Timing of medical therapy and surgery in liver metastatic colorectal cancer

Interview with Gianluca Masi[1] *and* Alessandro Ferrero[2] *by* Donatella Marino[3]

Oncologist perspective:
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Surgeon perspective:
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Introduction

Colorectal cancer (CRC) is one of the leading causes of death from cancer worldwide, and is the third most commonly diagnosed cancer in males and the second most common in females [1]. Approximately 15-20% of CRC cases have synchronous metastases discovered at the time of first diagnosis, whereas one quarter of patients who have surgery will develop recurrence after curative resection; the liver is the most common site for distant metastases [2].

In recent decades, the survival of patients with metastatic CRC (mCRC) has dramatically improved due to advances in both medical and surgical care [3, 4]. In particular, in patients with limited metastatic disease, an integrated approach may result in cure for approximately 10–25% of patients [5]. At present, the definition of liver metastases resectability is exclusively technical and based on the likelihood of being able to completely resect all visible disease, leaving an adequately functioning parenchyma. This definition, by excluding all tumor features, implies that each patient must have their disease managed by a multidisciplinary team, including a medical oncologist, radiologist, interventional radiologist and radiation therapist, where all the specialists involved can correctly define resectability status [6]. Even if it is clear that integrating systemic treatment and surgery offers the best chance for cure, controversy remains about the exact timing of treatment delivery and the best schedule to use. In this interview, two experts will discuss the topic of resectable mCRC from two different perspectives, clarifying the pros/cons and risk/benefit of systemic treatment and surgical intervention.

1. Preoperative chemotherapy in resectable liver disease; is there enough evidence to propose it as standard treatment or should it be a case-by-case decision?

Oncologist perspective

In a nutshell, I would say that the decision about the indication for preoperative therapy should be the result of a multidisciplinary discussion in all cases. This statement is based on the fact that the concept of resectability today is very broad. Indeed, from a strictly surgical point of view, a patient can be defined as "technically resectable" even in the presence of several bilobar synchronous liver metastases and also a limited number of extra-hepatic metastases. Therefore, it is important to try to define as best as we can the possible prognostic impact of the resection from an oncological point of view. In summary, we can identify three categories of patients: those with "easily resectable" disease, "borderline resectable" disease and "potentially resectable" disease. It should be stressed that there are not clear boundaries between these 3 categories and therefore they cannot be conclusively defined. Evidence suggests that the long-term outcome of patients undergoing hepatic resection can be predicted from five criteria (node-positive primary, disease-free interval from primary to metastases <12 months, number of hepatic tumors >1, largest hepatic tumor >5 cm, and carcinoembryonic antigen level >200 ng/mL) [7]. Patients fulfilling up to two of these criteria can have a favorable outcome whereas patients with three, four, or five criteria should be considered high risk. In a very practical way, we can define "easily resectable" patients as those with a limited number of metastases (maximum 4) in locations technically simple to resect and an absence of important adverse prognostic factors (e.g. Fong Score 1-2). "Borderline resectable" patients are those in whom resec-

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tion is technically feasible, but with a complex surgery, or at risk of R1-R2 resection or serious complications. Finally, "potentially resectable" patients present with unresectable disease that might become resectable only after a response to chemotherapy, and have important adverse prognostic factors (e.g. Fong Score 3 to 5). In borderline and potentially resectable patients it is reasonable to administer preoperative therapy (as neoadjuvant therapy or with the intent of conversion to resectability) even though there is a current lack of phase III clinical trials specifically designed in this setting. Neoadjuvant treatment is also highly recommended where there is any doubt about the presence of extrahepatic metastases and in the presence of important negative prognostic factors.

The case is more complex when dealing with "easily" resectable patients. In fact, randomized trials of adjuvant chemotherapy after resection [8] or perioperative treatment *versus* surgery alone [9] have so far shown clear benefit only for progression-free-survival (PFS), but no statistically significant improvement in overall survival (OS). In an updated analysis of the EORTC 40983 trial, for example, median PFS was 20.9 months in the systemic treatment group compared with 12.5 months in the surgery alone group (p=0.035), whereas the 5-year OS rate was improved only by 4.1% (from 48.3% to 52.4%, p=0.3). It must be said that the definition of resectability in this study was different from current practice (one to four liver metastases considered resectable, and no detectable extrahepatic tumors) and the lack of a postoperative chemotherapy group makes it difficult to draw any conclusions about which patients benefit the most from preoperative chemotherapy. Given that both options are technically correct, the decision on which approach to take must be the result of a multidisciplinary discussion.

Surgeon perspective

Surgical resection is the mainstay of treatment for hepatic CRC metastases. However, this is still considered only a "potentially" curative treatment because, even after successful hepatic resection, the majority of patients develop recurrent disease. Some retrospective studies have demonstrated that preoperative chemotherapy increases curative resection rates, enables more conservative surgery and facilitates the ability to tailor postoperative chemotherapy based on the preoperative response. However, the most disputed issue remains the oncologic benefit. The efficacy of newer regimens has expanded the use of chemotherapy in initially resectable patients because of several theoretical advantages. Firstly, it can be a test for tumor chemo-responsiveness. Cohort study data suggest that tumor progression on chemotherapy predicts poor outcomes after resection [10].

Nevertheless, tumor progression may also be considered a proxy of an aggressive tumor biology whose natural course might not be influenced by hepatic resection. Secondly, preoperative systemic treatment could, in theory, eliminate micrometastatic deposits within and outside the liver. Thirdly, it may facilitate and allow a technically simpler liver resection by decreasing tumor burden and, as a result, the magnitude of resection needed [11]. Finally, pathologic assessment of response to chemotherapy may provide more reliable stratification of patient prognosis and serve as selection criterion for adjuvant therapies. In contrast, histological tumor regression, graded by the extent of fibrosis and presence of residual tumor cells, is emerging as a powerful prognostic tool and surrogate marker of tumor biology [12].

Despite these benefits, there is still no universal agreement amongst treating surgeons and medical oncologists about whether to give neoadjuvant chemotherapy prior to hepatectomy in resectable patients. This is partly due to the question of the oncologic benefits [13], but also to the well-known drawbacks, including hepatic toxicity, and the possibility of inducing a complete radiologic response, which may render some patients with initially resectable liver metastases inoperable because of the disappearance of residual visible tumor.

The management of patients with disappeared liver metastases (DLM) is complex. Considering the absence of any reliable preoperative tool to assess complete pathological response (CPR), only surgical resection with concomitant pathologic examination of the specimen enables a definitive diagnosis. In addition, the complete disappearance of metastases on imaging should not contraindicate surgery, since a majority of these patients (30-86%) will not have a CPR [14]. In our series [15], 10.3% of patients treated by resection after preoperative chemotherapy had one or more DLM on all preoperative imaging techniques. Of these, 67% was found intraoperatively, most frequently with the use of intraoperative ultrasound (IOUS). By combining pathologic data on residual viable tumor cells and follow-up data on *in situ* recurrences for those lesions left untreated at the time of operation, we found that two-thirds of DLM were not cured (persistent disease rate of 61.2%). Therefore, in patients with DLM, resection of the site of metastases is mandatory when clearly identified with the use of IOUS. Conversely, in the 30-70% of patients in whom DLM cannot be identified at IOUS, blind resection of the site is recommended when hepatectomy can be easily performed. Observation might be the preferred choice for deeply-located DLM, which would require major hepatectomy.

Finally, progression during chemotherapy may also result in patients who otherwise would have been offered a potentially curative treatment being defined as unresectable. It has been shown that primary resistance to chemotherapy associated with tumor progression is infrequent (~7%) with one-third of these patients still remaining resectable [11]. However, particular attention should be given to ill-located metastases in which tumor progression could preclude resection.

In conclusion, there is currently not enough evidence to propose preoperative chemotherapy as a standard treatment in resectable colorectal hepatic metastases.

2. Upfront surgery; what are the possible acceptable indications?

Oncologist perspective

In general, I think that neoadjuvant therapy should be avoided in the following patient groups:

- those who have easily-resectable, small, metastases that might disappear after a few cycles of chemotherapy, making the subsequent radical resection more complicated or impossible;
- those with synchronous metastases and symptomatic primary tumors where synchronous resection of both primary and metastases can be made;
- those with chemoresistant disease, such as liver metastases appearing after <6 months from the completion of adjuvant chemotherapy, in particular if FOLFOX or XELOX were administered.

Surgeon perspective

In resectable cases, surgery is the only potentially curative treatment. Surgery achieves 5-year survival rates of up to 50% [5]. Survival improvement reflects not only better disease control, but also a potential increase in cure rate. This progress is associated with a reduction in liver recurrences and better disease control whenever recurrence does occur.

Currently, the indication for resection of liver metastases is determined by two factors. Firstly, the technical feasibility of surgery, which essentially depends on the location of metastases and their relationship with vascular structures, the status of the underlying liver parenchyma (i.e. non-alcoholic fatty liver disease or sinusoidal dilatation by oxaliplatin-/irinotecan-based chemotherapy), and, if a major hepatic resection is planned, on the volume of the remnant liver (FLR). The safe FLR obviously depends on the status of the underlying liver parenchyma: if the underlying liver is normal, a preoperative FLR >25% seems to be safe, whereas if the liver is injured, preoperative FLR should be >31-40% [16]. The second factor is the possibility of performing a clear margin resection. Thereafter, over time, the conventional indications for surgical therapy of colorectal liver metastases have given way to more aggressive indications. Nowadays, colorectal liver metastases should be considered resectable whenever the disease can be completely resected, two adjacent liver segments can be spared, adequate vascular inflow and outflow and biliary drainage can be preserved, and the FLR is sufficient.

However, the combination of surgery with systemic chemotherapy has resulted in improved long-term outcomes, even in patients with advanced disease at presentation. Timing of surgery is crucial in the management of mCRC. Nevertheless, policies vary widely between different surgical centers. According to our experience and available studies (despite the low level of evidence provided), surgery may be attempted in some indications. Upfront surgery is preferred in cases of metachronous solitary metastasis or if there is a risk of metastases disappearing. Moreover, if the scheduled liver resection wouldn't change after preoperative chemotherapy because of the metastasis site (i.e. peripheral bile duct infiltration), an upfront hepatectomy should be considered. In patients with up to three metastases, no recommendations can be made (except for metachronous solitary lesion). In such cases, our center usually plans immediate resection, but the final decision should be based on a case-by-case evaluation considering the whole prognostic profile of the patient in a multidisciplinary setting. Synchronous presentation of metastases should not be considered an absolute indication for neoadjuvant chemotherapy. Simultaneous hepatic and colorectal resection is defined based on the complexity of hepatic resection and patient performance status.

3. In cases of synchronous mCRC, what is the optimal timing for primary and hepatic surgery?

Oncologist perspective

Patients with synchronous metastases are unquestionably the most complex, and for whom the therapeutic strategy decision-making must be made in a step-by-step manner by a multidisciplinary team, especially if the primary tumor is located in the rectum. In general, if the burden of liver disease is limited and does not require major liver resection, you can opt for a synchronous tumor and metastases resection, both up-front, with or without neoadjuvant therapy. In patients where liver resection is the most important and complex intervention, you can opt for starting with the primary tumor resection followed by chemother-

apy and then by liver resection, or to start with chemotherapy followed by resection of the primary tumor and then, after 1-2 months, by liver resection. Finally, in patients with no symptomatic rectal cancer, you can also opt for the so-called reverse-strategy (i.e. liver resection, then chemotherapy and radiotherapy, and finally resection of the rectum).

Surgeon perspective

The timing of CRC and liver surgery (simultaneous *versus* staged) has been debated since the 1980s. Theoretically, simultaneous resections have an increased risk of both anastomotic leak (splanchnic congestion after liver surgery) and liver failure (septic complications due to the combination of "clean" and "contaminated" procedures) [17]. These concerns were not supported by data from recent studies reporting similar outcomes after simultaneous or delayed resections [18]. Nevertheless, the debate is still ongoing: favorable data tend to related to "easy" hepatectomies while conflicting results are more likely to refer to simultaneous major hepatic resections.

In 2007, we compared 31 simultaneous major liver resections with 48 staged ones [19]. Mortality rates were similar in the two groups; given that delayed resections required two hospitalizations, morbidity and hospital stay were actually lower in the simultaneous group (33% *vs* 56%, and 14 *vs* 20 days, respectively). These data have been recently confirmed by the results of a meta-analysis [20]. In contrast, a US multicenter database [21] reported increased mortality and morbidity rates after simultaneous major hepatectomy compared with delayed resection (8% *vs* 1%, and 44% *vs* 27%, respectively). With respect to long-term outcomes, simultaneous liver and colorectal resections for metastatic colorectal cancer appear to offer similar results compared with staged procedures [22, 23].

Another possible scenario, a "reverse" strategy, was first proposed in 2006 by Mentha [24]. This consists of a two-stage surgery with liver resection as the first procedure, and long-term results were acceptable. The theoretical advantages of this therapeutic strategy are that it avoids unnecessary primary tumor resection if the patient cannot undergo radical resection of CRC and hepatic resection can be performed within the optimal time frame, during responses to preoperative chemotherapy that are unsusceptible to the primary tumor treatment. In our opinion, this approach is reasonable for patients with asymptomatic primary tumors and advanced hepatic disease. Furthermore, in the setting of rectal surgery, it easily enables the inclusion of preoperative radiation treatments after resection of liver metastases.

Finally, careful patient selection is mandatory to achieve good outcomes. Particular attention should be paid in elderly patients, who experience the worst outcomes [19, 20]. Thus, in the absence of evidence and avoiding making specific recommendations, the timing of surgery should be tailored on a case-by-case basis within a multidisciplinary discussion.

4. Newer treatment schedules integrating biologic agents with chemotherapy and molecular characterization have changed the treatment landscape in mCRC; is there sufficient evidence to integrate them in the perioperative setting?

Oncologist perspective

Absolutely. Targeted therapies in combination with standard chemotherapy agents have dramatically improved survival in mCRC. According to the latest studies, median OS (independent of resectability status) has almost tripled in the last 20 years and this is primarily due to the availability of several novel compounds beyond fluropyrimidines [25, 26]. Using more effective treatment combinations also significantly improves the response rate (RR), providing hope for conversion or potentially curative treatments. Several trials, many non-randomized phase II studies, have explored the role of both anti-endothelial growth factor receptor (EGFR) or anti-vascular endothelial growth factor (VEGF) therapies in the neoadjuvant setting; the results have shown improved treatment activity and increased the rate of secondary hepatic resections [27]. For example, a study by Ye et al. [28] showed that the addition of cetuximab to therapy with FOLFIRI or FOLFOX resulted in a significant increase in the response rate (from 30% to 50%), an increase in hepatic resection (from 7% to 26%), and a significant improvement in PFS and OS. Another example is the OLIVIA study [29] in which a more aggressive schedule of FOLFOXIRI-bevacizumab was compared to mFOLFOX6 as frontline conversion treatment in hepatic-only, initially unresectable mCRC. The triplet plus bevacizumab was associated with a significant increase in response rate (from 60% to 80%), an increase in hepatic resection (from 23% to 49%) and prolonged PFS.

Nevertheless, there is one exception where targeted therapy should be withheld as neoadjuvant treatment. According to the New-EPOC study [30], patients with resectable or suboptimally resectable CRC liver metastases did not benefit from the addition of cetuximab to standard chemotherapy. In this study, the experimental arm showed a worse outcome in terms of PFS (14.1 *vs* 20.5 months, p=0.030) and OS, suggesting a detrimental

effect of a more aggressive treatment in case of resectable disease.

Surgeon perspective

Several recent studies have reported that adding a biological agent to chemotherapy could further increase response and resectability rates. Currently, higher RR primarily result in more 'unresectable' patients becoming candidates for resections. Nevertheless, there is considerable variation in reported mCRC resection rates, and it is difficult to draw definitive conclusions about the relative efficacy of biological agents in terms of converting unresectable colorectal liver metastases to resectable lesions. Moreover, recent insight into EGFR biology restricted the benefit of anti-EGFR treatment to a subgroup of patients with All-RAS wild-type mutational status.

Bevacizumab, as a potent inhibitor of angiogenesis, has the potential to adversely affect liver regeneration, increase bleeding and impair wound healing. Even if data are emerging on the safety of hepatectomy after bevacizumab administration, concerns about how long bevacizumab should be stopped prior to surgery still remain. Available data suggest that the incidence of complications is low if bevacizumab is discontinued 6-8 weeks before surgery. Therefore, avoidance of bevacizumab during the last chemotherapy cycle is recommended. An interesting finding is that bevacizumab may protect against sinusoidal damage (SOS), as first described by Ribero et al. [31]. However, the mechanisms by which bevacizumab influences the development of SOS and hepatic fibrosis are not fully understood and have not been prospectively validated.

Regarding the effect of EGFR inhibition on hepatic regeneration, preclinical data show conflicting results. Whereas one report showed strong genetic evidence that EGFR is essential in hepatic regeneration, another report showed that cetuximab administration does not adversely affect hepatectomized mice. In the clinical setting, there are relatively few data available regarding the safety of administering cetuximab prior to hepatectomy.

Overall, based on available evidence, biologic agents should be integrated with chemotherapy in the preoperative setting in order to increase the resection rate in patients with advanced disease.

5. How should treatment-induced toxicity and patient age impact on decision-making in resectable mCRC?

Oncologist perspective

If the goal of a multidisciplinary approach is to achieve liver resection, then it is important to avoid any kind of complications. Adverse events from systemic treatment are well known and generally manageable. Predictors of toxicity are available, such as dihydropyrimidine dehydrogenase (DPD) deficiency for severe potential lethal toxicity from fluoropyrimidine (0.3-1.5% of patients), or UGT1A1 polymorphism for irinotecan-related adverse events. Although routine testing for these variants is not recommended, they should always be taken into account to prevent severe toxicity.

Fluoropyrimidine-induced cardiotoxicity is not always predictable but can have a negative impact on the chances of a patient being able to undergo subsequent surgery [32]. Some predisposing factors, such as history of cardiopathy or continuous infusion, have been highlighted but there is no consensus about which patients should be treated or not.

It is clear from studies in the palliative setting that biological age and comorbidities should be taken into account in the initial evaluation of the patient. However, age by itself should not be a contraindication to preoperative chemotherapy or surgery. In elderly or unfit patients it is preferable to administer less intensive regimens with a shorter treatment duration to minimize the risk of complications [33].

In conclusion, I suggest that patients should be given the most active regimen that they can tolerate for the minimum time necessary to make resection possible in order to minimize possible adverse events.

Surgeon perspective

Although preoperative chemotherapy has many advantages, there has been growing concern about the potential for hepatic toxicities caused by various systemic agents and regimens. In particular, synergistic toxicity is likely when patients are treated with a combination of systemic agents. Two types of chemotherapy-related liver injuries (CALI) have been identified: injury to sinusoidal endothelial cells (SOS) and non-alcoholic fatty liver disease (steatosis, steatohepatitis). The first is strictly correlated with administration of oxaliplatin, while the second is more common in patients treated with irinotecan-based chemotherapy. CALI have been reported to worsen operative mortality and morbidity rates [34]. In particular, irinotecan-induced steatohepatitis appears to have clinically relevant consequences, with significantly higher 90-day mortality rates compared to patients without this complication (14.7% *vs* 1.6%, respectively) [35]. Although liver failure in patients with oxaliplatin-induced SOS has rarely been reported, a number of case reports have described the development of portal hypertensive sequelae, such as ascites, variceal bleeding and increased spleen size. Some reports have shown that patients who

received perioperative oxaliplatin-based chemotherapy had a higher incidence of complications (25%) than those who had surgery alone (16%) [11].

There are two potential strategies for improving postoperative outcome in patients treated with preoperative chemotherapy. The first is the meticulous attention to surgical technique needed to decrease intraoperative blood loss. The second is prevention of the development of CALI, which could be achieved in different ways (e.g. limiting the number of chemotherapy cycles and waiting an adequate interval [at least 4 weeks] from the end of the chemotherapy before liver surgery). Finally, since the significant risk related to CALI is postoperative liver dysfunction, parenchyma-sparing ultrasound-guided surgery must be planned whenever possible, avoiding unnecessary sacrifice of healthy liver parenchyma. This strategy is especially important in elderly patients, who have a progressive reduction in organic functional reserve. Indeed, age by itself is not a contraindication for surgery and selected elderly patients with mCRC could benefit from resection with just a small increase in postoperative morbidity and mortality [36].

6. What is the standard of care in patients with liver-only mCRC in your institution?

Oncologist perspective

In my institution, patients with very limited (1-2 metastases) and easily resectable disease undergo resection upfront and subsequent adjuvant chemotherapy. Patients with easily resectable disease but with 3-4 metastases or with a Fong Score of 2-3 are treated with a perioperative therapy (FOLFOX for 3 months then surgery and then three additional months of FOLFOX). The patients with borderline resectable disease are treated with chemotherapy + biologic for 3 months and then surgery if they show a response, then they continue the same therapy for a total of 6 months. Finally, patients with potentially resectable metastases are treated with chemotherapy + biologic and re-evaluated for resection every 3 months, with the aim of performing a resection at the time of maximum response. In fit patients, chemotherapy options are doublet + anti-EGFR for RAS and RAF wild-type patients, and FOLFOXIRI + bevacizumab for RAS or RAF mutant patients. However, I again would stress importance of systematic and regular discussion of all cases in a dedicated multidisciplinary team, both at diagnosis and during subsequent treatment, because there is significant clinical heterogeneity and only a dedicated multidisciplinary team can optimize the overall therapeutic algorithm for each individual patient.

Surgeon perspective

A multidisciplinary committee including surgeons, oncologists, radiologists, radiotherapists, and endoscopists define patient management on a case-by-case basis. The management of mCRC can be individualized, with the approach to treatment dictated by the resectability of liver metastases. Notably, definition of resectability is influenced by our surgical policy of using a parenchymal sparing strategy.

For patients with mCRC who have resectable metastases, neoadjuvant chemotherapy is recommended in patients with a locally advanced primary tumor (cT4), more than 3 metastases (both synchronous and metachronous), risk of non-radical resection because of the site of metastasis and its relationship with intra-hepatic vascular structures, and for lesions with a difficult location for which tumor response would enable easier and/or more conservative surgery. Upfront surgery is preferred when there is metachronous solitary metastasis, a risk of metastases disappearing, and up to three metastases (if the overall prognostic profile is favorable).

For patients with unresectable metastases, preoperative chemotherapy integrated with biologic agents is used, with early restaging after 4 cycles. When patients cannot safely undergo surgery because the future liver remnant after scheduled hepatectomy would be too small, portal vein occlusion is a safe procedure to decrease the risk of postoperative liver failure. Two-stage hepatectomy is also an effective strategy in cases of multiple bilateral metastases. Usually, chemotherapy is not administered during the interval between first and second stage.

In cases with synchronous presentation, patients with an asymptomatic primary tumor are managed with neoadjuvant chemotherapy (if required) with the primary tumor *in situ*. For patients with a symptomatic primary tumor, colonic endoscopic stent positioning could be evaluated as an alternative to resection. In cases where it is impossible to position a colonic stent or if this is ineffective, a colorectal resection is considered. Simultaneous colorectal and liver resection is considered as the initial approach in cases of resectable mCRC, upfront or after preoperative chemotherapy.

There are three situations where simultaneous resections are contraindicated: high American Society of Anesthesiology (ASA) score; bulky primary tumor requiring prolonged and difficult dissection; and emergency colorectal resection because of intestinal obstruction or perforation. Primary rectal tumor and/or planned major hepatectomy are not absolute contraindications to a simultaneous surgical approach.

The liver-first approach is preferred in patients with ad-

vanced hepatic disease or those requiring complex liver procedures. This strategy could also be favored in cases with a primary rectal tumor in order to permit neoadjuvant radiotherapy when required (cT3N+).

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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