Surgical management of hepatic metastases of colorectal origin

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Abstract

Colorectal cancer is the most frequent digestive cancer. Prognosis is greatly depending on the TNM stage at the time of diagnosis. Fifty percent of all patients shall develop, synchronously or metachronously, liver metastases. Different means such as chemotherapy, targeted therapies, radiofrequency ablation, portal vein embolization and two-stage hepatectomy may be used to make these metastases eventually resectable and to increase overall survival. This is a short review of these different methods used to increase resectability but also on the integration of these parameters in a larger approach of colorectal liver metastasis surgery especially insisting on multidisciplinary discussion. (Acta gastroenterol. belg., **2009**, 72, **321-326**).

Key words : review, metastasis, colorectal cancer, surgery, chemotherapy, radiofrequency ablation, liver.

Introduction

Colorectal cancer is the most frequent digestive cancer in Western Europe and six thousand new cases are diagnosed each year in Belgium (1). Prognosis is greatly depending on the TNM stage at the time of diagnosis. Overall survival at 5 years ranges between 40 and 50% all stages included. Metastatic disease even if associated with a lower survival cannot be considered any longer as a palliative situation. In this review we report the different means which can be used to improve long-term survival in patients with metastatic colorectal cancer.

Why should we always try to resect colorectal liver metastases ?

At the time of the diagnosis, 20 to 25% of patients show clinically detectable liver metastases and 40 to 50% will eventually develop liver metastases after resection of the primary, usually within the first three years of the follow-up (1-5). However, there is a strong heterogeneity among these metastatic patients and their prognosis strongly depends on the pattern of the liver disease. Three separate groups can be made based on that point : the first group (concerning about 10% of the metastatic population) includes directly fully resectable patients. A complete resection in this setting allows a 5-year overall survival ranging between 40 and 48% (6). The benefit of this complete resection can be even seen at very long term (10-year overall survival of 25%) (7).

The second group includes the definitively non resectable patients who can only be treated in a palliative mean. Their long-term prognosis is very poor with a 5-year overall survival of 3% in spite of an increasing effectiveness of systemic chemotherapies in terms of response and median survival (8).

The third group includes initially non resectable patients who, after neo-adjuvant treatment, can eventually be eligible for surgery. They represent about 30% of the metastatic patients and their 5-year overall survival after resection is 35% (9). Aggressive surgery (directly or after neo-adjuvant treatment) is therefore the only chance for long-term survival. Some teams strongly advocates for a change in the actual cancer staging to directly include the idea of potential resectability in it (10).

What is a non-resectable liver metastasis ?

We must consider to this day that a hepatectomy must be performed when a complete resection is technically feasible. Irresectability does not depend on tumorous characteristics but exclusively on technical criteria. A planned hepatic resection of more than 70% of functional liver, an invasion of the 3 hepatic veins (without possible vascular reconstruction), a severe hepatocellular insufficiency (Child-Pugh B or C cirrhosis), an impairment of global status (WHO scale 3 or 4) contraindicate liver surgery (11,12). Extra-hepatic disease is no longer a contraindication for liver surgery if a complete resection can be achieved (3). Bad prognosis factors (6,13) (Table 2) should not prevent resection since latest studies confirmed that the 5-year overall survival after resection in these cases was far better than without surgery (6).

In case of associated lung metastasis

It is the most frequent extra-hepatic disease, but when completely resected, it allows a 5-year overall survival

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Table 1. — **Hepatic resection classification according to the surgical technical difficulties**

Type 1 resection	Usual hepatectomy (4 segments or less, leaving more than 40% of residual parenchyma)
Type 2 resection	Complex or very large hepatectomy (more than 4 segments) requiring a difficult and/or risky procedure (eg : central hepatectomy with vascular exclusion, extended right hepatectomy, vascular reconstruction)
Impossible resection	Involvement of the 2 portal pedicles ; involvement of 1 portal pedicle and of the contralateral hepatic vein ; involvement of the 3 hepatic veins

Table 2. — **Criteria for bad prognosis of hepatic colorectal metastases**

Size ≥ 5 cm
Number > 3
Bilobar involvement
Invasion of hilar lymph node
Elevated angiotensine converting enzyme

ranging between 20 and 31% (14,15). Radiofrequency, in this setting, can be used as efficiently as surgery to treat lesions less than 3 cm, especially those deeply located to avoid large lung resection and spare pulmonary tissue (in case another procedure is required in the future or because of poor global status) (16). Pulmonary resection is usually scheduled 2 to 3 months after liver surgery if synchronous resectable hepatic disease is present at the time of diagnosis (17).

In case of associated ovarian metastasis

Isolated ovarian metastasis of colorectal cancer is an excellent indication for bilateral ovariectomy because survival benefit is as good as a complete hepatic metastasis resection (17). This ovarian metastasis resection must be done even in case of non resectable extra-ovarian metastasis because of the particular resistance to chemotherapies of this localization (18). Some teams therefore recommend systematic ovarian resection for menopausal women in case of colorectal cancer (19).

In case of associated peritoneal carcinomatosis

The hyperthermic intraperitoneal chemotherapy (HIPEC) principle is to treat the macroscopic peritoneal disease with a complete surgical resection and the residual microscopic disease with a local chemotherapy. Associated to a limited but completely resectable hepatic disease, it allows a 5-year overall survival of 50%. This treatment cannot be given if the hepatic resection scheduled is concerning more than 3 segments because perioperative mortality in this setting is nearly 100% (20,21). The best regimen of chemotherapy is still undefined. Nevertheless, this treatment is very aggressive by itself and cannot be given to every patients suffering from colorectal liver metastasis. It must be performed in experienced centres (17).

In case of hepatic lymph node invasion

Overall survival after hepatic resection in case of lymph node invasion greatly depends on the extent of invasion. After surgery, 5-year overall survival is 25% when positive hilar lymph nodes are present and 0% in case of positive coeliac or lumbo-aortic lymph nodes. Anyway, median survival is greater after liver resection than when suspected lymph node invasion, whatever their localization, had contraindicated the technically feasible surgery (22).

In case of other extra-hepatic disease

Other localizations (brain, adrenal, bone, spleen) are usually associated to an extended non resectable disease but survival benefit has been reported when complete resection was achieved and therefore should be discussed (17) (23-26).

How can we increase liver resectability ?

Survival greatly depends on a complete resection (6). When technical criteria contraindicate surgery, neo-adjuvant treatment can eventually allow resectability by different means.

Systemic chemotherapy

More and more efficient, with a response rate ranging from 39 % to 66% (27) for the most intensive regimen, systemic chemotherapy decreases tumorous volume, allowing a complete resection in up to 36% of the initially non resectable cases. The actual trend in the literature is to give the most active chemotherapy in first line to ensure resectability since if less active therapies were given, induced chemoresistance would lower the further response rate and therefore resectability. Chemotherapy is also used as a therapeutic test to avoid operating on a patient in tumorous progression (28,29). FOLFOXIRI is recommended in first line treatment of initially unresectable disease to achieve a 71% response rate allowing downsizing and a resectability rate of 54% (28). In case of initially resectable disease, perioperative chemotherapy FOLFOX4 type must be discussed (30).

Intra-arterial hepatic chemotherapy

Administration of chemotherapy in the common hepatic artery by means of surgically or radiologically implanted catheter seems very promising to get a first or second-line response (31-33). Nevertheless, these results still need to be confirmed before being integrated in routine handling of liver metastasis.

Chronomodulated chemotherapy

Some teams have shown a benefit of a chemotherapy administration according to circadian rhythm. This attitude remains highly controversial (34,35).

Targeted Therapies

Cetuximab is a monoclonal antibody aimed towards epidermal growth factor receptor (EGFR). It results in an inhibition of cellular proliferation and stimulation of cellular death hereby preventing metastases formation (27). It may be efficiently used in first line with a response rate of 41 to 72% depending on the studies but also in second line in case of tumorous progression with a response rate between 20% and 25% (27) (36-38). Bevacizumab is another monoclonal antibody aimed towards vascular endothelial growth factor (VGEF) (7).

This good response can be potentially used to increase resectability.

Radiofrequency ablation (RFA)

RFA consists in the deliverance of high-frequency (460-500 Hz) alternating current through a probe positioned in the tumour, which is turned into heat (> 50°C) that causes tissue hyperthermia and cellular destruction. Peroperative RFA of deeply located lesion of less than 3 cm, distant from large vessels and at more than 1 cm far from biliary tract can be used to increase the resectability rate but also spare healthy adjacent hepatic tissue in view of further recurrence (39-42).

Portal vein embolization (PVE)

If to achieve complete resection, residual functional liver volume is estimated to be less 30% by scanographic volumetry (or 40% in case of intensive pre-operative chemotherapy), a selective PVE should be proposed to induce a hypertrophy of the future remaining liver and therefore to prevent postoperative hepatic insufficiency. Two different techniques are available, a percutaneous transhepatic approach and a surgical approach with a direct canulation of an ileocolic vein. Different agents can be used (fibrin glue, ethanol, gel foam, metal coils and cyanoacrylate). After embolization, a delay of 5 to 6 weeks must be observed before liver surgery to ensure enough liver growth. Chemotherapy must be continued to avoid intercurrent tumorous progression but a 3-week period must be observed after PVE to prevent interference with initial liver regeneration (43). The risk of tumorous progression of the lesions in the non embolized liver must be prevented with a surgical resection (two-stage procedure) or with a percutaneous radiofrequency ablation (44). 5-year overall survival of liver surgery for colorectal metastasis after portal vein embolization is similar to that observed in patients with initially resectable liver disease (45).

Two-stage hepatectomy

This approach consists in realizing two successive liver surgeries, using the natural regeneration of the liver between the two procedures to obtain a complete tumorous resection without risk of postoperative liver failure. The aim of the first stage is a "cleaning" of the less invaded hepatic lobe usually (but not always) associated to a portal venous embolization of the contralateral lobe. The second stage takes place 6 weeks later when enough liver regeneration is achieved, removing the shrinked embolized lobe (46,47). After the first hepatectomy, the second hepatic resection could be performed in 81% of patients with a 5-year overall survival of 35%. A systemic chemotherapy is usually given between the two stages, 3 weeks after the initial step, to avoid tumorous intercurrent progression (43).

Replacement of inferior vena cava and hepatic veins

The replacement of vena cava and/or hepatic veins is required when tumour is close and/or invading these vessels. It is a technically difficult surgery, it requires adequate material (i.e. total vascular exclusion of the liver, topical and internal cooling, extracorporeal circulation). This technique allows a 5-year overall survival of 38.3%. This surgery should remain restricted to experienced centres (48,49) to achieve these results.

Hepatic surgery first (3,57,58)

Some teams believe that the long-term survival of metastatic colorectal cancer patients is mainly due to liver metastasis removal and if there is progression during the treatment of primary tumour, it prevents resection and therefore cure. So they proposed to treat hepatic metastases first and the primary lesion after. The initial results seem encouraging with a benefit on overall survival at 5 years (50).

Liver transplantation for colorectal cancer metastasis

Liver transplantation to this day has no place in the treatment of non-resectable liver metastases although some case reports showed very long-term survival (51).

What to do in case of progression during chemotherapy ?

In this particular setting, results after liver resection are bad (5-year overall survival of 8%) and in this case, surgery must be delayed and replaced with another line of chemotherapy (associated or not to targeted therapy) to control the tumorous progression before considering surgery again.

When should the resection be performed ?

The length of neo-adjuvant chemotherapy must be as short as possible and resection must be considered as

soon as it is technically feasible because there are three main risks of prolonged treatment :

– Progression during treatment which contraindicates surgery and requires a switch in chemotherapy regimen (with a lesser response rate, decreasing therefore resectability rate) (52).
– Radiological disappearance of the liver lesions which is barely meaning complete histological response, recurrence occurring in 85% of the cases when the initial site of the nodule is not resected (53).
– Hepatotoxicity (fibrosis, steatosis, steatohepatitis, vascular lesions, Sinusoïdal Occlusive Syndrome) which seems to increase post-operative morbidity (and mortality from steatohepatitis) (54-56).

For these reasons, most of the teams recommend a radiological evaluation every 2 months of systemic treatment to be sure not to miss the optimal therapeutic window. This implies a close collaboration between the oncologist and the surgeon. Anyway, to avoid chemotherapy related morbidity, 3 weeks must be waited before surgery after the last chemotherapy and 5 weeks when targeted therapy is associated.

Who should perform the resection ?

The volume of activity has a positive effect both on short- and long-term outcome for patients subjected to major hepatic resection (3,57,58). Membership of an multidisciplinary oncology team (MDT) is also improving outcomes in upper gastrointestinal cancers (59).

In Belgium there is no official competence recognition as hepatobiliary surgeon. Legally, all surgeons have the right to perform hepatic resection but since global results are correlated to the activity, this attitude has to be clarified. To solve this problem, the French federation of digestive oncology (FFCD) defined two types of resection regarding their complexity and eventually recommends type 1 resection to be performed in any centre but type 2 to be restricted to experienced centres (Table 1) (60).

Should we resect liver metastasis in elderly patients ?

In 2010, 9% of Belgian population shall be more than 75-year old and 2.5% more than 85. In 2003 in Belgium men have a life expectancy of 75.85 years and women 81.69 (61). Liver surgery for colorectal cancer metastasis among the elderly population has a 5-year overall survival of 35% and studies show that age is no longer the only criterion of selection for surgery (6). A decision must be taken after global geriatric evaluation including dependence level and especially associated comorbidities. Resection should be proposed every time possible (62).

What to do in case of recurrence after liver resection

When recurrence occurs, lesions must be considered as the initial hepatic metastases and a re-resection should be proposed whenever possible. The 5-year overall survival is respectively 38, 32 and 32% after a second, third and fourth hepatectomy (1,6). Radiofrequency ablation is an alternative choice with good result although not fully validated in case of liver recurrence (41).

Conclusion

Complete resection of colorectal liver metastasis should be considered as an endpoint from the beginning of the treatment because it is the only hope for long-term survival. Many means allow a patient to benefit from surgery for an initially non resectable disease. Research greatly focuses on these neo-adjuvant treatments to eventually increase resectability. Search for accurate predictive factors of chemotherapy response, with great interest in genomic analysis, might help to tailor individual effective chemotherapy before starting the treatment. Another expected line of research in this preoperative treatment is the identification of new molecular targets for which targeted therapies could be given. One interesting experimental technique of preoperative treatment, issued from limb sarcoma and melanoma, consists in an isolated liver perfusion with high dose of chemotherapy under total vascular exclusion and shows good results but is technically difficult and associated to a high morbidity and mortality (63,64). These means must be integrated into a global approach of the disease and the result of a multidisciplinary team discussion. To this day, resection criteria are exclusively technical and bad prognostic factors, as well as extra-hepatic resectable disease, should not exclude liver resection anymore. When metastatic disease resectability is beyond technical criteria, one option is being more and more discussed in the surgical community. Once considered an absolute contra-indication because of poor prognosis and donor shortage, liver transplantation is being reconsidered since latest series show a 5-year survival of 18% probably because recent chemotherapy in colorectal cancer achieve better systemic disease control with increased response rate, results of liver transplantation in general are increasing, imaging is more accurate in the global staging and latest immunosuppression protocols are more adapted to liver transplantation for cancer. A new evaluation on short and long term results of liver transplantation in patients with isolated unresectable liver metastases from colorectal cancer might bring interesting results (65-67). To ensure a good quality of care and assure surgery is not denied because of individual inability, resectability must be evaluated by a confirmed hepatobiliary surgeon. This recognition based on an adequate training still lacks in many countries. Recurrence in the liver should be treated as the initial disease and resected whenever possible.

Imaging development and improvement is essential in an early diagnosis. Finally, isolated age is no longer a contra-indication for metastases surgery and resection should be proposed to all patients as long as their performance status is good. Many teams are developing interesting predictive scales although some are overpredicting mortality and therefore denying surgery. Further studies on the topic are needed.

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