, 12].

However, the majority of patients with CRLM have a disease which is too advanced to allow initial surgical treatment or are assessed as having borderline resectable lesions. Both technical resectability (and maintaining at least a 30 % future liver remnant) and prognostic aspects (whether resection is in the interest of the patient) should be considered [13], and hence, there is no consensus regarding resectability. ESMO guidelines [14] list both technical and oncological contraindications to hepatic resection in patients with CLRM.

Neoadjuvant chemotherapy (NACT) has a long established role in downstaging initially borderline or unresectable liver metastases [15], but remains controversial in easily resectable tumours/single metastases. Response is a prognostic factor, as tumour progression during neoadjuvant chemotherapy

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✉ Daniel Krell
danielkrell@nhs.net

[1] Royal Free Hospital, Pond Street, London NW3 2QG, UK

[2] Barnet Hospital, Barnet, London, UK

[3] Mount Vernon Centre for Cancer Treatment, London, UK

(NACT) is associated with a worse outcome, even when surgical resection can still be performed with a curative intent.

In colorectal cancer, chemotherapy strategies and drug combinations are usually considered in two separate categories either as 'adjuvant' following resection of the primary—or in contrast as 'advanced/metastatic' (with or without the primary in situ). For metastatic disease, standard chemotherapy agents (5-fluorouracil, capecitabine, oxaliplatin, irinotecan) have been supplemented by targeted therapies directed against the epidermal growth factor receptor (EGFR) (cetuximab, panitumumab) or angiogenesis (bevacizumab, aflibercept, regorafenib). Currently, there is no proven role for the addition of biological agents in the postoperative adjuvant setting.

The treatment of liver metastases lies uneasily between these two settings (adjuvant and advanced/metastatic) and raises specific questions which remain to be answered regarding the optimal chemotherapy schedules, the duration of chemotherapy and the role of biological agents both prior to and following resection. Chemotherapy for CRLM can be administered before (neoadjuvant or induction), after (postoperative adjuvant) or before and after (perioperative) surgical resection. Trials in CRLM have been difficult to perform and generally underpowered because of the paucity of patients randomised.

For easily resectable CRLM, there is no robust evidence in favour of either adjuvant or neoadjuvant systemic chemotherapy in addition to surgery. The EORTC trial (EPOC trial) in patients with resectable liver-limited CRC randomly assigned to treatment with surgery alone or perioperative chemotherapy (neoadjuvant and postoperative) with FOLFOX—infusional fluorouracil, leucovorin and oxaliplatin. Eligible patients had a relatively favourable prognosis as only a single metastasis was present in 51 % of patients, the majority of whom had metachronous metastases. The risk of subsequent relapse after surgery in patients randomly assigned to receive perioperative FOLFOX was reduced by 25 % [16], but improvement in OS was not observed. In contrast, the 'new EPOC' trial reported inferior outcomes for *KRAS* WT patients with resectable and borderline resectable liver metastases who received cetuximab in combination with oxaliplatin-based chemotherapy when compared with chemotherapy alone [17••].

For borderline or unresectable metastatic disease, chemotherapy is started upfront. Response will be observed in about 50 % of patients, but the duration of response is usually short and tumours tend to develop resistance within a few months.

There are also questions regarding the optimal sequence of surgery for primary and liver disease and the role of radiotherapy in rectal cancer. A number of different investigational strategies are tabulated in Table 1.

Uptake of further postoperative adjuvant chemotherapy after liver resection is generally poor. Hence, neoadjuvant chemotherapy (NACT) has significant potential advantages, which include better compliance, compared to chemotherapy given in the adjuvant setting, and offers the possibility of measuring early in vivo response to systemic treatment (see Table 2). For resectable patients, the prime objective of NACT was to provide a time interval before surgery for assessment of the tumour biology, to treat potentially occult disease and to

Table 1 Chemotherapy/biological agent strategies currently being integrated to deliver systemic doses of chemotherapy in the treatment of CRLM

Integrating triple chemotherapy schedules (FOLFOXIRI) into preoperative chemotherapy schedules
Integrating additional targeted agents into preoperative chemotherapy schedules
Integrating induction chemo (IC) *prior to* or following preoperative CRT or short-course preoperative radiotherapy SCPRT in CRLM from rectal cancer
Integrating consolidation chemo (CC) with systemic doses *after* resection with or without the original targeted agents
Examining what is the optimal duration of the induction chemotherapy
Examining what is the optimal duration of the postoperative chemotherapy
Combinations of the above

Table 2 Advantages and disadvantages of preoperative/neoadjuvant chemotherapy in CRLM

Advantages	Disadvantages
Allows assessment of chemotherapy responsiveness	Some patients will have no response and a small number will even progress (Of these, 50 % progress outside the liver. So probably would not have benefitted from hepatic resection anyway)
Allows tumour shrinkage to achieve R0 resection	May increase surgical morbidity and increase mortality if continued too long
Allows tumour shrinkage to remove less normal liver	Tumours can completely disappear, i.e. complete radiological response, and not be found at surgery
(NACT/perioperative chemotherapy) can reduce the risk of relapse	Chemotherapy-associated liver injury remains a concern if a long duration of chemotherapy is required and is associated with a poorer short-term prognosis
NACT obviates the need for radical surgery in those patients with aggressive biology who progress rapidly	Patients who fail to respond to NACT fare badly
	Intensive chemotherapy regimens (FOLFOXIRI) may be less effective in patients who have received prior adjuvant chemotherapy

avoid surgery in those patients with rapidly progressive disease as a result of primary resistance to chemotherapy. A second objective in these resectable patients was to achieve cytoreduction both to limit the extent of liver resection and potentially postoperative morbidity and to facilitate a margin-free R0 liver resection.

Currently, systemic chemotherapy in combination with liver resection for CRLM is accepted as the standard of care: the National Comprehensive Cancer Network (NCCN) [18] recommends 6 months of perioperative systemic chemotherapy, and in the UK, the National Institute for Health and Care Excellence (NICE) [19] recommends considering the use of systemic chemotherapy prior to liver resection. In borderline or unresectable cases, standard chemotherapy agents in combination with biological agents appear to have increased the resection rate of these patients. ESMO guidelines [14] recommend that patients with clearly resectable disease and favourable prognostic criteria can be treated with upfront resection and perioperative treatment may not be necessary. In contrast, in patients with technically resectable disease where the prognosis is unclear or unfavourable, perioperative combination chemotherapy is recommended. ESMO guidelines also acknowledge that in resected patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy. Hence, there is consensus that combination chemotherapy should be part of such neoadjuvant regimens—usually oxaliplatin and a fluoropyrimidine, but there is no consensus regarding the timing, nor the selection of targeted therapy in this regard—nor whether the targeted therapy, if administered prior to resection, should continue following successful resection.

The aim of this review was to examine past and ongoing trials employing systemic (rather than intra-hepatic) chemotherapy strategies—neoadjuvant, perioperative or adjuvant—for resectable or borderline resectable liver metastases.

Methods

A systematic review of available literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. The review criteria included randomised phase II or phase III controlled trials reporting on the outcomes of overall survival (OS), progression-free survival (PFS)/disease-free survival (DFS) and grade 3–4 complications in patients with resectable CRLM. Potentially relevant trials were selected by a search using Medical Subject Headings (MeSH) terms and specific text-words terms: colorectal cancer liver metastases, neoadjuvant therapy, neoadjuvant chemotherapy, adjuvant chemotherapy and perioperative chemotherapy. Relevant studies were identified by reviewing the titles and abstracts.

Current trials were identified using ClinicalTrials.gov to include currently recruiting and recently terminated trials investigating treatments for metastatic colorectal cancer in the neoadjuvant and adjuvant setting. The following terms were used as in the search criteria: neoadjuvant, adjuvant, metastatic, colorectal and cancer.

Results

We found only 4 randomised phase III controlled trials with a total of 1098 patients and 14 ongoing randomised phase II and prospective phase III or IV trials. The main details of the published randomised trials are tabulated in Table 1.

Ongoing or Planned Trials

1. CHARISMA: Neo-adjuvant chemotherapy followed by surgery versus surgery *a*lone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial

This multicentre phase III randomised control trial aims to evaluate the impact of neoadjuvant chemotherapy in high-risk patients (Fong's clinical risk score 3–5) with resectable colorectal liver metastases, without extrahepatic disease. Such high-risk patients will be randomised to receive surgery alone versus neoadjuvant oxaliplatin-based chemotherapy prior to surgery. The primary study endpoint is OS. Secondary endpoints are progression-free survival (PFS), quality of life, morbidity of resection, treatment response on neoadjuvant chemotherapy and whether CEA levels can predict treatment response.

2. NCT02510378—Short Course Radiotherapy Combined With Chemotherapy in Stage IV Rectal Cancer With Resectable Liver Metastases

In this phase II trial, patients with rectal cancer and resectable liver metastases are treated neoadjuvantly with short-course radiotherapy 25 Gy in five fractions to the pelvis followed by at least four cycles of consolidation XELOX chemotherapy. Patients will be evaluated after neoadjuvant therapy and those with resectable rectal cancer and liver disease will undergo surgery. Those patients with unresectable lesions will receive chemotherapy. The primary outcome measure is R0 resection rate. The secondary endpoint is radiotherapy toxicity rate.

3. NCT01923987—Short Course Radiotherapy and Biochemotherapy With Delayed Surgery for Rectal Cancer With Synchronous Distant Metastasis

Primary rectal cancer presenting with synchronous metastastatic disease is often a locally advanced disease and needs downsizing before surgery. In such patients, it is reported that pelvic recurrence rates and distant metastasis rates outside the liver are 30–35 and 60 %, respectively. Therefore, combined treatment with radiotherapy and chemotherapy is used. However, the sequence of treatment modalities is not yet definitely established and preoperative chemoradiotherapy and surgical resection is accepted as an option of treatment. Conventional long-course chemoradiotherapy delays administration of full-dose chemotherapy, and metastatic lesions could progress during chemoradiotherapy. In this multicentre phase II study, the efficacy of short-course radiotherapy followed by full-dose chemotherapy with delayed surgical resection of the primary tumour and metastases was investigated. The primary outcome measure is R0 resection rate of primary and metastatic lesions. Secondary endpoints include OS and PFS rates, tumour regression grade and toxicity.

4. NCT01722903—Detection of CTCs in Patients Undergoing Surgery for Stage IV Colorectal Cancer

CTCs are believed to cause metastasis and may provide a non-invasive alternative to organ biopsies for the detection, characterisation and monitoring of solid cancers. CTC numbers have been shown to be a strong predictor of progression-free survival and overall survival for mCRC patients. The CellSearch system is currently the only FDA-approved test for the evaluation of CTC numbers in metastatic colorectal cancer. In this protocol, the CellSearch system will be compared to a new technology, called the Flexible Micro Spring Array (FMSA) device.

In this prospective observational study, CTCs will be harvested from patients undergoing liver or lung metastatectomy for colorectal cancer. The primary outcome measure will be to ascertain the quantity of CTCs isolated during liver and/or lung metastatectomy. The secondary outcome measure will be 3-year overall survival rate.

5. NCT00630045—Phase 3 Study of Surgery Combined With Neoadjuvant Chemotherapy(XELOX) in Colorectal Cancer With Resectable Liver Metastasis

In this randomised phase III study, patients with colorectal cancer and resectable liver metastases patients were randomised to receive two to three cycles of neoadjuvant Xelox chemotherapy versus no neoadjuvant chemotherapy prior to resection of liver metastases. The primary aim of the study is to establish if neoadjuvant chemotherapy improves 3-year disease-free survival rate in this setting. Secondary endpoints include R0 resection rate and 5-year overall survival rate.

6. NCT01505166—Randomized Phase II Adjuvant Chemotherapy ± FANG™ in Colorectal Carcinoma With Liver Metastases (FANG-CLM)

In this randomised phase II study, patients with colorectal carcinoma with either synchronous or metachronous liver metastases will receive either sandwich/adjuvant chemotherapy and an intradermal autologous Vigil™ cancer vaccine or sandwich/adjuvant chemotherapy and placebo following resection ± ablation of primary tumour and liver metastases with curative intent. The primary aim of the study is to investigate if overall survival rate is increased with the addition of the Vigil cancer vaccine to chemotherapy in patients with colorectal cancer and liver metastases being treated with curative intent.

7. NCT00070265—Neoadjuvant and Adjuvant Capecitabine and Oxaliplatin in Treating Patients With Resectable Liver Metastases Secondary to Colorectal Cancer

This phase II trial is studying the efficacy of capecitabine and oxaliplatin when given in combination before and after surgery in patients with resectable CRLMs. The primary outcome measure is rate of R0 resection. Secondary outcome measures include response rate, improvement in survival associated with downstaging based on metastatic colorectal prognostic score, disease-free and overall survival.

8. NCT00264979—Evaluation of 2 Resection Strategies of Synchronous Colorectal Cancer Metastases (METASYNC)

The surgical strategy for the treatment of synchronous colorectal cancer liver metastases has still not been defined. The purpose of this study is to compare two treatment strategies for liver resection in this setting. In the first arm, liver metastases are resected at the same time as the primary resection. In the second arm, liver metastases are resected 12–14 weeks after the primary resection. The primary endpoint is the rate of patients with at least one postoperative severe complication within 60 days after each surgery. Secondary endpoints include the rate of recurrence and survival.

9. NCT01269229—A Trial of Neoadjuvant FOLFOX6 With Short Course Radiotherapy in Patients With Unresectable Rectal Cancer and Liver Metastasis

The purpose of this phase II study is to investigate if neoadjuvant FOLFOX chemotherapy in combination with SCRT improves resection rates in patients with unresectable rectal cancer and liver metastases. The primary endpoint is R0 resection of rectal and liver lesions.

10. NCT01762813—ACROBATICC Study-Assessment of clinically related outcomes and biomarker analysis for translational integration in colorectal cancer: study protocol for a population-based, consecutive cohort of surgically treated colorectal cancers and resected colorectal liver metastasis

This is an observational study exploring prognostic and predictive biomarkers in a population-based, consecutive cohort of patients with surgically resected colorectal cancer and CRLMs. Long-term outcomes assessed will be cancer-specific survival, recurrence-free survival and overall survival at 5 years. The study incorporates the analysis of circulating tumour cells and novel biomarkers such as immune cells and microRNAs. The project aims to generate results that can help better discern prognostic groups in stage II/III cancers, explore prognostic and predictive biomarkers and help detail the biology of CRLM for better patient selection and tailored treatment.

11. NCT01564810—Cetuximab in combination with chemotherapy for the treatment of metastatic colorectal cancer

This phase IV study aims to assess the effect of cetuximab in combination with chemotherapy in the treatment of unresectable metastatic CRC. Patients are eligible for inclusion if they are KRAS wild type with synchronous liver-confined metastases deemed non-resectable and if their primary tumour has been resected. Patients are randomly assigned to chemotherapy plus cetuximab or chemotherapy alone. The primary endpoint is the conversion rate to radical resection for liver metastases. Secondary endpoints include PFS, OS and tumour response rate.

12. NCT01632722—A Randomized Phase II Study of Perioperative Chemotherapy Plus Bevacizumab Versus Postoperative Chemotherapy Plus Bevacizumab in Patients With Upfront Resectable Hepatic Colrectal Metastases (APPROACH)

This phase II study aims to compare the effectiveness of combination chemotherapy plus bevacizumab in the perioperative versus postoperative setting in patients with resectable CRLM. The primary endpoint is 2-year recurrence-free survival.

13. NCT01972490—Study of Avastin in combination with chemotherapy for the first treatment of metastatic CRC

This phase IV study of patients with CRC with synchronous unresectable liver metastases aims to assess if the addition of avastin to chemotherapy could improve the resection rate of liver metastases in patients with RAS mutant-type, unresectable colorectal liver-limited metastases compared with chemotherapy alone. The primary endpoint is the rate of patients converted to recection for liver metastases. Secondary endpoints include PFS, OS and response rates.

14. NCT02162563—Treatment Strategies in Colorectal Cancer Patients With Initially Unresectable Liver-only Metastases: CAIRO5 a Randomised Phase 3 Study of the Dutch Colorectal Cancer Group (DCCG)

In this study, CRC patients with initially unresectable liver-only metastases will be tested for RAS and BRAF tumour mutation status. Patients with RAS mutant tumours will be randomised between doublet chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab (schedule 1) and triple chemotherapy (FOLFOXIRI) plus bevacizumab (schedule 2). Patients with RAS wild-type tumours will be randomised between doublet chemotherapy (FOLFOX or FOLFIRI) plus either bevacizumab (schedule 1) or panitumumab (schedule 3). The primary endpoint is PFS. Secondary endpoints include R0/1 resection rates, mOS, response rate, toxicity, pathological complete response rate and postoperative morbidity.

Discussion

Curative liver resection is a well-established therapy for CRLM in both the synchronous and metachronous settings and can impact on OS. It has been shown that resection rates correlate with response rates to chemotherapy and are higher for selected rather than unselected patients with CRLM [21]. Outcomes and the risk of recurrence after resection depend on factors such as the site of the primary (rectum or colon), the number and size of the liver metastases [22], the time from primary tumour treatment to hepatic metastases, the involvement of lymph nodes, the preoperative carcinoembryonic antigen level, any extrahepatic spread and a non-radical resection [23, 24], which probably reflects the innate tumour biology rather than poor surgical technique [25]. Hence, does response to chemotherapy simply identify patients who have a pre-determined favourable prognosis? Or can the response modify the course of the disease? Earlier trials were more selective with fewer liver metastases and hence better prognosis with less intensive and less rigorous follow-up.

For patients with widespread metastatic colorectal cancer, doublet chemotherapy regimens incorporating 5FU in combination with either irinotecan or oxaliplatin offer higher response rates than 5FU alone [26, 27]. Response can be even higher if biological agents are added. For this reason, vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) blockers, when combined with cytotoxic chemotherapy agents, are considered currently the

standard of care for those patients with appropriate molecular markers [14, 18]. But these biological agents have not offered added benefit in the adjuvant setting following resection of the primary colon cancer when combined with standard adjuvant chemotherapy schedules such as FOLFOX or 5FU/capecitabine. Nevertheless, retrospective subset analysis from first-line trials of cetuximab and panitumumab in combination with chemotherapy has drawn the conclusion that as a consequence of the responses, improved curative resection rates have been reported compared to chemotherapy alone [28, 29].

Some retrospective subset analyses from trials of bevacizumab in combination with chemotherapy have also reported improved curative resection rates compared to chemotherapy alone [30]. Intriguingly, bevacizumab added to standard cytotoxic chemotherapy may also be associated with higher complete pathological response rates in patients undergoing resection of CRLM [31] and can be safely administered without increasing postsurgical complications [32–34].

The use of triple chemotherapy regimens incorporating 5FU, oxaliplatin and irinotecan (FOLFOXIRI) also increases response rates, and retrospective analyses of prospective data suggest R0 resections may also be increased with triplet chemotherapy compared to doublet regimens [35–37]. In the METHEP randomised phase II trial, FOLFIRINOX showed high response rate and the best conversion rate in CRLM compared with standard chemotherapy [38•].

The addition of biological agents to FOLFOXIRI has also been investigated, leading to high response rates from panitumumab [39]. The combination of bevacizumab with FOLFOXIRI chemotherapy also significantly improved response rates in the TRIBE study compared to bevacizumab plus FOLFIRI (65 versus 53 %, respectively); however, the rate of successful secondary resections of liver and other metastases was similar in both arms [40].

In contrast, quadruple therapy, where both an EGFR inhibitor and a VEGF inhibitor are given in combination with doublet chemotherapy, has also been investigated, but has produced significantly inferior PFS and OS [41, 42].

For colon or rectal cancer, there are no proven differences in indications for chemotherapy or targeted EGFR inhibitors or antiangiogenic drugs [43, 44], although there are ongoing arguments regarding a differential response to biological agents depending on left- or right-sided tumours [45, 46]. The approach for rectal cancer and CRLM has also been complicated by the potential and debated requirement for radiotherapy/chemoradiotherapy.

NACT is a potentially useful therapeutic approach for locally advanced operable, primarily unresectable or borderline resectable cancers of many different primary origins. Although there remains considerable variability in treatment decisions on what qualifies as resectable, improved surgical techniques for liver resection in combination with downsizing CRLM with chemotherapy, interventions to induce liver hypertrophy before resection (portal vein embolization) and the use of locally destructive techniques (radiofrequency ablation) reduce the tumour and allow an increase of normal liver volume thereby increasing the number of patients who are candidates for liver resection. In addition, the cytotoxic activity of chemotherapy treatment can be supplemented with various interventional procedures as an addition or alternative, which include transarterial chemoembolization (TACE) (using standard chemotherapy or irinotecan-loaded drug-eluting beads), transarterial embolization (TAE), microwave ablation (MWA), radiofrequency ablation (RFA), cryotherapy and selective internal radiation therapy (SIRT).

Recent trials in metastatic disease have shown patients with Ras-wild-type tumours survive 30–36 months [47–49] with chemotherapy and biological agents. Yet, outcomes in CRLM depend on performance status, age and sex as well as the RAS, BRAF and MSI profiles. In addition, left- and right-sided tumours may exhibit innately different outcomes and different responses to targeted agents [45, 46, 50].

NACT in patients with resectable liver metastases may destroy micrometastatic disease and hence reduce the risk of subsequent liver and other distant failure. Several authors have reviewed the evidence [51–54]. The use of neoadjuvant chemotherapy has significant potential advantages including better compliance, compared to chemotherapy given in the adjuvant setting offering the possibility of measuring early in vivo response to systemic treatment. The EORTC trial (EPOC trial) in patients with resectable liver-limited CRC randomly assigned to treatment with surgery alone or perioperative chemotherapy (neoadjuvant and postoperative) with FOLFOX—infusional fluorouracil, leucovorin and oxaliplatin. The risk of subsequent relapse after surgery in patients randomly assigned to receive perioperative FOLFOX was reduced by 25 % [16], but improvement in OS has not been observed. However, there is little evidence that NACT and the chance of non-response can actually lead to non-resectable metastases [16, 55]. Postoperative complications were significantly more frequent after NACT in 40/159 (25 %) compared with surgery alone in 27/170 (16 %), but these problems did not impact on PFS [16]. However, these complications may depend both on the number of cycles of chemotherapy [56], the intensity of the chemotherapy regimen and the interval left between the end of chemotherapy and surgery. However, more ambitious resections such as major hepatectomy, defined as resection of four or more liver segments [57] and extended hemihepatectomy (i.e. right or left trisectionectomy), are now routinely performed. Yet, the incidence of complications correlates with the extent of liver surgery and the duration of chemotherapy [58–61]. Long-term intensive chemotherapy is therefore a two-edged sword for the surgeon.

Hence, for easily resectable colorectal liver metastases (CRLM), there is no robust evidence in favour of either adjuvant or neoadjuvant systemic chemotherapy in addition to

surgery. Biological agents, such as vascular endothelial growth factor inhibitors and epidermal growth factor receptor blockers, when combined with cytotoxic chemotherapy agents are considered currently the standard of care for those patients with appropriate molecular markers in the treatment of metastatic colorectal cancer (CRC) [14, 18], but have not shown benefit in the adjuvant setting following resection in primary colon cancer when combined with standard adjuvant chemotherapy schedules such as FOLFOX or 5FU/capecitabine. However, many studies are underpowered to show a significant difference in overall survival. Although adjuvant chemotherapy appears of benefit in the adjuvant setting in stage III colon cancer [62–64], the MOSAIC trial [63] required more than 2000 patients with colon cancer to show an improvement in both DFS and OS (and most evident in high-risk pN2 patients).

Initial tumour response to chemotherapy is associated with improved disease-free survival after resection of CRLM, but for many patients, this RECIST response is transient and further disease progression occurs rapidly after stopping chemotherapy. In the randomised trials specifically investigating treatment-free intervals versus maintenance chemotherapy (COIN, AIO 0207 and CAIRO3), the median time from the end of chemotherapy treatment to progression without chemotherapy was 3.0–4.1 months [65–67]. This rebound effect may be more pronounced with the use of combined cytotoxic and biological agents to downstage the CRLM [17••]. Ultimately, considerable time is required for notification of completion of chemotherapy, any MDT discussion, clinic appointments and assessment and preparation for surgery. Some retrospective studies have shown the rate of growth of CRLM in this interval following chemotherapy is rapid (2.3 % per week), with a calculated tumour doubling time (DT) of 46 days [68]—as opposed to a DT of untreated CRLM between 63 and 112 days [69, 70]. It remains uncertain whether this rapid tumour regrowth can influence disease-free survival in resectable CRLM after resection or whether outcomes are simply determined by the initial response to chemotherapy.

Decrease in size of these lesions may indicate a distant effect in terms of dealing with micrometastatic disease, whereas the rebound growth of macroscopic hepatic lesions after stopping chemotherapy may not be associated with the recovery of these smaller peripheral micrometastases. However, if chemotherapy is used to downsize CRLM of borderline resectability, this rapid rebound after stopping chemotherapy may lead to the lesions becoming unresectable again, and liver resection at a sooner time point may be desirable in this group. Retrospective analyses suggest that selection of patients by clinical prognostic characteristics such as clinical risk score (CRS) (Fong score) may define a patient population expected to benefit more or less from chemotherapy [71]. Many previous studies of perioperative chemotherapy combined with liver surgery often excluded patients with a high CRS—who would have the highest risk of recurrence [72]. For instance, the EORTC trial included 51 % of patients with only a single liver metastasis, and >25 % of patients had only two metastases. The Liver Met Survey database examined patients with solitary, metachronous, primarily resectable metastases. These patients have more favourable tumour biology and the data suggest they do not benefit from perioperative chemotherapy [73]. Other investigators also report that chemotherapy is unlikely to impact on OS in patients with clearly resectable lesions limited to the liver [74]. Hence, patients with a relatively low risk of recurrence may not benefit so much from such

Table 3 Randomised trials of adjuvant treatment for patients with CRLM

Trial	Time period of trial	Strategy	No. of patients	Treatment arms	Median DFS (95 % CI) in months
Portier 2006 [76] FFCD ACHBTH AURC 9002	1991–2001	Post-op adjuvant	171	Control versus FUFA	17.6 (12.3–22.9) versus 24.4 (17.3–31.5) HR 0.66 (0.46–0.96) $p = 0.03$
Ychou 2009 [77]	2001–2006	Post-op adjuvant	306	FUFA versus FOLFIRI	21.6 (14.6–30.4) versus 24.7 (18.7–38.9) HR 0.89 (0.66–1.19) $p = 0.44$
Nordlinger 2013 [16] EPOC/ EORTC 40983	2000–2004	Perioperative	364	Surgery alone versus perioperative FOLFOX	12.5 (9.7–17.7) versus 20.0 (15.9–27.6) HR 0.81 (0.64–1.02) $p = 0.07$
Primrose 2014 [17••] New EPOC	2007–2012	Perioperative	257	Perioperative chemotherapy versus perioperative chemotherapy plus cetuximab (multiple regimens allowed)	20.5 (16.8–26.7) versus 14.1 (11.8–15.9) HR 1.48 (1.04–2.12) $p = 0.03$

CI confidence interval, *DFS* disease-free survival, *NA* not applicable, *NR* not reported, *OS* overall survival

chemotherapy, blurring the benefits to more high-risk patients. Many studies do not adequately stratify into risk groups for the different arms.

Systemic chemotherapy before and after the study period may also influence the end points either positively or negatively. For instance, some studies of chemotherapy in advanced disease (even though the study did not aim to convert patients with liver metastases into candidates for surgical resection) suggest prior adjuvant chemotherapy may be a disadvantage for an intensified upfront chemotherapy regimen [75]. In addition, the incremental benefit of further chemotherapy following NACT and liver resection remains unproven, but needs to be controlled for (Table 3).

Conclusions

Liver resection can be curative for CRLM, but can also lead to significant perioperative morbidity and mortality. The rationale for NACT in resectable CRLM derives partly from large adjuvant colon studies, which randomised several thousand patients. In contrast, most perioperative chemotherapy studies in CRLM randomised only a few hundred patients. With the lack of evidence of benefit for any targeted antibody in adjuvant treatment in stage III colon cancer and in the perioperative treatment of resectable metastatic disease, FOLFOX remains the standard of care for patients with resectable CRLM, although the benefits for one to three easily resectable metastases are probably small. The combination of FOLFOXIRI ± bevacizumab should be further investigated in more trials or borderline or not optimally resectable CRLM.

Yet, it remains unclear whether perioperative FOLFOX provides significant additional benefit in terms of either DFS or OS when compared to single-agent 5FU-based chemotherapy in the adjuvant treatment in patients with resectable CRLM. The appropriate trials have never been performed in the context of CRLM.

It is also unclear whether there should be different strategies for those with a solitary metastasis, compared with a few (1–3) but resectable metastases and finally those with borderline resectable metastases (some shrinkage required to allow sufficient liver volumes). Risk assessments in terms of Fong score are rarely applied, and factors such as performance status, age and sex as well as the RAS, BRAF and MSI profiles are not used as stratification factors. In addition, left- and right-sided primary tumours may exhibit innately different outcomes and different responses to targeted agents. One of the major challenges for the future is the determination of predictive markers of response or resistance to induction treatments. A comprehensive molecular and genetic analysis of specimens from all the phase III clinical trials to show any biological differences within subsites of right versus left colon is now required.

Also, no trial has been performed to determine the optimal duration of neoadjuvant therapy when resectability is achieved. Novel destructive, interventional and surgical techniques in combination with downstaging chemotherapy can improve resectability of borderline/unresectable CRLM but demand a close multidisciplinary cooperation. Open questions remain regarding the selection of patients who benefit from resection or local treatment, the optimal sequencing of the different modalities and the integration and duration of more effective treatments with higher response rates to treat remaining micrometastases.

However, the lessons learnt from the available phase III trials examining the addition of perioperative and adjuvant chemotherapy are that small underpowered trials, with heterogeneous inclusion criteria, performed with variable quality of surgery are likely to fail to produce robust results which can be translated into everyday practice.

There is a need for larger simple clinical trials. Larger trials with selection and stratification according to Fong scores and other risk factors should investigate new combinations of cytotoxic drugs and targeted agents in both the adjuvant and perioperative setting against both single-agent 5FU and FOLFOX.

Compliance with Ethical Standards

Conflict of Interest Daniel Krell has served on an advisory board for Servier.

Rob Glynne-Jones has received speaker's honoraria from Merck and Servier; has served on advisory boards for Eli Lilly & Co., Roche, Home Nutrition, Servier, Eisai and Amgen; and has participated in ESMO's preceptorship program.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Leporrier J, Maurel J, Chiche L, et al. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg. 2006;93:465–74.
2. Huiskens J, van Gulik TM, van Lienden KP, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). BMC Cancer. 2015;15:365.

3. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239:818–25.
4. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg. 2007;205:676–83.
5. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996;77(7):1254–62.
6. Sharma S, Camci C, Jabbour N. Management of hepatic metastasis from colorectal cancers: an update. J Hepatobiliary Pancreat Surg. 2008;15:570–80.
7. Lygidakis N, Ziras N, Parissis J. Resection versus resection combined with adjuvant pre- and post-operative chemotherapy—immunotherapy for metastatic colorectal liver cancer. A new look at an old problem. Hepatogastroenterology. 1995;42:155–61.
8. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study. J Clin Oncol. 2002;20:1499–505.
9. Parks R, Gonen M, Kemeny N, Jarnagin W, D'Angelica M, DeMatteo R, et al. Adjuvant chemotherapy improves survival after resection of hepatic colorectal metastases: analysis of data from two continents. J Am Coll Surg. 2007;204:753–61.
10.• Laurent C, Adam JP, Denost Q, Smith D, Saric J, Chiche L. Significance of R1 resection for advanced colorectal liver metastases in the era of modern effective chemotherapy. World J Surg. 2016;40(5):1191–9. **This retrospective study of 466 patients treated between 1999 and 2010 in a major centre of expertise suggests that with modern combination chemotherapy, R1 resection is less crucial in responders to neoadjuvant chemotherapy. Additional postoperative chemotherapy may also protect from recurrences whatever the margin resection status**.
11. Sanoff HK, Sargent DJ, Campbell ME, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol. 2008;26:5721–7.
12. Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307(13):1383–93.
13. Adam R, De Gramont A, Figueras J, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist. 2012;17:1225–39.
14. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422.
15. Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996;224:509–20.
16. Nordlinger B, Sorbye H, Glimelius B, EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007–16.
17.•• Primrose J, Falk S, Finch-Jones M, Valle J, Sherlock D, Hornbuckle J, et al. A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: the new EPOC study. Lancet Oncol. 2014;15(6):601–11. **This randomised phase III trial has caused huge controversy (see J Clin Oncol correspondence Nordlinger et al 2015).The study suggests that the addition of cetuximab to chemotherapy in resectable (but multiple) CRLM is associated with a worse outcome. Criticisms have focussed on the changing eligibility criteria, multiple options for chemotherapy and poor quality of the surgery**.
18. National Clinical Practice Guidelines in Oncology (NCCN Guidelines): Rectal Cancer Version 2.2016 www.ncrn.org. (last accessed 15/06/2016)
19. NICE. Colorectal cancer: The diagnosis and management of colorectal cancer. Available from: https://www.nice.org.uk/guidance/cg131/resources/guidance-colorectal-cancer-pdf.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
21. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol. 2005;16:1311–9.
22. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol. 2014;25:1018–25.
23. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247:125–35.
24. Jang KU, Kim CW, Kim KH, Lim SB, Yu CS, Kim TW, et al. Prognostic factors in terms of the number of metastatic nodules in patients with colorectal cancer liver metastases. Ann Coloproctol. 2016;32:92–100.
25. Margonis GA, Sasaki K, Kim Y, Samaha M, Buettner S, Amini N, et al. Tumor biology rather than surgical technique dictates prognosis in colorectal cancer liver metastases. J Gastrointest Surg. 2016;6 [Epub ahead of print].
26. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938–47.
27. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905–14.
28. Douillard J, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28:4697–705.
29. Van Cutsem E, Kohne C, Lang I, Folprecht G, Nowacki M, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29:2011–9.
30. Okines A, Puerto O, Cunningham D, Chau I, Van Cutsem E, Saltz L, et al. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. Br J Cancer. 2009;101:1033–8.
31. Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer. 2007;110(12):2761–7.
32. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with

potentially curable metastatic colorectal cancer. J Clin Oncol. 2008;26(11):1830–5.
33. Bertolini F, Malavasi N, Scarabelli L, et al. FOLFOX6 and bevacizumab in non-optimally resectable liver metastases from colorectal cancer. Br J Cancer. 2011;104(7):1079–84.
34. Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol. 2011;22(9):2042–8.
35. Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology. Br J Cancer. 2006;94:798–805.
36. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25:1670–6.
37. Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst. 2011;103:21–30.
38.• Ychou M, Rivoire M, Thezenas S, Quenet F, Delpero JR, Rebischung C, et al. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. Ann Surg Oncol. 2013;20(13):4289–97. **In this phase II study in patients with initially unresectable or not optimally resectable CRLM, FOLFOXIRI showed a conversion rate to resectability of 67 %, and was much more effective than the standard conventional chemotherapy (FOLFIRI/FOLFOX4).On this basis the randomised phase II METHEP-2 confirmed triplet chemotherapy, in association with a targeted therapy, showed a higher rate of R0/R1 resections than standard (FOLFIRI or FOLFOX4) combined with the same targeted therapy, but with a statistically significant difference in terms of OS**.
39. Bendell JC, Zakari A, Peyton JD, et al. A phase II study of FOLFOXIRI plus panitumumab followed by evaluation for resection in patients with metastatic KRAS wild-type colorectal cancer with liver metastases only. Oncologist. 2016;21(3):279–80. doi:10.1634/theoncologist.2015-0439.
40. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015;16(13):1306–15.
41. Hecht J, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672–80.
42. Tol J, Koopman M, Cats A, Rodenburg C, Creemers G, Schrama J, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–72.
43. Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll H, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer. 2015;14(1):1–10.
44. Fakih M. Metastatic colorectal cancer: current state and future directions. J Clin Oncol. 2015;33:1809–24.
45. Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst. 2015;107(3). doi:10.1093/jnci/dju427.
46. Wang F, Bai L, Liu TS, Yu YY, He MM, Liu KY, et al. Right-sided colon cancer and left-sided colorectal cancers respond differently to cetuximab. Chin J Cancer. 2015;34(9):384–93.
47. Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol. 2014;32:5s (suppl; abstract LBA3).
48. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1065–75.
49. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32:2240–7.
50. Venook AP, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34:suppl; abstract 3504.
51. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94:982–99.
52. de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250:440–8.
53. Spelt L, Andersson B, Nilsson J, Andersson R. Prognostic models for outcome following liver resection for colorectal cancer metastases: a systematic review. Eur J Surg Oncol. 2012;38:16–24.
54. Nigri G, Petrucciani N, Ferla F, et al. Neoadjuvant chemotherapy for resectable colorectal liver metastases: what is the evidence? Results of a systematic review of comparative studies. Surg – J R Coll Surg Edinb Irel. 2015;13:83–90.
55. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg. 2004;240(6):1052–61.
56. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006;243(1):1–7.
57. Reddy SK, Barbas AS, Turley RS, et al. A standard definition of major hepatectomy: resection of four or more liver segments. HPB (Oxford). 2011;13:494–502.
58. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006;24:2065–72.
59. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg. 2007;94:274–86.
60. Grat M, Hoówko W, Lewandowski Z, et al. Early post-operative prediction of morbidity and mortality after a major liver resection for colorectal metastases. HPB (Oxford). 2013;15:352–8.
61. Choti MA, Thomas M, Wong SL, et al. Surgical resection preferences and perceptions among medical oncologists treating liver metastases from colorectal cancer. Ann Surg Oncol. 2016;23(2):375–81.
62. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant

chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198–204.
63. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–16.
64. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29(11):1465–71.
65. Adams RA, Meade AM, Seymour MT, MRC COIN Trial Investigators, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet Oncol. 2011;12:642–53.
66. Hegewisch-Becker S, Graeven U, Lerchenmüller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol. 2015;16:1355–69.
67. Simkens LHJ, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet. 2015;385:1843–52.
68. Finlay IG, Meek D, Brunton F, McCardle CS. Growth rate of hepatic metastases in colorectal cancer. Br J Surg. 1989;76:652.
69. Kito A, Tanaka K, Fujimaki H, Nakazawa M, Togo S, Minami M. Tumor doubling time and local immune response to hepatic metastases from colorectal cancer. J Surg Oncol. 2007;96:525–33.
70. Lim E, Wiggans MG, Shahtahmassebi G, et al. Rebound growth of hepatic colorectal metastases after neo-adjuvant chemotherapy: effect on survival after resection. HPB (Oxford). 2016;18(7):586–92.
71. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18. discussion 318-21.
72. Adam R, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg. 2010;252(5):774–87.
73. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575–80.
74. Lehmann K, Rickenbacher A, Weber A, Pestalozzi BC, Clavien PA. Chemotherapy before liver resection of colorectal metastases: friend or foe? Ann Surg. 2012;255(2):237–47.
75. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371(17):1609–18.
76. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol. 2006;24:4976–82.
77. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009;20(12):1964–70.