Abstract
Systemic therapy for colorectal cancer liver metastases (CRLM) has undergone significant development in the past 15 years. Therapy regimens consisting of combinations of cytotoxic chemotherapeutic agents have demonstrated greater efficacy and contributed to a significant survival improvement. As the majority of patients who undergo resection for liver-only CRLM are at risk of disease recurrence and cancer-related death, combining resection with systemic therapy appears sensible. However, trial-based evidence is sparse to support this concept. Peri-operative FOLFOX has demonstrated a progression-free survival benefit in a single Phase III trial; the safety of chemotherapy and subsequent operations was acceptable and only a few patients showed initial progression. Chemotherapy-associated liver injury (CALI), including sinusoidal obstruction syndrome and steatohepatitis, has been observed after cytotoxic therapy, and should have implications for chemotherapy plans prior to hepatectomy. In general, pre-operative chemotherapy should not extend beyond 3 months. For patients with unresectable liver-only CRLM, a response to chemotherapy could establish resectability and should be considered an initial treatment goal. In patients with unresectable CRLM, oxaliplatin- or irinotecan-containing combinations represent the standard options, although single-agent choices may be appropriate for individual patients. The addition of bevacizumab carries the potential for a greater response and possibly for reduced CALI risks. In tumours without K-ras mutations, anti-epidermal growth factor receptor (EGFR) agents are also reasonable choices for a greater response and improved survival outcomes. It is crucial that all systemic CRLM treatment decisions include proper definitions of treatment goals and endpoints, and are derived based on appropriate multidisciplinary considerations for other potentially applicable local or regional modalities.

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Systemic therapies for resectable disease
Nearly half of the patients with metastatic colorectal cancer (mCRC) present with metastases confined to the liver.1 In this setting, a complete surgical resection of all known disease provides the only chance of a cure and when feasible, should always be considered as part of the integrated multidisciplinary treatment. The aim of combining chemotherapy and surgical treatment of colorectal liver metastases (CRLM) is to reduce cancer relapse that occurs in approximately 70% of patients after resection, and thereby to impart a survival benefit. Before the availability of contemporary chemotherapeutic agents, surgical resection series of CRLM reported overall 5-year survival rates of 30% to 40%. The rationale to improve these survival outcomes after a hepatectomy with additional systemic therapy has now been explored through post-operative and pre- or peri-operative application of chemotherapy.
Postoperative or adjuvant chemotherapy

Systemic 5-fluorouracil (5-FU)-based chemotherapy after resection of CRLM has been widely applied and reported, but only been evaluated in two prospective randomized trials. As both trials had insufficient power, a pooled analysis of these two trials showed that post-operative 5-FU-based chemotherapy was associated with a trend towards improved disease-free survival. The benefit was not statistically significant, as the median progression-free survival (PFS) was 27.9 months in the surgery plus chemotherapy versus 18.8 months in the surgery alone group [hazard ratio (HR): 1.32; 95% confidence interval (CI): 1.0–1.8; \( P = 0.058 \); the median overall survival (OS) was 62 months after chemotherapy compared with 47 months without (HR: 1.32; 95% CI: 0.95–1.82; \( P = 0.095 \)). The use of irinotecan or oxaliplatin as an adjuvant therapy for patients after hepatic resection of CRLM has been studied. No benefit was found over 5-FU-leucovorin (LV) alone for an irinotecan-containing chemotherapy regimen in a Phase III randomized controlled trial. There are no randomized studies comparing oxaliplatin-containing post-operative chemotherapy regimens and 5-FU-LV. However, in the United States, the combination of 5-FU, folinic acid and oxaliplatin (FOLFOX) is a widely used regimen for post-resection treatment. Survival results after adjuvant FOLFOX in single-centre series have been superior to the pre-oxaliplatin era, with a 5-year overall survival (OS) of around 55%. In contrast to the use of FOLFOX, there is no established role for biological-targeted agents in the use of post-operative treatment after CRLM resection.

Adjuvant hepatic arterial infusion therapy has been evaluated in phase II and phase III trials. Different regimens including 5-FU or floxuridine have been tested, and have primarily led to a liver recurrence-free survival (RFS) benefit. Because of a lack of long-term OS benefits, the hepatic arterial infusion approach has not been generally accepted as a standard of care.

Pre- and peri-operative chemotherapy

The potential advantages of pre-operative chemotherapy are: to facilitate resection of a large tumour in the situation of a major response; to assess the tumour responsiveness to the agents used; and to induce a pathological response that has been shown to be a strong predictor of outcome after resection of CRLM. The EORTC 40983 intergroup phase III trial study has compared peri-operative chemotherapy with 5-FU, leucovorin and oxaliplatin with surgery alone in 364 patients with 1 to 4 potentially resectable CRLM. After a median follow-up of 3.9 years, the primary endpoint of PFS at 3 years in eligible patients was increased by 8.1% in the peri-operative chemotherapy + surgery group versus the surgery alone group (36.1% versus 28.1% respectively; \( P = 0.041 \)). In summary, this study showed that peri-operative FOLFOX4 chemotherapy contributed to a significant delay of cancer recurrence, and was compatible with major surgical treatment. Several general underlying characteristics of this trial are noteworthy: first, the absolute benefit in PFS observed with the combination of chemotherapy compared with resection alone (8 to 9%) is within the range of that observed in other positive trials in gastrointestinal oncology. Second, although patients were supposed to have resectable metastases at diagnosis, 17% of patients in each treatment arm could not undergo resection mainly because of more extensive disease than expected at randomization. Inability to resect was considered as an early event for PFS. Third, according to protocol patients in the combined treatment arm underwent resection with a time delay of 4 months compared with the resection-only group. This difference in lead time was addressed by considering that all events between weeks 0 and 20 were set at week 10, which explains the early drop in the PFS curves. Fourth, the results of EORTC 40983 and of the meta-analysis of two trials of post-operative chemotherapy cannot be compared, as the patient populations were different. Ineligible patients, patients with unresected metastases and patients with post-operative complications that delay or prohibit post-operative chemotherapy remain in the analysis of EORTC study 40983, but are excluded from trials evaluating post-operative treatment because randomization takes place after patients have recovered from the operation and a final pathological report is obtained.

Tumour progression of CRLM during chemotherapy has been regarded as a potential disadvantage of pre-operative chemotherapy. In the EORTC Intergroup phase III study 40983, progressive disease was observed in 12 out of 182 (7%) and was in the majority as a result of the appearance of new extra-hepatic lesions; it is likely that these new lesions would have occurred after immediate resection, too, and it can be considered an advantage to discover them before an unnecessary operation. The results of the EORTC 40983 trial also confirm that the use of pre-operative chemotherapy is associated with a slight but significant increase in the risk of post-operative reversible complications. Of note, these complications resulted mainly in a prolongation of the hospital stay, while the mortality rate was not affected.

Some other important principles regarding pre-operative therapy for resectable CRLM have been obtained from outcome evaluations with lower-level evidence. The duration of pre-operative chemotherapy has been shown to correlate with the post-operative complication rate after CRLM resection; more than six pre-operative treatment cycles are thus not recommended for resectable disease. In addition, extensive pre-operative chemotherapy does not improve the pathological response, but increases the risk for post-operative liver insufficiency. There is an interest in combining targeted agents with chemotherapy such as FOLFOX in patients who are candidates for resection of CRLM. This is currently being evaluated in randomized controlled trials, such as in the EORTC trial 40091 evaluating the addition of bevacizumab or panitumumab to FOLFOX (NCT01508000). In contrast to other cancer resections, initial evidence for the pre-operative addition of the vascular endothelial growth factor (VEGF) antibody bevacizumab indicates that pre-operative bevacizumab does not increase the morbidity of a subsequent CRLM resection. In addition, bevacizumab may protect against oxaliplatin-induced liver injury. Interesting preliminary results
with respect to survival outcomes after resection of patients peri-operatively treated with bevacizumab-containing regimens reported a promising 89% 2-year OS.\textsuperscript{21}

Altogether, the use of pre-operative chemotherapy is safe provided careful monitoring of the duration of the treatment.\textsuperscript{16,19–21} In patients with resectable CRLM, a liver resection can be proposed after short-course chemotherapy, i.e. four to six cycles. At the moment, no objective data exist that support the combination of cytotoxic and biological agents for the peri-operative treatment of patients with resectable CRLM. Ongoing and future clinical trials are addressing this question. A formal multidisciplinary evaluation for patients with resectable CRLM is recommended prior to any therapy initiation, so that peri- versus post-operative treatment plans and the exact duration of any pre-operative component can be determined up front. Based on retrospective evidence, pre-operative chemotherapy is generally not recommended for a longer duration than 3 months if a resection can take place at that time point.\textsuperscript{17,18}

Consensus statement

1. For resectable CRLM, peri-operative chemotherapy with resection has shown progression-free benefits compared with resection alone. The use of an oxaliplatin-containing regimen is the reference treatment for this approach.

2. In patients who did not receive pre-operative chemotherapy, post-operative chemotherapy can be administered after resection. While FOLFOX or 5-FU-LV are acceptable choices, evidence does not support FOLFIRI for this approach.

3. Targeted agents can be considered as part of pre-operative therapy regimens for CRLM based on higher response rates and the potential for protection against liver injury in spite of the absence of level I evidence.

Systemic cytotoxic therapies for unresectable disease

The majority of patients with colorectal cancer who develop metastatic disease do not have resectable CRLM. However, in part as a result of advances in systemic therapy, those patients with unresectable CRLM are now living longer than ever before. This section will address approaches to newly diagnosed patients with unresectable CRLM with no prior treatments. Treatment goals in this patient group vary widely, from establishing resectability of liver-only CRLM through to systemic treatment over life-prolonging but non-curative therapy to means of disease-specific symptom-oriented palliation.

Chemotherapy remains the core of mCRC treatment. Infusional fluoropyrimidine schedules have by now been widely embraced. The results of Tournigand et al., indicating that there is no significant difference between FOLFIRI (folinic acid, infusional and bolus 5-FU and irinotecan) and FOLFOX regimens as first-line mCRC therapy when patients are switched to the other regimen upon progression, have been seen elsewhere, although no true non-inferiority study has ever been conducted.\textsuperscript{22,23} However, while there is good evidence that in second-line therapy oxaliplatin should be given together with 5-FU, no information suggests that FOLFIRI after FOLFOX is superior to irinotecan alone.\textsuperscript{24} Therefore, starting with FOLFOX as first-line chemotherapy, the choice of next regimens can be either FOLFIRI or single agent irinotecan. However, if starting with FOLFIRI, then single agent oxaliplatin is not a reasonable second-line regimen.\textsuperscript{24} Regardless of the sequence, it is clear that as more chemotherapy agents have become available and larger numbers of patients have been exposed to all three active agents (5-FU, irinotecan and oxaliplatin), survival has increased, at least for those eligible for clinical trials.\textsuperscript{25}

The newer regimens, FOLFIRI and FOLFOX, have resulted in significantly longer PFS in first-line therapy.\textsuperscript{22,23,26–28} This is particularly important in the use of oxaliplatin with its potential for cumulative neuropathy. To study the means of ameliorating neuropathy and optimizing the use of oxaliplatin, the OPTIMOX trial randomized patients to either FOLFOX7 for six cycles followed by the 5-FU-LV regime without oxaliplatin, and upon progression or after a set time to reintroduce oxaliplatin, versus FOLFOX4 until disease progression;\textsuperscript{28} relevant differences between the regimens are the higher dose of oxaliplatin (130 mg/m\textsuperscript{2}) and the lack of a bolus 5-FU in FOLFOX. This trial showed no differences in the response rate (RR), OS or PFS for the ‘OPTIMOX’ regimen (FOLFOX 7 arm) compared with standard FOLFOX 4.\textsuperscript{28} Neuropathy was less severe in the OPTIMOX arm. Many patients in the OPTIMOX arm never had oxaliplatin re-introduced as suggested by the study; those patients who did, appeared to do better, suggesting that this strategy may have more benefits than simply reducing neuropathy.\textsuperscript{28} Subsequently, a randomized phase II trial, OPTIMOX 2, was conducted comparing the original OPTIMOX regimen with a slightly lower dose of oxaliplatin (100 mg/m\textsuperscript{2}) and 5-FU-LV versus no chemotherapy during the treatment-free interval.\textsuperscript{29} In this study, the primary endpoint of duration of disease control (13.1 versus 9.2 months; $P = 0.046$) and the secondary endpoint of PFS (8.6 versus 6.6 months; $P = 0.0017$) were inferior when all chemotherapy was stopped. OS results suggested that full breaks may be inferior (23.8 versus 19.5 months) but failed to reach statistical significance ($P = 0.42$). Therefore, caution should be taken in stopping all drugs before progression in first-line therapy of mCRC. Regarding treatment breaks from FOLFIRI, one study randomized patients to either continuous FOLFIRI versus 2 months of treatments alternating with 2 months off chemotherapy.\textsuperscript{30} There was no difference in PFS (6.5 versus 6.2 months, $P = $NS) or OS (16.9 versus 17.6 months, $P = $NS) between the two arms, although the frequency of disease evaluation was less than in most mCRC trials.\textsuperscript{30} In a second-line setting, a small randomized trial of stopping irinotecan after 6 months versus continuing irinotecan showed no survival difference, but because of randomization at initiation of second-line irinotecan the majority of patients had progressed prior to the 6-month time point resulting in a very underpowered study.\textsuperscript{31}
Another important question revolves around the need for aggressive therapy at the start. Two randomized trials\(^{32,33}\) suggested that starting with 5-FU-LV (on the MRC FOCUS trial) or with capecitabine (on the CAIRO trial) had a shorter PFS but similar OS compared with starting with combination chemotherapy in first-line therapy. Importantly, survival times on the MRC FOCUS trial were generally lower (range: 13.9–16.7 months on 5 arms) than are obtained on most current phase III trials in mCRC.\(^{32}\) While these data suggest that there is probably a patient population that might benefit from a less aggressive initial approach, it is difficult to recommend starting a good performance status patient with a regimen that will be effective for a shorter duration of time. In stark contrast to CAIRO and FOCUS, the Italian FOLFOXIRI (folinic acid, oxaliplatin and irinotecan) trial randomized patients to this 3-agent regimen versus FOLFIRI.\(^{34}\) FOLFOXIRI patients had a better OS (22.6 versus 16.7 months, \(P = 0.032\)) and PFS (9.8 versus 6.9 months, \(P = 0.0006\)) compared with FOLFIRI, with a tolerable toxicity profile. However, a second trial performed in Greece with a slightly different regimen of FOLFOXIRI compared with FOLFIRI did not demonstrate any difference in OS (21.5 versus 19.5 months) or PFS (8.4 versus 6.9 months).\(^{35}\)

Based on their response to initial chemotherapy, some patients with initially unresectable CRLM may be rendered candidates for resection. As their outcome mirrors that of patients with primarily resectable CRLM, this sub-group of patients should also be considered for operative therapy.\(^{36}\) These considerations are of crucial importance to select the best first-line therapy. Indeed, a linear correlation has been shown between RR and the surgical resection rate underlining the importance of developing increasingly active regimens for this purpose.\(^{37}\) Quality of imaging, completeness of staging, type and duration of induction therapy are all crucial components that influence subsequent resection options and patient outcomes.

**Consensus statement**

1. For unresectable CRLM, it is crucial to establish the overall goal of therapy prior to choosing the regimen: downsizing the tumour for potential resection versus non-curative therapy with prolongation of survival.
2. For downsizing of CRLM, while FOLFOX and FOLFIRI represent two chemotherapy backbones of similar efficacy, there is a possibility that the three-drug regimen FOLFOXIRI may provide a higher likelihood of a response.
3. For non-curative therapy of mCRC, while FOLFOX and FOLFIRI represent two chemotherapy backbones of similar efficacy, there may be some patients for whom a less aggressive, initially single-agent approach is appropriate.
4. Capecitabine plus oxaliplatin represents a reasonable alternative to FOLFOX, but capecitabine plus irinotecan is not an alternative to FOLFIRI. Single-agent capecitabine should not be used after progression on prior 5-FU-containing regimens.

**Molecular targeted therapies**

The combination of 5FU-LV with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) have traditionally represented the two main treatment options for mCRC. The therapeutic algorithm for mCRC has become more complex with the introduction of targeted agents.\(^{38-41}\) While anti-EGFR agents cetuximab and panitumumab have revealed their efficacy in improving the tumour RR, treatment with the anti-VEGF antibody bevacizumab has demonstrated minor shrinkage activity and more consistently delayed tumour progression.\(^{39,40,42}\)

The first targeted agent to show efficacy in a randomized trial for mCRC was bevacizumab, an antibody to VEGF-A. When added to IFL (irinotecan, bolus 5-FU and leucovorin), survival was better with bevacizumab than with the placebo (20.3 versus 15.6 months, respectively, \(P < 0.0001\)).\(^{39}\) Similar but non-significant results for OS were determined for 5-FU-LV + bevacizumab compared with 5-FU-LV alone in a smaller randomized phase II trial (16.6 versus 12.9 months, respectively, \(P = 0.16\)).\(^{43}\) However, as IFL was no longer in widespread use, bevacizumab has largely been given with FOLFOX or FOLFIRI. In combination with second-line FOLFOX, bevacizumab significantly prolonged PFS (7.3 versus 4.7 months, \(P < 0.0001\)) and OS (12.9 versus 10.8 months, \(P = 0.0011\)) compared with FOLFOX alone in E3200;\(^{44}\) however, the HR of 0.83 (95% CI: 0.72–0.95, \(P = 0.0023\)) was not as good when bevacizumab was added to first-line FOLFOX in the N016966 trial.\(^{38}\) FOLFIRI was never tested against FOLFIRI + bevacizumab in a randomized trial, but the OS for FOLFIRI + bevacizumab of 28 months in the BICC-C trial was among the longest seen in a randomized trial in patients with mCRC.\(^{27,45}\)

Observational cohort studies have twice demonstrated a longer survival for patients treated with bevacizumab beyond progression (BBP) after disease progression on bevacizumab-containing first-line therapy, but treatment choices and decision making were not randomized or controlled.\(^{46,47}\) Therefore, they primarily serve as hypothesis-generating data sets for an ongoing trial that compares BBP + chemotherapy to chemotherapy alone in second-line treatment of mCRC. In recently released information, bevacizumab prolonged the survival of patients treated beyond progression.\(^{48}\)

Among multiple inhibitors of VEGF signaling,\(^{49}\) two agents that target VEGF have recently demonstrated evidence of activity in patients with mCRC. Aflibercept (VEGF trap), a unique VEGFR fusion agent that is likely to bind more forms of VEGF than bevacizumab, was studied in a randomized trial of second-line aflibercept + FOLFIRI versus FOLFIRI alone, with the aflibercept arm yielding significantly longer PFS and OS.\(^{50}\) The median OS was 13.5 months for aflibercept and 12.06 months for placebo (HR = 0.817; 95.34% CI, 0.713–0.937; \(P = 0.0032\)).\(^{51}\) This held true for all subsets of patients on the study including those who had previously received bevacizumab. How this agent is integrated into the therapy of mCRC may depend in part on the presented results of the randomized trial evaluating the question of BBP.\(^{48}\)
The second agent, regorafenib, is a tyrosine kinase inhibitor (TKI) of the VEGF receptors in addition to other receptor tyrosine kinases. As last line therapy, this agent was tested against best supportive care in a randomized trial. A total of 760 patients were randomized in a 2:1 fashion to regorafenib or placebo. Regorafenib succeeded in achieving its endpoints, including the primary endpoint of OS, extending the median survival by 1.4 months from 5 to 6.4 months with a HR of 0.77 (P = 0.0052). The PFS was also improved with a HR of 0.47 (P < 0.00001). Toxicity in form of hand-foot syndrome, fatigue, diarrhoea, hypertension etc. led to discontinuation of regorafenib in 8.2% compared with 1.2% in patients receiving the placebo. Other VEGF inhibitors are still being evaluated in patients with mCRC and may also prove beneficial.

The other known target for biological agents in patients with mCRC is EGFR. Blocking EGFR with antibodies, such as panitumumab or cetuximab, has resulted in a clinical benefit for patients with mCRC. Cetuximab as last-line therapy for unselected patients resulted in an improved OS (6.1 versus 4.6 months, respectively, P < 0.001) and PFS compared with best supportive care in a randomized trial with no cross-over allowed. In a randomized trial of panitumumab versus best supportive care allowing cross-over, survival was not significantly different for the two arms, but the PFS (1.9 versus 1.7 months, P < 0.001) was improved for panitumumab-treated patients. Later, as K-ras was evaluated as a biomarker of efficacy, both trials showed more clinically significant benefits for cetuximab and panitumumab. Prior to these two trials, the BOND trial had shown that cetuximab + irinotecan was more effective in terms of PFS (4.1 month versus 1.5 months, P < 0.001) than cetuximab alone without improved survival (8.6 versus 6.9 months, P = 0.48), in spite of prior treatment with irinotecan. Therefore, it was logical to evaluate panitumumab and cetuximab in earlier lines of therapy in combination with common chemotherapy regimens. Both agents have demonstrated improved response rates and PFS in earlier lines of therapy when added to chemotherapy compared with chemotherapy alone, but with multiple lines of therapy now available, it is increasingly difficult to see differences in OS on first-line and even second-line trials. Of note, K-ras mutations have clearly been a biomarker of efficacy in almost all trials with EGFR inhibitors whether given alone or in combination with chemotherapy.

Based on this insight, it appears reasonable to propose a simplified algorithm consisting of cetuximab, panitumumab or bevacizumab-based treatment in patients with K-ras wild-type and bevacizumab-based treatment in patients with K-ras mutant tumours. There is no current consensus among oncologists to favour either targeted therapy for patients with unresectable CRLM and K-ras wild-type tumours. First, to date, no randomized studies have provided a head-to-head comparison between these two treatments, and the results are awaited from the CALGB C80405 (NCT00265850, http://clinicaltrials.gov/ct2/show/NCT00265850) and FIRE-3 (NCT00433927, http://clinicaltrials.gov/ct2/show/NCT00433927) trials. Moreover, one should be concerned about a traditional ‘tumour response’ as the unique objective of treatment in this setting. Even if it seems that cetuximab offers better chances of radiological tumour down-sizing than bevacizumab, recent studies have provocatively sustained the efficacy for the anti-VEGF strategy in inducing a high degree of pathological responses. The real importance of this surrogate end-point is not well established, but it strongly correlates with OS after resection in patients with CRLM. It is important that radiological or pathological responses as well as secondary resection rates are only surrogate endpoints and in this setting, as the primary objective is still life-prolonging, or potentially curative in those patients who are rendered resectable.

In the future, in addition to clinical considerations, molecular markers may provide critical information for selecting patients who might benefit preferentially from one of these drugs. Indeed, the tumour’s pathology and patient’s metabolism is driven by genetic make-up, influencing the individual response as well as the agent’s toxicity. The selection of therapy should be based on the best achievable, individualized balance of toxicity, efficacy and costs. In contrast to the ‘good clinical practice’ of the past, as a result of the introduction of new targeted drugs a slow but dramatic revolution is being experienced. K-ras mutations in the treatment of patients with mCRC are a clear example of how a molecular marker has completely changed the way clinicians approach everyday clinical decision-making. The challenge of a treatments’ optimization through specific biomarkers gain special value for a potentially curable disease such as CRLM. Unfortunately, progress in utilizing biomarker-driven treatment decisions has been slow for at least two reasons. First, the high degree of complexity of the biological systems makes the discovery of determinant biomarkers a demanding endeavour per se. On the other hand, researchers face all the difficulties of prospective verification and clinical validation of the most promising factors. Nevertheless, molecular-targeted therapy has entered the arena of mCRC combination therapy, and further significant advances in molecular-targeted systemic therapy are expected in the future.

**Consensus statement**

1. Anti-VEGF- and anti-EGFR-targeted antibodies have increased the efficacy of chemotherapy in first-, second- and third-line treatment.
2. Bevacizumab is an appropriate biological agent to add to either first- and/or second-line chemotherapy backbones.
3. The EGFR inhibitors panitumumab or cetuximab are appropriate for first-, second- or third-line use in combination with chemotherapy, or as single third-line agents, but only in patients with wild-type K-ras.
4. Predictive markers such as K-ras should be used when possible to increase the efficacy of combination molecular-chemotherapeutic regimens.
Patients with metastatic disease who have a response to chemotherapy in combination with targeted antibodies may still benefit from subsequent curative-intent resection.

**Hepatotoxicity of chemotherapy**

A potential drawback to the evolving options for pre-operative CRLM cytotoxic chemotherapy-based treatment rests in chemotherapy-associated liver injury (CALI). Clinical consequences of CALI have recently been characterized in this setting and are the subject of active investigation. The three recognized types of CALI include steatosis, steatohepatitis, and sinusoidal obstruction syndrome, and their prevalence, aetiology related to chemotherapeutic regimen and clinical implications are well established today.

Steatosis corresponds to accumulation of lipids in hepatocytes and has been reported by some in 30% of patients treated with 5-FU. Steatosis may have multiple causes. Its incidence is common and ranges from 15% of the general population in Italy to 31% in the USA, affecting primarily individuals with risk conditions such as obesity, diabetes or alcohol consumption. Studies associating steatosis and 5-FU are mainly based on radiological evaluation. However, ultrasound sensitivity for diagnosis of steatosis is only 60–94% and specificity is 66–95%, whereas CT-scan sensitivity is 82% and specificity is 100%. Of note, imaging cannot distinguish steatosis from steatohepatitis. The few studies that include histological evaluation have not included a liver biopsy before pre-operative chemotherapy.

The steatohepatitis (SH) diagnosis is based on a histological triad: steatosis, hepatocellular ballooning and polymorphonuclear neutrophil inflammation. Its link to the use of chemotherapy is not uniformly established. Chemotherapy associated SH (CASH) has mainly been reported by North-American authors and may be partly explained by the difference in average body mass index (BMI) in the general US population. CASH has been described after cytotoxic therapy, most often after irinotecan treatment, particularly in the at risk population of non-alcoholic liver disease, with a BMI of >25 kg/m². Macroscopically, it results in a ‘yellow liver’.

Sinusoidal obstruction syndrome (SOS, previously named veno-occlusive disease or VOD) has been associated with the use of oxaliplatin. Macroscopically, the affected liver typically has a blue-red marbled appearance, commonly called ‘blue liver’. SOS is the consequence of an initial toxicity to sinusoidal endothelial cells. Histologically, it is characterized by centrilobular sinusoidal dilatation, often associated with erythrocyte extravazation into the perisinusoidal space (haemorrhage), compatible with a rupture of the sinusoidal wall. It is occasionally associated with perisinusoidal fibrosis and centrilobular vein obstruction, in addition to peliosis or the development of nodular regenerative hyperplasia (NRH).

From a clinician’s perspective, the implications of CALI have been elucidated within the pre-operative, operative or early post-operative period. Post-operative morbidity correlates with the number of cycles of pre-operative chemotherapy. CALI can specifically prolong the operative procedure and the subsequent hospital stay, decrease the accuracy of metastasis detection at the time of pre-operative imaging assessment, increase the risks of peri-operative haemorrhage, post-operative infections, liver failure after a major hepatectomy owing to poor liver function reserve, portal hypertension or ascites and be responsible for a persistent thrombocytopenia. Rare cases of death as a result of CALI have been reported.

Although a reliable diagnosis of CALI is essential to allow for a proper selection of patients for liver operations, the current absence of specific diagnostic tools makes pre-operative recognition especially of SOS challenging. SOS risk factors may include abnormal pre-operative gamma-GTP or APRI value (ratio index of aspartate aminotransferase to platelet count), age, female gender, the indocyanin green retention rate, the number of cycles of chemotherapy, or a short interval between the end of chemotherapy and the liver resection. Computed tomography is not directly diagnostic but can play a role in supporting the diagnosis through demonstrating the presence of splenomegaly and ascites.

As many patients still experience recurrence of CRLM after initial multidisciplinary treatment, subsequent cytotoxic and local therapies frequently need to be decided upon. An open question therefore is whether CALI, notably SOS and NRH, is reversible once the cause has stopped, and if so, in which time frame. For the short term, the histological persistence of SOS and NRH is observed in the setting of two-stage hepatectomies, suggesting that there is no advantage in delaying an operation that is otherwise well timed in terms of tumour response to chemotherapy. Increased post-operative morbidity associated with an early hepatectomy performed within 4 weeks of pre-operative chemotherapy compared with later operations therefore does not appear to be linkable to the histological manifestation of CALI. For the long term, the question of persistence is less certain: analogy with settings of toxic oil syndrome in which NRH and portal hypertension was noted 2.5 years after consuming the oil, and of azathioprine and 6TG treatment suggest that changes are not always reversible; persistent SOS, NRH and even fibrosis may occur several months after the end of chemotherapy. While a SOS-associated splenomegaly can decrease over 1–3 years, the incidence of chronic liver disease is not yet well evaluated, particularly for patients who receive multiple cycles of adjuvant or maintenance chemotherapy.

A better comprehension of the molecular events underlying chemotherapy-associated hepatic injury might also be a source of help in patient management. Global gene analysis has shown activation of several pathways in human liver with oxaliplatin-related SOS, namely acute phase response, coagulation, fibrosis/hepatic stellate cell activation, oxidative stress, hypoxia and angiogenesis. This provides new insights into mechanisms underlying CALI in humans and potential targets relating to its diagnosis, prevention and treatment. Activation of VEGF and coagulation pathways...
could explain, at a molecular level, the clinical observations that bevacizumab\textsuperscript{20,71,76,89} and aspirin\textsuperscript{69} have a preventive effect in SOS. In case of aspirin, a significantly decreased frequency of CALI has been observed in a multivariate analysis of 146 patients undergoing a liver resection within 3 months of chemotherapy (HR: 0.07, 95% CI: 0.01–0.37; \(P = 0.002\)).\textsuperscript{69}

**Consensus statement**

1. Cytotoxic chemotherapy may have drawbacks with potential clinical consequences, especially when given before a major hepatic resection. Risks for significant chemotherapy-associated liver injury need to be balanced against benefits in patients for whom resection of CRLM is planned.
2. Clinically relevant CALI has been linked to specific agents: steatohepatitis is associated with irinotecan, whereas SOS, fibrosis and NRH are associated with oxaliplatin.
3. Bevacizumab and aspirin have demonstrated some preventive effect on SOS severity.

**Conflicts of interest**

None declared.

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