

Colorectal Cancer with Liver Metastases – is there a Chance for Cure?

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Rezumat

Cancerul colorectal cu metastaze hepatice – există șanse de vindecare?

Tratamentul multimodal care include rezecția metastazelor hepatice și chimioterapia este standardul pentru pacienții cu cancer colorectal cu metastaze hepatice care pot fi aduse la rezecabilitate și o metodă foarte eficientă de a ameliora supraviețuirea pacienților. O strânsă colaborare între chirurghi și oncologi este obligatorie pentru a asigura acestor pacienți șansa unei supraviețuiri pe termen lung. Pacienții cu boală rezecabilă trebuie să urmeze chimioterapie adjuvantă în timp ce pacienții cu boală inițial nerezecabilă sau marginal rezecabilă pot beneficia de reducerea în dimensiuni a metastazelor după chimioterapie neoadjuvantă urmată de reevaluare chirurgicală în vederea rezecției metastazelor hepatice și apoi chimioterapie adjuvantă. Un număr impresionant de tehnici inovatoare pot asigura succesul rezecției hepatice în timp ce o pleiadă de agenți chimioterapeutici și biologici de ultimă generație asigură rate de răspuns, rate de rezecabilitate mai înalte și o supraviețuire superioară pe termen lung.

Cuvinte cheie: cancer colorectal, metastaze hepatice, tratament multimodal, rezecție hepatică

Abstract

Combined treatment with chemotherapy and surgery is the currently accepted standard for patients with metastatic colorectal cancer which can be rendered to resectability and a very efficient way to increase survival of patients with hepatic metastases from colorectal cancer. Cooperation between surgeons and oncologists is mandatory to insure these patients' best chance for survival. Patients with resectable disease must follow adjuvant chemotherapy, while patients with initially unresectable / marginally resectable disease after downsizing with the help of chemotherapy must be given the chance of surgical reevaluation for having the metastatic disease resected, and then follow adjuvant chemotherapy. An impressive amount of new surgical techniques warrants the success of hepatic resection in metastatic disease while a whole constellation of novel chemotherapeutical and even more effective targeted agents assure better response rates, surgical resection rates and overall survival in these patients.

Key words: colorectal cancer, liver metastases, multimodal treatment, hepatic resection

Introduction

Colorectal cancer is a major health concern, third as prevalence globally after lung and gastric cancer. Over one million new cases occur each year and over half a million die due to this disease. Patients die mainly from metastatic disease, with a poor survival of 55% of patients alive five years after diagnosis for colorectal cancer of all stages (1). Over 50% of the patients with colo-rectal cancer present with liver metastases or develop liver metastases (2). At the moment of diagnosis, 15-25% of the

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patients have liver metastases. Another 35-45% will develop liver metastases as a result of disease progression. In approximately 50% of patients with liver metastases the liver is the sole site of metastases (3). The prognosis of metastatic colorectal cancer has substantially improved in the last 20 years due to the unprecedented development of cytotoxic and targeted therapy, and on the other hand due to advancements in surgical technique, improvements in the safety of hepatic resection. Both opportunities for surgery and the efficacy of chemotherapy have improved a great deal. Surgical resection, barely used in the 1990's, is a standard approach today, being applied in specialized centers in up to 20% of the patients with metastatic colo-rectal cancer (4). An indicator of the extent of hepatic surgery in colorectal cancer liver metastases is the modification of the staging system, the 7th edition of TNM classification dividing stage IV M1 disease in M1a (metastases in one organ) and M1b (metastases in the peritoneum or two or more organs)(5). Since 1957, 5-Fluorouracil has been the backbone of chemotherapy in colorectal cancer (CRC) providing a median survival of 6 to 12 months in metastatic disease, regardless of the administration schedule (bolus / continuous infusion). Novel chemotherapy agents as oxaliplatin, irinotecan improve the median survival, bringing it to a 17-21 month plateau. Targeted agents as bevacizumab, cetuximab, panitumumab are responsible for increasing the median survival above 2 years in metastatic setting. Despite all the advances of chemotherapy, this does not confer cure to this category of patients, the 5-year overall survival being 1-2%. A second and major development in these patients is the increased recognition of the role of surgery in this setting (6).

1. The role of surgery

Surgery is needed to further increase this percentage, and in cases in which liver resection can be performed the 5-year survival is 30-40% in historical series (7). A randomized clinical trial which investigated patients treated with or without surgery has never been conducted because it was not considered ethical for patients with resectable disease, but no other treatment has demonstrated similar results. The majority of monoinstitutional studies report survivals between 21-48% at five years (8,9). Although these retrospective studies have been criticized for suffering from selection bias, they have been able to show that long-term overall survival is possible in metastatic disease. A number of studies demonstrated long-term survival rates of 22-24% at 10 years (10), and others reported survival over 20 years of patients with resected metastases (11). Thus, surgery of hepatic metastases has become the standard of care and the only curative therapy. Resection is possible in approximately 20% of patients with disease limited to the liver, meaning 5-10% of the total number of patients (12). The decision to resect metastases is taken according to several factors, resectability being the main one. The definitions of resectability in liver metastases have been multiply changed along the years. Historically, metastases were considered unresectable if they were poorly located, large, multiple or if extrahepatic disease was found (13,14,15). Nowadays, these

criteria have grown in laxity and differ from center to center and country to country (16,17). Today, hepatic resection requires preserving a minimum of 30% of functional liver tissue with adequate vascular supply and biliary drainage, 40% in case of liver cirrhosis. Other factors are the experience of the center and mostly of the surgeon, prognostic factors after resection like stage of primary tumour, disease free interval, number of metastases and co-morbidities (18,19). It is also important that the resection shall not be too risky due to location in terms of proximity to large vessels. The only prerequisite is attaining a complete macroscopic and microscopic resection (20,21). Age is not a contraindication for metastasectomy in patients with a good performance status, but it is known that mortality increases with age: 1.5% in patients younger than 70 years and 4.5% in patients older than 70 years (22). The general consensus of a panel of experts established in 2009 that, probably, a perfect definition of resectability will never be found because of the highly diverse patterns of presentation. An interesting idea promoted by the same panel advocates that it is better to remove a metastasis practicing an R1 resection than to leave it in place (23).

Advancements in surgical approach

Introduced by Makuuchi (24,25,26), intraoperative ultrasound (IOUS) has been integrated in the armamentarium of the hepatic surgeon, playing a valuable role in hepatic resection. IOUS can detect lesions that can be missed by preoperative imaging techniques and intraoperative palpation (in 10-50% of the patients comparing to preoperative imaging), and also allows the description of unsuspected proximity of the metastases to intrahepatic vasculature, plus the segmental hepatic resection which can spare precious hepatic parenchyma, and intraoperative checking of distance between dissection plane and the metastases which ensures adequate resection margins. The sensitivity of the method is so high that it has a role even after preoperative magnetic resonance imaging (27). Intraoperative blood loss is a significant prognostic factor for postoperative mortality after hepatic resection (28). Another advance in surgical approach is blood loss control by vascular occlusion techniques, which is an independent prognostic factor of postoperative outcome, significant hemorrhage occurring in 1-3% of cases. Minimizing blood loss allows the surgeon to pursue an aggressive approach in the condition of limited hemorrhage (29). This percentage is lowered by using low central venous pressure anesthesia (under 5 mm Hg) and vascular clamping techniques such as Pringle maneuver (compression of hepatoduodenal ligament) (30) which has the disadvantage of important hepatic ischemia unless it is frequently released and half-Pringle maneuver (unilobar vascular inflow control and normal flow to contra-lateral lobe). Another innovative strategy which prevents ischemic hepatic reperfusion consists of exposure of the liver to short episodes of ischemia-reperfusion before a longer ischemic period, technique called ischemic preconditioning – a much more well tolerated one, with smaller percentage of serum transaminases elevation (31). Another option is infrahepatic caval clamping (32). Using both techniques (low CVP and intermittent inflow occlusion) the

incidence of hemorrhage and postoperative morbidity is significantly lower (33). Reducing hemorrhage translated in shorter intensive care periods and fewer total hospitalizations. Novel devices of parenchymal transection have been implemented in order to limit blood loss which can occur in hepatic surgery either during the dissection of the vena cava and hepatic vein or most commonly during parenchymal transection. There are in use devices using water-jet dissectors and also ultrasonic dissectors which enhance hemostasis compared to the classical approach (34,35). The novel device TissueLink uses saline and radio-frequency energy and pre-coagulates liver parenchyma and closes small vessels. The advantage of these devices is that they allow hemostatic parenchymal transection without need for inflow occlusion (36). Radiofrequency ablation is very useful in assisting surgery and allowing complete eradication of hepatic disease in conjunction with surgery, but cannot be recommended to replace surgical resection. It can be used by itself only in patients with comorbidities that prevent them from undergoing surgery.

Controlled anatomic hepatectomy: glissonian technique

The studies of Couinaud allowed a rapid evolution of controlled parenchymal-sparing segmental hepatic surgery. The basis of the technique consists in the knowledge that Glisson's capsule surrounds the hepatic trinity structures. The advantages of the Glissonian technique are preservation of normal liver parenchyma, which limits the incidence of postoperative liver failure. It also allows repeated hepatic resections in the conditions of recurrent intrahepatic disease demonstrated to occur in approximately 60% of cases (37). An approach pursued in the last decade is an aggressive one, consisting in repeated hepatic resection, complex multivisceral resection, en-bloc vascular resection.

Repeated hepatectomy

In a multicentric French study, recurrence occurred in the same hepatic lobe in 28% of patients and opposite lobe in 35% of the patients who had benefited from hepatic surgery. Retrospective studies reported that repeated hepatectomies can be achieved with a mortality rate of 1.6 to 9% and a complication rate of 40%, however with a high recurrence rate of approximately 70%, the liver remaining the main site of recurrence. Even threefold hepatectomy insures a much higher survival rate comparing to palliative chemotherapy (32% versus 5%)(38,39).

Complex multivisceral resection

Traditionally, the extension of metastatic disease beyond the liver was considered a contraindication for hepatectomy. Hepatic resection extended to removal of intrathoracic or intraabdominal organs (lung, pancreas, bowel, diaphragm) is nowadays pursued on a large scale in specialized centers, of course with an increased risk of morbidity and mortality (40). Some authors found that extrahepatic procedures within multivisceral resections are a predictor of postoperative mortality, while others did not demonstrated a similar correlation (41,42).

En-bloc vascular (IVC, hepatic vein) resection

Lesions situated in the posterior or central segments that may involve the hepato-caval confluence and inferior vena cava were in the past also considered contraindications to hepatic surgery. Now, in the era of innovative surgical techniques using veno-venous bypass, total hepatic vascular exclusion, ex-vivo hepatic resection, this resection has become possible (43).

Hepatic pedicle lymphadenectomy

Portal lymph node metastases are an indicator of systemic disease and were a classic contraindication for hepatic surgery. Jaeck was the first who changed this belief and performed complete hepatic pedicle lymphadenectomy in conjunction with hepatic metastasectomies. The prognosis of patients who had nodal metastases in the portal triad was better than of those who had lymphatic metastases along the hepatic artery and celiac axis (38% versus 0% survival at 3 years) (44). Taking into account a 5 year overall survival of 12% of this category of patients, the value of hepatic pedicle lymphadenectomy has to be seriously questioned. Among innovative approaches to allow complete resection of liver metastases are: preoperative portal vein embolization or ligation, staged hepatic resection and some new methods that improve surgical resection margins.

Preoperative portal vein embolization and/or ligation

In the case that the remnant liver is not functionally adequate in inoperable or even operable metastases, a proven method to prevent postoperative liver failure is portal vein embolization or ligation as a first operative step preceding liver resection. The portal vein embolization initiates compensatory liver hypertrophy, a technique developed by Makuuchi (45). After portal vein embolization/ligation a median 42% gain in liver remnant volume was described, that allowed resection in 63% of patients considered initially inoperable (46). Some authors proceed to portal vein ligation at the time of the colon resection, then after a period of palliative chemotherapy, hepatic resection is performed (47).

Staged hepatic resection

Staged hepatic resection is a strategy developed by Adam and Bismuth, consisting of planned two-staged hepatic resection. The first resection removes the highest number of metastases possible, followed by chemotherapy, while the second resection removes the residual lesions while the remnant liver hypertrophies. A perioperative death rate as high as 15% is a direct consequence of high tumor burden, technically difficult procedures and general toxicity of chemotherapy (48). Belghiti proposed an approach consisting of resection of metastases from the left liver concurrently with right portal vein ligation for bilobar metastases, then a right hepatectomy (49). A surgical resection margin of 10 mm has been identified as a significant prognostic factor after metastasectomy. A negative margin less than 10 mm has been demonstrated to have negative impact on prognosis, increasing significantly the

recurrence rate, while a positive margin doubles it. In patients in which a negative surgical margin is difficult to obtain, radio-frequency energy can be used to treat the edge, creating thusly a zone of ablated tissue which has no viable tumor cells (50).

2. The role of systemic chemotherapy and targeted therapy

Three treatment situations are distinguished: patients with resectable disease, patients with potentially resectable disease and patients with metastases which are unlikely to become resectable even after very active chemotherapy treatment. For patients who have unresectable metastases the goal is to improve the quality of life and to prolong overall survival with palliative chemotherapy. For patients with resectable disease it is important to know the results of adjuvant and neoadjuvant chemotherapy. Disease free survival is a surrogate parameter for adjuvant/neoadjuvant chemotherapy.

- a. Patients unlikely ever to become resectable after most active chemotherapy regimens do not benefit from surgery, the median survival in this category of patients can exceed 24 months with the addition of targeted therapy due to the advances in the last decades.
- b. Patients with initially unresectable metastases

Chemotherapy is the only method which has proved survival benefit in randomised clinical trials in metastatic colorectal cancer, but it is also a method to achieve resectability which has superior results. Patients which have benefited of all therapeutic options have superior outcomes. Among the first studies that have proved successful resection of liver metastases after neoadjuvant chemotherapy were those conducted by Fowler 20 years ago and later Giacchetti (51,52). Initial studies used 5-fluorouracil and folinic acid regimens while later ones added oxaliplatin or irinotecan. In the study conducted by Giacchetti resected patients had a 50% overall survival rate at five years while non-resected ones had a median overall survival of 15 months. An observational study conducted by Rene Adam reported five year and ten year overall survival of 25% respectively 33% in patients with initially unresectable disease who underwent successful hepatectomies and chemotherapy (53). Also a retrospective study demonstrated that the response rate to neoadjuvant chemotherapy is correlated with the resectability rate (54). The response rate of chemotherapy when doublets of 5-fluorouracil with oxaliplatin or irinotecan are used is 40-50% (55,56,57). The observed resectability rate for the FOLFOX regimen in a prospective multicentre was 33% (58). According to the hypothesis that the response rate is correlated with the resectability rate, more active regimens with higher response rates than standard doublets are needed in order to increase the number of patients which can benefit of a curative resection. Current recommendation in this setting is to treat patients with initially unresectable disease with the most active regimen in terms of progression free survival that he can tolerate and to undertake the surgical resection as soon as possible to minimize the toxic effects of chemotherapy on the liver. Such combinations are chemotherapy triplets and combination of chemotherapy with targeted therapies.

Chemotherapy triplets

The combination of 5FU/folinic acid with oxaliplatin and irinotecan known as FOLFOXIRI or FOLFIRINOX have much higher response rates than classical doublets (60% versus 34%) and a higher R0 resection rate in initial unresectable metastases (15% versus 6%, $P=0.033$)(60). A French phase II study obtained a 71% response rate with standard-dose triplet therapy and a R0 liver resection rate of 27% (61).

Targeted therapy

Both epidermal growth factor receptor inhibitors and monoclonal antibody blocking vasculo-endothelial growth factor have been demonstrated in clinical trials to enhance the response rate in metastatic colorectal disease, progression free survival and overall survival. Cetuximab has proven its efficacy in wild type K-ras patients, in clinical trials CRYSTAL, OPUS and COIN. In trials using the combination of oxaliplatin-based chemotherapy OPUS and COIN response rates varied between 57% and 59% using targeted therapy, statistically significantly improved compared with chemotherapy alone (62,63). In the OPUS trial progression free survival was also significantly prolonged (8.3 months versus 7.2 months, $P<0.01$). The subgroup analysis of patients with liver limited metastases showed a 71% response rate with FOLFIRI + cetuximab versus 44% with FOLFIRI ($P=0.002$) and 76% with FOLFOX + cetuximab compared with 39% with FOLFOX ($P=0.02$). The CRYSTAL trial comparing FOLFIRI $\pm$ Cetuximab response rate was ameliorated with a very high statistic significance (59% versus 40%, $P<0.001$), as well as the progression free survival ($P<0.01$) and overall survival ($P<0.01$), also a higher rate of R0 metastasectomies (5.1% versus 2%, $P<0.05$)(64,65). In the CELIM trial patients were randomized between two arms of treatment containing FOLFOX+Cetuximab versus FOLFIRI + Cetuximab in patients with non-resectable liver metastases in neoadjuvant setting. The trial found a 70% response rate in K-ras wild type patients and a 34% R0 resection rate (66). In the PRIME trial, FOLFOX+Panitumumab demonstrated a 55% response rate and a significantly prolonged progression free survival ($P<0.05$) (67). Bevacizumab added to conventional chemo-therapy regimens like IFL or FU/folinic acid, have increased response rates by 9-10%, but not in a very spectacular manner (45% versus 35% and 34% versus 25%)(68,69). Added to FOLFOX/CapeOx in trial NO16966 bevacizumab has not demonstrated a benefic effect in terms of response rate (38% versus 38%) and resection rate (8.4% versus 6.1%)(70). It results thus, that in neoadjuvant setting the most efficient regimens are FOLFOX+cetuximab or FOLFIRI+cetuximab in KRAS-wild-type patients and FOLFOXIRI.

Resectable metastases

For patients with resectable metastases there is a debate going on whether they do need neoadjuvant treatment or adjuvant treatment is sufficient. The necessity of adjuvant treatment in stage IV patients with resected metastases comes from the extrapolation of the results of adjuvant treatment in

stage II and III colorectal cancer and a few prospective clinical studies. In the United States and Europe, chemotherapy is administered following hepatic resection, even if the benefit was not demonstrated in clinical trials. There are few randomized studies for adjuvant therapy after liver resection. Two studies investigated the role of 5-FU-folinic acid adjuvant chemotherapy but were ended early because of poor recruitment. One study was conducted by Langer et al, on 129 patients and failed to demonstrate a significant improvement in disease free survival (71). The other study, conducted by Portier et al on 171 patients, showed a significant improvement in disease free survival (72). The metaanalysis of both trials showed a trend towards an improved disease free survival and overall survival, but with no statistic significance ($P=0.058$) (73). However, multivariate analysis of the pooled data showed that chemotherapy is a statistically significant prognostic factor. Another phase III study comparing FOLFIRI adjuvant chemotherapy with 5-FU / folinic acid reported disease free survival of 24.7 versus 21.6 months for FOLFIRI and 5FU/folinic acid, 2-year overall survival of 63% versus 46% and no statistic significant difference was shown between the arms. Therefore adjuvant chemotherapy after liver resection is considered an option especially in patients who did not receive chemotherapy pre-operatively (74).

The question whether perioperative chemotherapy brings benefit to patients with resectable metastases was also addressed. The EORTC 40983 trial randomised patients with resectable hepatic metastases either to perioperative chemotherapy (3 cycles of FOLFOX preoperatively and 3 cycles postoperatively) or to surgery alone. The trial was negative in the intention to treat analysis with a strong trend to improve disease-free survival (HR 0.79 (0.62-1.02), $P=0.058$). Using the common definition of progression-free survival for the patients actually resected, the results were positive, that is why the interpretation is that patients do benefit after perioperative chemotherapy (75). Because the situation for the patients with resectable disease was unclear, a literature based meta-analysis was performed comparing surgery alone with the combined approach consisting in any preoperative or postoperative chemotherapy added to surgery. Because this meta-analysis showed significant benefit for disease-free survival it is considered that surgery alone is no longer acceptable even in case of resectable metastases (76).

The question whether neoadjuvant therapy is necessary or adjuvant treatment is sufficient remains unanswered. For the benefit of neoadjuvant chemotherapy stands the fact that almost a quarter of the patients enrolled in the EORTC study did not receive adjuvant therapy. Against it stands the fact that neoadjuvant chemotherapy increases perioperative morbidity. At present there are two studies enrolling patients for clarifying this situation. A NSABP (NCT01189227) and a German AIO study (NCT01266187) are randomizing resectable patients to perioperative versus postoperative chemotherapy, the first using FOLFOXIRI/bevacizumab, the second FOLFOX /cetuximab.

While European guidelines recommend a perioperative

approach, the German guidelines recommend neoadjuvant or adjuvant therapy without clear recommendation. Chemotherapy before surgery of the resectable metastases can increase pathological complete response rate, facilitate limited hepatectomies, treat micrometastases, test chemoresponsiveness and identify aggressive disease, prolong disease free survival, benefits demonstrated by the EORTC 40983 trial.

Conclusions

Resectability in patients with hepatic metastases of colorectal cancer is not a good end-point in clinical trials because it is far too subjective. The term "cure" changed its meaning in patients with colorectal cancer, being possible even in advanced or metastatic stage. The aim of the treatment should be to achieve adequate tumor shrinkage that enables surgery. With this combined approach and cooperation between surgeons and oncologists even metastatic disease can be cured with 10 years survival of 22-24%.

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