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Oncosurgical strategies for metastatic liver cancer

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A B S T R A C T

Patients with liver metastases from colorectal cancer (CRC) present a major public health challenge with approximately, 1.2 million cases of CRC occur yearly worldwide. Resection of colorectal liver metastases (CRLM) is the only treatment offering the possibility of cure and has been shown to provide clear survival benefits. However, only 10% to 20% of patients with CRLM are eligible for this procedure upfront. During the last decade, major advances in the management of CRLM have taken place involving three fields: oncology, interventional radiology, and surgery. These advances have increased the resectability rate to 20%-30% of cases with a 5-year survival of 35%-50%. Neoadjuvant treatment with chemotherapeutic agents such as irinotecan and oxaliplatin, and hepatic artery infusion combined with systemic therapy and biologic agents (bevacizumab, cetuximab) play an important role in increasing the number of patients eligible to secondary resection. However, with the progressive use of neoadjuvant chemotherapy further studies are necessary to answer questions such as the risk: benefit ratio in maximizing response rates versus vascular changes in the liver (current opinion still divided concerning their importance). These questions remain challenging and should not be underestimated.

In this review, we have described the current oncosurgical strategies employed in patients with resectable and non resectable CRLM, their benefits, and future treatment strategies.

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Estrategias oncoquirúrgicas en el cáncer hepático metastásico

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Embolización de la vena portal

RESUMEN

Los pacientes con metástasis hepática debida a cáncer colorrectal (CCR) constituyen un gran reto de la salud pública, con alrededor de 1,2 millones de casos de CCR anuales en todo el mundo. La resección de las metástasis hepáticas del cáncer colorrectal (MHCR) es el único tratamiento que ofrece la posibilidad de curación y ha demostrado aportar claros beneficios de supervivencia. Sin embargo, sólo entre el 10 y el 20% de los pacientes con MHCR reúnen inicialmente los requisitos para este procedimiento. Durante el último decenio, han tenido lugar importantes avances en el manejo de la MHCR, especialmente en tres campos: la oncología, la radiología intervencionista y la cirugía. Estos avances han aumentado la tasa de resecabilidad en un 20-30% de los casos, con una supervivencia a los 5 años del 35-50%. El tratamiento neoadyuvante con agentes antineoplásicos como el irinotecán y el oxaliplatino, y la infusión arterial hepática combinada con la terapia sistémica y los agentes biológicos (bevacizumab, cetuximab) desempeñan un papel importante al aumentar el número de pacientes aptos para una resección secundaria. Sin embargo, con el uso progresivo de la quimioterapia neoadyuvante, más estudios son necesarios para poder responder a temas como la relación riesgo/beneficio a la hora de maximizar las tasas de respuesta frente a los cambios vasculares en el hígado (la opinión actual continúa dividida en cuanto a la importancia de esta cuestión). Estas preguntas constituyen aún un reto y no deben subestimarse.

En esta revisión, hemos descrito las estrategias oncoquirúrgicas actuales empleadas en pacientes con MHCR en los que la resección está indicada o no, sus beneficios y las estrategias de tratamiento futuro.

Introduction

Patients with liver metastases from colorectal cancer (CRC) present a major public health challenge. Approximately, 1.2 million cases of CRC occur yearly worldwide, with 412,900 new cases diagnosed in western Europe alone and 150,000 in the United States.[1,2] Resection of colorectal liver metastases (CRLM) is the only treatment offering the possibility of cure and has been shown to provide clear survival benefits.[3] Unfortunately, only 10% to 20% of patients with CRLM are eligible for this procedure upfront.

On the other hand, during the last 10 years, major advances in the management of CRLM have taken place involving principally three different fields: Oncology (new and more effective chemotherapeutic agents), interventional radiology (portal embolisation and radiofrequency), and surgery (better instruments and newer techniques). These advances as part of a multidisciplinary team approach have gradually but effectively increased the resectability rate to 20%-30% of cases with a 5-year survival of 35%-50%, marked improvement compared to previous figures.[4]

Expanded application of resection for CRLM

Liver resection is the current preferred treatment for CRLM patients and should be undertaken whenever feasible and potentially curative (R0), regardless of prognostic factors and presence of extrahepatic metastases. So far, data from several series support the expansion of indications for liver resection, including the LiverMetSurvey[5] (an international registry of patients who have undergone hepatectomy for CRLM). With 12143 patients included as of December 2009, 40% of patients are alive at 5 years and 25% at 10 years. Other studies have demonstrated post-hepatectomy 5-year survival rates exceeding 50%.[6,7] In contrast, the results for untreated patients are very poor with the majority of them succumbing to their disease within 12 months of diagnosis. Five-year survival in untreated patients is extremely rare with only 0.9% reported rates.[3] Furthermore, improvement in surgical techniques have minimized adverse outcomes, as demonstrated by the most recent series of patients undergoing resection of liver metastases with a mortality ranging from 0% to 3.7% and morbidity between 15% and 46%.[7-13]

Considering the inferior outcomes obtained for patients undergoing incomplete or no resection, it is of paramount importance to perform a complete resection with curative intent. In addition, an attempt should be made during surgery to remove all sites of previous metastases that no longer appear on images studies. In our series,[14] the pathologic analysis of 205 resected tumors that had responded well to preoperative chemotherapy showed that only 6% of patients (12 of 205) had complete tumor necrosis, suggesting that 94% still had active tumor despite chemotherapy response.

The main limiting factors to perform curative resection of CRLM are: presence of bilobar or bulky disease and presence of extrahepatic disease. Resection in patients with multiple or bulky lesions may result in insufficient residual hepatic tissue (i.e., less than 30% functional parenchyma). In such cases, portal vein embolization to induce hypertrophy of the remnant liver and two-stage hepatectomy procedures can effectively increase resectability. Additionally, radiofrequency ablation and cryosurgery techniques are being applied to lesions that are difficult to access surgically.

In patients with concomitant extrahepatic tumors, hepatic lymph node involvement has a particularly poor prognosis. For example, 5-year post-hepatectomy survival rate of 145 patients with hepatic lymph node metastases was 3,5% (n=5) in a systematic analysis of 15 studies.[15] Only one of the five patients alive at 5 years was disease-free, two had recurrent disease, and two had unknown status. Because resection is unlikely to enhance long-term survival of these patients, it is applicable only when tumors respond to preoperative chemotherapy.

At our institute, the presence of regional lymph node metastases in patients with CLM has never been considered an absolute contraindication for surgery, provided that response or stabilization during preoperative chemotherapy is observed. This oncosurgical treatment, was evaluated in a study conducted by us involving 763 patients who underwent liver resection for colorectal metastases.[16] Of these, 47 (6%) underwent simultaneous resection of histologically confirmed metastatic regional lymph nodes. In 19 patients (40%), lymph node involvement was diagnosed before hepatectomy, and in the remaining 28 patients (60%) lymph node metastases were identified intra-operatively. All patients that were preoperatively diagnosed with regional lymph node involvement responded to or were stabilized by preoperative chemotherapy. When regional lymph node involvement was diagnosed intra-operatively, hepatectomy combined with lymphadenectomy was only performed if all metastatic disease could be resected completely. By combining hepatectomy with lymphadenectomy in patients treated preoperatively with chemotherapy, a 5-year survival rate of 18% could be achieved without any operative mortality. Most favorable outcomes were observed in patients with pedicle lymph node involvement (5-year survival rate 25 vs 0% for patients with celiac and/or para-aortic lymph node metastases), and in patients younger than 40 years (5-year survival rate 45% vs 10% for older patients).

In relation to our results and those reported by others, we recommend combining hepatectomy with lymphadenectomy only for young CLM patients presenting with pedicle lymph node involvement, in the absence of disease progression after preoperative chemotherapy. On the other hand, patients presenting with celiac or para-aortic lymph node involvement should not be subjected to this oncosurgical treatment strategy.

On the other hand, concomitant pulmonary metastases should not be considered a contraindication to surgery. Patients with only pulmonary metastases as a site of extrahepatic disease have a particularly good outcome after complete metastasectomy of both liver and lung disease. Five-year survival rates ranged from 22% to 50% in patients with metastases limited to the lungs.[17]

Also, selected patients with complex multiorgan metastases have been associated with prolonged survival after a multimodality treatment. Patients with simultaneous hepatic and extrahepatic disease (EHD) do, however, need to be selected for surgery. Elias et al stated that EHD, when resectable, is no longer a contraindication to hepatectomy.[18] More importantly, the total number of metastases, whatever their location, has a strong prognostic effect than the site of the metastases. In addition, a study conducted at our centre demonstrated that patients with concomitant EHD who were resected experienced a lower 5-year survival than those without EHD (28% vs 55%, $P<.001$). Five poor prognostic factors were identified with multivariate analysis: EHD-location other than lung metastases, EHD concomitant to colorectal liver metastases recurrence, CEA-level>10 ng/ml, >6 colorectal liver metastases and right colon cancer. The five-year survival ranged from 64% (0 factors) to 0% (>3 factors).[19]

Neoadjuvant chemotherapy in patients with resectable CRLM

Despite major survival improvements achieved with successful primary hepatectomy for CRLM,[7-13,20] many of these patients experience disease recurrence. Data indicate that pre or post-operative chemotherapy may provide a meaningful benefit, although controlled trials are needed. Tanaka et al[21] reported a retrospective analysis of patients with multiple CRLMs, wherein use of neoadjuvant chemotherapy was an independent predictor of survival by multivariate analysis. In 71 patients undergoing hepatectomy for more than five bilobar liver tumors, 3- and 5-year survival rates were superior ($P<.05$, log-rank) in the neoadjuvant chemotherapy group (n=48; 67.0% and 38.9%) than in the hepatectomy-alone group (n=23; 51.8% and 20.7%). Furthermore, neoadjuvant treatment reduced the need for extended (>4 segments) hepatectomies (39 of 48 neoadjuvant vs 23 of 23 control patients; $P=.027$).

Data from the LiverMetSurvey[5] also indicate a survival improvement with neoadjuvant treatment. In 207 patients with more than five metastases resected, 5-year survival was better with neoadjuvant treatment, although not significantly (20% vs 15%) and among 1,045 patients who had only one liver metastasis resected, 5-year survival rates were 49% and 57% with and without neoadjuvant chemotherapy, respectively.

Similar results were reported in a metanalysis by Mitry et al,[22] which showed a strong trend toward better disease-free survival with adjuvant 5-FU treatment (HR 0.76, $P=5.8$), and a trend toward favorable overall survival (HR 0.76, $P=9.8$). In addition, a phase III randomized study (The EORTC Intergroup) examined perioperative FOLFOX4 (5-fluorouracil [5-FU], leucovorin, oxaliplatin) chemotherapy for patients with potentially resectable CRLM.[23] A total of 364 patients

with up to four CRLM were randomized between perioperative FOLFOX4 (oxaliplatin 85 mg/m² and LV5FU2), six cycles before and six cycles after surgery (CT), vs surgery alone (S). Eleven of 182 patients were ineligible in each arm, mostly due to more advanced disease; 31 and 30 patients in the CT and S arms, respectively, could not undergo resection. At a median follow-up of 3.9 years, progression-free survival (PFS) was significantly better with CT in the group of resected patients, although the trial was formally not positive in the intention-to-treat (ITT) analysis (HR 0.79, *P*=.058).

In terms of postoperative chemotherapy in resectable patients with CRLM data from United States and Europe show better survival in patients receiving adjuvant chemotherapy after resection of CRC liver metastases.[24] Use of adjuvant or neoadjuvant systemic treatment is widely recognized as standard of care in cases of liver resection, and was the focus of single-center studies with XELOX/FOLFOX[25] and XELOX plus bevacizumab.[26]

So far, only one study has as yet shown a clear benefit.[27] In this randomized trial, 109 patients (75 assessable) with one to three hepatic lesions received hepatic arterial floxuridine plus intravenous 5-FU (n=30) or no further therapy (n=45) after hepatectomy. The 4-year recurrence-free rates (46% vs 25%; *P*=.04) and 4-year liver recurrence-free rates (67% vs 43%; *P*=.03) were significantly better in the adjuvant therapy group. Median survival differences were not statistically significant (64% vs 49%; *P*=.6, log rank), however, the trial was insufficiently powered to evaluate overall survival.

Systemic chemotherapy in patients with nonresectable CRLM

Systemic chemotherapy is currently the main treatment approach for nonresectable CRLM. Incorporation of drugs such as oxaliplatin and irinotecan have led to a improvement of median survival as well as response rates compared with those achieved previously with 5-fluoracil (5-FU)/leucovorin-based regimens. Development of oral fluoropyrimidines has also improved treatment options in these patients. Median survival duration after systemic chemotherapy alone is approximately 20 months,[28,29] however, only 1% to 2% of such patients remain alive at 5 years.[3,30] On the other hand, the improved efficacy of newer regimens in downstaging tumors is rendering more patients resectable.[14,31]

Currently, however, there is an increasing trend to use combinations of more than two chemotherapy drugs. Thus, the triple combination of 5-FU, irinotecan and oxaliplatin (Folfirinox) gives a response rate of 70.6%, and also helps in notably increasing the resectability (26.5% of R0 resection).[32] The other possibility is to combine classic chemotherapy with biologic agents. For example, in the phase III CRYSTAL trial, which included 1,217 patients, combined use of cetuximab with FOLFIRI (5-fluorouracil, irinotecan, leucovorin) improved response rates (59% vs 43%, *P*=.004) and PFS (HR 0.68, CI 0.50-0.94, *P*=.02) in patients with *K-ras* wildtype(wt) tumors and increased R0 resection rates of patients with initially unresectable metastatic CRC (4.8% with FOLFIRI + cetuximab vs 1.7% with FOLFIRI alone [includes both *K-ras* wt and mutant tumor status]).[33]

Similarly, the OPUS trial (FOLFOX ± cetuximab vs standard chemotherapy alone) showed a response rate in patients with *K-ras* wild-type tumors of 61% with the addition of cetuximab vs 37% with standard chemotherapy.[34] A study involving cetuximab/FOLFOX6 or cetuximab/FOLFIRI as neoadjuvant treatment of nonresectable liver only metastases, demonstrated response rates of 43% and 45% in the FOLFOX6 and FOLFIRI arms, respectively. In a combined analysis of both arms, the response rate was 53% in patients with wild-type K-ras tumors.[35] An independent analysis, evaluating the response rate and secondary respectability of CRLM following neoadjuvant chemotherapy with cetuximab demonstrated an improvement in resectability rates from 32% to 60% in patients treated with cetuximab combined to chemotherapy.[36]

Improved response rates with the use of new targeted therapies for CRLM has further increased the proportion of patients eligible for secondary resection. The main two agents are: bevacizumab, a recombinant humanized monoclonal antibody that targets the vascular endothelial growth factor, and cetuximab, a chimeric human-murine monoclonal antibody to the epidermal growth factor receptor. As mentioned in the earlier paragraphs, combining these agents with modern oxaliplatin- or irinotecan-based regimens, tumor response rates greater than 50% to 60% have been produced.[34] Disease control rates (complete response [CR] + partial response [PR] + stable disease [SD]) exceeded 90% in a study using as first-line FOLFOX-4 (oxaliplatin/5-FU/folinic acid) plus cetuximab in nonoperable patients with epidermal growth factor receptor-expressing metastatic CRC. Objective response rate (CR+PR) was 79% according to independent expert review. Based on the apparent linearity between objective response and resectability rates, use of highly active chemotherapy regimens offers hope for many more patients to have potentially curative hepatectomy procedures. Indeed, 10 of 42 patients (24%) in this trial became eligible for resection for previously inoperable liver metastases following chemotherapy, nine of whom (21%) had R0 resection.

Data from the Paul Brousse series has shown that use of targeted agents in second-line therapy also augments the proportion of resectable patients. A total of 131 patients with epidermal growth factor receptor-positive CRLM who had progressed following two or more lines of FOLFOX or FOLFIRI regimens were treated with cetuximab.[37]

The contribution of interventional radiology

Advances in interventional radiology, in particular the so called pro-generative procedures such as portal vein embolisation (PVE) and radiofrequency thermal ablation (RFA) have contributed to the management of patients with CRLM aiming to increase the proportion of the liver that will remain after a resection.

Portal vein embolisation

Since the initial use of portal vein embolisation (PVE) by Makuuchi to induce compensatory hypertrophy of the future remnant liver in patients planned for major liver resection for cancer, a large experience has been gained by surgeons and interventional radiologists making this technique a very important part of the specialized armamentarium of every hepatobiliary unit.[38,39]

The PVE indications (more frequently performed on the right) depend on the quality and volume of liver parenchyma. Three dimensional CT volumetric measurement is necessary to calculate the total liver volume and the volume of the future remnant liver volume. In patients with an otherwise normal liver, current guidelines recommend preoperative PVE when the ratio of the remnant liver volume to the total estimated liver volume is less than 25%.[40] However, high risk patients (treated by heavy neoadjuvant chemotherapy) should undergo PVE when the ratio is less than 40%.[41]

The clinical impact of PVE has been evaluated by a number of investigators. In a study on 30 patients with unresectable CRLM due to a small remnant liver at the initial evaluation, PVE increased the remnant liver from a mean of 26% to a mean of 37%, allowing curative surgery in all cases.[42]

PVE is a safe procedure with a low 30-day mortality rate. Complications are uncommon and are similar to those associated with other percutaneous transhepatic procedures.[43] However, it is important to avoid spill over of the embolic material into the portal branches that supply the future liver remnant, and bilateral or main portal vein occlusion remains a risk. PVE has clearly contributed increasing the number of patients who can be resected without post-operative liver failure. Another potential problem with portal vein embolisation in patients with bilobar metastases is the growth of the tumor lesions on the contralateral side. It was indeed observed that during liver regeneration after right portal embolization, the growth rate of liver metastases on the left side was more rapid than that of the liver parenchyma.[44] In a Japanese study (Cancer Institute Hospital, Tokyo, Japan), a significant increase of the tumor volume following PVE was reported (from 223 to 270 mL - $P<.016$). However, no correlation was found between the increase in parenchymal volume and in tumour volume. The conclusion was that PVE increases tumour growth and probably is associated with enhanced recurrence of disease.[45]

For these reasons, in patients with bilobar disease who need a pro-generative procedure, all lesions from the side that will undergo preoperative hypertrophy preferably should be dealt with using either:

1) 2 stage-hepatectomy (with surgical removal of all lesions on the side that will remain after the second stage) and simultaneous right portal ligation with portal vein embolisation or by the iliac vein during the operation;
2) radiofrequency ablation of the lesions in the ipsilateral liver and contralateral PVE.[46,47] Using these different strategies, no mortality is observed in patients who undergo a large hepatectomy after neoadjuvant chemotherapy for CRLM.

Radiofrequency thermal ablation (RFA)

RFA is the most widely used technique for local destruction of CRLM and has gained popularity because of its relative easy usage, and its effectiveness as an adjuvant treatment.[48] For the treatment of CRLM, RFA can be used as: 1) a definitive treatment per se; 2) a complementary procedure to surgery, or 3) in the treatment of recurrent metastatic disease after surgery.

Results so far show that RFA must be restricted to cases in which the size of the dominant lesion is less than 3 cm or when a maximum of three tumours are present.[49] In a study on percutaneous RFA for CRLM, local control was achieved in 78% of tumours <2.6 cm, but only in 47% of tumours 2.6-4.0 cm and 32% of tumours >4.0 cm.[42]

The anatomic location of a metastasis is an additional limitation of RFA. In the vicinity of a large hepatic vessel, the heat sink effect significantly increases the risk of incomplete ablation. Also, the risk of thermal injury is increased when nodules are close to main biliary structures or to extrahepatic organs. In these cases, new RFA techniques or additional procedures, such as hepatic inflow occlusion or intraductal cooling, have to be considered.[50,51]

Because of the high local recurrence rates, and of the anatomical limitations described above, there is still no place for RFA in patients with resectable colorectal metastases. Surgical RFA for small resectable CRLM could only be acceptable in a randomised trial comparing resection with surgical RFA,[52] and it was shown that hepatic resection is still the treatment of choice for CRLM and that RFA alone provides survival only slightly superior to non-surgical treatment.[53] This is the case also for patients with solitary liver metastases who are treated with RFA (higher LR rate and shorter recurrence free and overall survival).[54]

Radiofrequency ablation has been proposed to treat a limited number of small metastases, simultaneously with right PVE.[46,47] Although this strategy is theoretically appealing because it limits the number of surgical operations, its effectiveness compared to two-step hepatectomies is doubtful.

The place of RFA in the treatment of CRM is limited: it is most useful for early recurrences detected as small lesions after resection, because it is not mandatory to stop the chemotherapy, except for the use of bevacizumab, and because RFA allows a ''test of time'' that helps to select out patients with very aggressive/disseminated disease that would not benefit from repeated surgery.

Advances in hepatic surgery

Liver surgery has progressed in parallel to the improvements in chemotherapy and interventional radiology. Ill located tumors (situated deeply or close to critical vascular or

biliary structures) can now be safely resected thanks to the availability of sophisticated instruments such as the ultrasonic dissector, argon gas diathermy and new techniques such as the one of low-central venous pressure anaesthesia that allows an almost bloodless field. With the routine use of intraoperative ultrasound examination precise localization of liver lesions and planning of the resection is done aiming at removing all possible lesions with a clear margin and at the same time preserve the maximum of liver parenchyma. This improvement in surgical planning and techniques has been directly responsible for the low hospital mortality.

The risk of liver resection for CRLM has decreased in specialized hepatobiliary centres probably below the figures observed after colorectal surgery. The mortality of elective liver resection on non-cirrhotic livers is estimated to be around 1%[55,56] at a time when patients' age and disease complexity are increasing, in addition to the associated changes of SOS and CASH often present in chemotherapy patients undergoing surgery.

The experience of the centre has a major impact on outcome: the mortality and morbidity of liver resections decreased inversely to the number of cases performed in the institution.[57] It has been shown in US that patients resected at high volume centres (>25 cases/year) for liver cancer have not only a better perioperative outcome, but also a better long-term survival,[58] and similar results concerning the correlation between high volume surgery and specialization and outcome were observed in Europe.[59]

As part of the above mentioned surgical improvements, there are a number of techniques which include the following:

Two-stage hepatectomy

This is a surgical strategy used when dealing with non resectable colorectal liver metastases (following preoperative chemotherapy) because of multinodular/bilateral or very large metastases that cannot be resected in a single surgical setting. Usually, the most common reason for the unresectability is the small remnant liver volume, if the resection of the metastases were to be performed.

This type of intervention consists of two hepatectomies, enabled by the regenerative capability of liver. The aim of the first hepatectomy is to render the second hepatectomy curative. During the first stage, the largest number of metastases should be resected from the less involved liver lobe. After an interval during which the future remnant liver regenerates, the remaining tumor lesions localized in the contralateral lobe are resected (the second intervention). To control the growth of the tumor between the two interventions, chemotherapy is usually administered. The majority of cases treated now by this technique require also additional PVE. In general (as noted above), the indication for an associated PVE is an anticipated future remnant liver volume of <30% or 40% in patients treated with heavy chemotherapy.

The first results of two-stage hepatectomy were reported in 2000 by our team.[60] After the first hepatectomy, the second hepatic resection could be performed in 81% of patients, with a 3-year survival of 35%. No operative deaths occurred at the first hepatectomy, compared to a perioperative mortality of 15% at the second hepatectomy. The morbidity rates are higher after the second hepatectomy compared to the first intervention (45% vs 31%). These results have recently been confirmed by our group, with a 31% survival at 5 years in intention to treat and 42% for those who completed the two,[61] as with other centers.[62]

Despite, the increased mortality and morbidity rates related to the second intervention, the two stage procedure can offer long term survival, however, this approach has a limitation as it can be offered only to highly selected patients.

Repeat hepatectomy

The liver is the primary site of tumor recurrence after hepatectomy. In such cases, repeat hepatectomy has been associated with 5-year survival benefits comparable to those achieved with primary surgery with similar low surgical risks.[19,20,26,63] Data from Paul Brousse Hospital show similar 5-year survival rates from time of last hepatectomy in patients undergoing the first (n=416; 36%) or second (n=139; 28%) hepatectomy for CRLM. Notably, among 60 patients undergoing three hepatectomies, 32% were alive at 5 years. In contrast, survival rate was 5% at 3 years in patients with recurrence after second hepatectomy who did not undergo surgery, and 15% at 2 years in third hepatectomy was incomplete (P=.0001).[18] The 65% 5-year survival rate after third resection, when estimated from the first resection, is also impressive. None of the 60 patients died during or within 2 months of the third procedure, and 25% had postoperative complications (mortality and morbidity rates similar to those observed in primary and second liver resections).[6-12,14,19,64,65] Thus, while it is acknowledged that repeat hepatectomies may be more challenging surgical procedures, evidence from these series and others indicate low procedural risks.

Extreme liver surgery

Involvement of major vascular structures (vena cava or hepatic veins) by liver metastases has been considered as a contraindication to surgery for colorectal liver metastases. However, at the present time this clinical situation is no longer considered as contraindication due to the experience gained with total vascular exclusion (TVE) of the liver combined with vascular reconstruction. These techniques have made the surgery possible even for this group of patients, without exposing them to the risk of massive intraoperative blood loss and gas embolism.

TVE consists on hepatic inflow and outflow occlusion.[66-68] This can be achieved by clamping the portal vein/ hepatic artery as well as the supra and infra hepatic vena cava. Alternatively, the hepatic veins are isolated and clamped in addition to the vascular portal structures. The latter technique is more advantageous as it can preserve the caval flow, however, in cases of caval infiltration by metastatic

lesion/s this technique is not feasible. On the other hand, if hemodynamic instability is encountered while the vena cava is clamped, a veno-venous bypass should be installed to overcome this complication.

Although, it is believed that the hepatic blood flow can be interrupted safely up to 60 minutes, when vascular resection/reconstruction is necessary, a 60 minute duration of ischemia may be not sufficient.[67] Hence, hypothermic perfusion of the liver should be instituted. The combination of TVE with in situ hypothermic perfusion was evaluated in our center.[68] We found that this combination was associated with a better liver tolerance to ischemia, a better liver function, and a significantly lower rate of complications compared to standard TVE >60 min.

In some cases, a combined liver and vascular resection may be required. Our experience with such cases (combined liver and vena cava resection) has shown that a 5-year survival of 38.3% can be obtained even for this group of patients.[69]

In conclusion, using TVE and vascular reconstruction techniques, surgery in cases with involvement of the vena cava or hepatic veins is not necessarily contraindicated. However, a very careful evaluation and selection of the cases should be done, making sure that the risks involved do not counterbalance the desired benefits.

Timing of surgery

Optimal duration chemotherapy and timing of liver surgery in responding patients have not been definitively established. For patients not considered resectable, in the clinical setting, most surgeons perform liver resection as soon as metastases become operable.

Similarly, there is still debate, whether chemotherapy should precede resection when metastases are synchronous, particularly when the primary tumor is in place and the surgery involves the resection of the primary tumor as well as a simultaneous major liver resection. At the present, many surgeons believe that the chemotherapy is a better choice for patients with synchronous liver metastases, although these conclusions come from retrospective or surgical series from a single center. Capussotti and colleagues have published several papers on this topic.[70-73]

There is only one randomized study (see Nordlinger et al)[23] which has evaluated the results of preoperative chemotherapy and demonstrating a absolute difference in favor of chemotherapy. However, this study has a drawback as it was not possible to separate the benefits of preoperative chemotherapy from those of adjuvant postoperative chemotherapy.

Another issue is the impact which the disease progression while on chemotherapy has on the timing of surgery. Disease progression during neoadjuvant chemotherapy indicates a poor prognosis. In a cohort of 131 patients undergoing rescue hepatectomy, 5-year survival rates were 8% if disease progressed during preoperative chemotherapy, 30% if disease was stable, and 37% in responders (P=.0001, log rank).[14] These findings suggest that hepatectomy for CRC metastases should be undertaken as soon as technically feasible and underscore the importance of collaboration between medical oncologists and surgeons in achieving that goal. Medical oncologists should be referring patients for surgery before tumor progression, and surgeons need to consider tumor evolution in addition to resectability. Thus, patients with biologically aggressive tumors unlikely to benefit from resection may be spared surgery upfront and can instead consult with the medical oncologist for a better regimen likely to induce tumor response or stabilization.

New treatment strategies

Today, patients with metastatic CRC should be treated by multidisciplinary teams including surgeons, oncologists and radiologists. Evidence of the benefit of perioperative chemotherapy over surgery alone[22] and the potential benefit of adjuvant chemotherapy (after liver resection)[72] caused a rethink among the experts particularly in terms of the timing of the administration of chemotherapy for CRC patients with initially resectable liver and lung metastases.

Poor prognostic factors for patients with liver metastases are multiple metastases, >5 cm in diameter, synchronous presentation, lymph node-positive primary and high tumor marker levels.[71] Thus, even when the metastases are technically resectable (in terms of number, location and size), when facing a patient with more than one of the poor prognostic factors listed above, the current trend is to refer patients for neoadjuvant chemotherapy before surgery. The data from the EORTC study showed quite clearly that nearly all patients were able to tolerate neo-adjuvant chemotherapy. Also, analysis of the PFS curves from the EORTC–EPOC trial shows that the main difference comes after the first 2 months when the curves drop down and then move out in parallel, suggesting that the benefit conferred by perioperative chemotherapy might be a consequence of a reduction in the occurrence of early cancer relapse as a consequence of preoperative chemotherapy.

An exception to preoperative chemotherapy is, however, those patients with a single resectable metachronous metastasis who could be directly referred to surgery,[74] with the recognition that this accounts for <10% of patients seen in routine clinical practice. All other patients with resectable metastases should be treated up front with chemotherapy, with the caveats that the patient is able to receive chemotherapy and the position of the lesion is not going to be lost.

On the other hand, it has also become a standard strategy to give postoperative adjuvant chemotherapy to all resected patients (if possible) based on the data for the resected patients in the EORTC–EPOC trial.[22]

For patients who are non responders, there are two treatment strategies available: 1) change to a new chemotherapy protocol or 2) liver resection before the metastatic disease becomes unresectable. At this point it is important to mention that, the decision to perform either treatment strategy should always be decided by a multidisciplinary.

Currently, it has become mandatory to select the systemic therapy regimen based on biological predictive factors, such

as KRAS mutation status. This strategy has had a double impact: first of all, it has helped to optimize the choice of first-line treatment, in turn decreasing the risk of immediate disease progression; secondly, it has also helped to better select the second-line 'rescue' treatment strategies with the possibility of resection.[37] However, considering that surgery is still the only treatment that has curative potential per se, in some situations this can be the treatment of choice, even if resistance to medical treatment generally means that the patient has a unfavorable tumor biology. The situation is much simpler for patients whose metastases are initially unresectable, where systemic therapy is administered until an adequate response has been achieved.

Conclusions

Hepatic resection of colorectal liver metastases after downsizing by chemotherapy provides the only chance of long term survival for patients with initially unresectable colorectal liver metastases.

Additional surgical techniques can be combined to chemotherapy to further improve resectability. The only absolute contraindication for resection is the inability to completely resect all metastases, avoiding postoperative liver failure by leaving enough functional liver parenchyma. The presence of poor prognostic factors no longer limits the indications for resection.

Neoadjuvant treatment with chemotherapeutic agents such as irinotecan and oxaliplatin, hepatic artery infusion combined with systemic therapy and biologic agents (bevacizumab, cetuximab) play an important role in increasing the number of patients eligible to secondary resection.

However, with the progressive use of neoadjuvant chemotherapy further studies are necessary to answer questions such as the risk: benefit ratio in maximizing response rates versus vascular changes in the liver (current opinion still divided concerning their importance). These questions remain challenging and should not be underestimated.

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