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Review Article

The surgical treatment of patients with colorectal cancer and liver metastases in the setting of the "liver first" approach

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Abstract: A surgical resection is the only curative method in the therapy of colorectal carcinoma and liver metastases. Along with the development of interventional radiological techniques the indications for surgery widen. The number of metastases and patients age should not present a contraindication for surgical resection. However, there are still some doubts concerns what to resect first in cases of synchronous colorectal carcinoma and liver metastases and how to ensure the proper remnant liver volume in order to avoid postoperative liver failure and achieve the best results. Through this review the surgical therapy of colorectal carcinoma and liver metastases was revised in the setting of "liver-first" approach and the problem of ensuring of remnant liver volume.

Keywords: Colorectal liver metastases; liver resections; remnant volume; "liver-first" approach

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Introduction

Treatment of colorectal cancer and liver metastases are an extremely important clinical issue since that there are nearly a million newly diagnosed cases and nearly half of the million reported deaths worldwide (1). In large number of countries the incidence continue to rise (2), although the standardized prevention national programs of early detection have developed and brought to an earlier detection and diagnosed cases in early stage of tumor (3-5). In Asian countries, such as China, Japan, South Korea, and Singapore, a 2-4-fold increase in the incidence of colorectal cancer in the past few decades is experienced (6). In Western World the colorectal cancer is reported as the third the most frequent cancer and the most frequent cancer in population older than 75 years (7).

Approximately 25% of newly diagnosed patients with colorectal cancer will have liver metastases at the time of diagnosis, another 25% will develop liver metastases during the course of the disease and two-thirds of all patients with liver metastases will die of them (8). The 10-year survival rate for patients with stage I disease is 90%, but for patients with inoperable stage IV disease, it is currently only 5% (9). For patients with liver metastases, the treatment strategy should be directed toward resectability (10).

The multidisciplinary therapeutic approach, consisting of new and more effective chemotherapeutic agents in single or combined therapy, an advanced role of interventional radiology with portal vein embolization (PVE) and tumor ablation and new strategies and techniques for hepatic resections, brought improved resectability rate of metastases to 20-30% of cases and has resulted in 5-year survival of 35-50% for selected cases (11-13). A need has been recognized for a new staging system that acknowledges the improvements in surgical techniques for resectable metastases and the impact of modern chemotherapy on rendering initially unresectable liver metastases from colorectal carcinoma resectable while distinguishing between patients with a chance for cure at presentation and those for whom only palliative treatment is possible (14).

There have been presented the predictive factors for survival and local recurrence (15,16). Traditionally, a staged approach (colorectal first) has been used in the management of patients with synchronous colorectal cancer and liver metastases. This involves the initial extirpation of the primary tumor. Systemic chemotherapy followed the operation, after which liver-directed operation was performed. The last 2 decades have brought an increased understanding of the biology of colorectal liver metastases, resulting in more effective targeted therapies in addition to decreased mortality after liver-directed operations (17,18).

The goal of this review is to focus onto the doubts concerning the operators all around the world in the context of reassuring the proper remnant liver volume and especially what to resect first in the cases of synchronous liver metastases of colorectal carcinoma.

The preoperative imaging and planning the surgical resection

The R0 resection is the ultimate goal of the surgical therapy. However the proper indication is essential in order to achieve adequate result of resection. Resectability depends onto the multiple factors: the number and location of metastases, the remnant liver volume and quality of the liver tissue that is not infiltrated by tumor. All lesions identified at the initial imaging records (CT or MRI) before any therapy is performed have to be accounted during planning the liver resection in order to predict the total risk and the outcome of surgical procedure. It is recognized that chemotherapy can induce toxic injury of liver tissue, primarily steatohepatitis and sinusoidal injury. Non-contrast CT and MRI could be used to assess steatosis (19-21), but steatohepatitis cannot be diagnosed with imaging. Sinusoidal injury can be judged by indirect signs of portal hypertension, particularly spleen size (22), or by using the liver-specific MRI contrast agent gadoxetic acid (23). The essential three points that are ultimate for complete resection are preservation of liver vascularity, the adequate remnant liver volume with reference to body weight and total liver volume, and that the quality of the remnant liver parenchyma is acceptable (24). The ultrasound (US), especially contrast enhanced ultrasound (CEUS) presents a unique imaging method for intraoperative assessment of unrevealed metastases, and the relation between tumor and vascular and biliar structures (25), sometimes even significantly more sensitive than CT and/or MRI preoperative imaging records (26). For the detection of extra hepatic metastases and local recurrence at the site of the initial colorectal surgery, apart from CT the use of FDG-PET is widespread. A high quality CT can detect the majority of extrahepatic disease, however the FDG-PET may reveal additional signs of disease as high metabolic activity. Although some studies showed a change in management in 10-20% of patients according to record of FDG-PET (27,28), some reports lower percentage and even seem to be more suspicious in its cost-effective role (29), especially in the context of FDG-records following the preoperative chemotherapy which reduces its sensitivity.

The surgical resection—what to resect first in synchronous metastases?

Surgical treatment of colorectal liver metastases remains the only treatment associated with a long survival time in patients with liver metastases from colorectal carcinoma, with a 40% survival at 5 years and almost 25% postoperative survival up to 10 years in specialized centers (30). The very important issue that the liver surgeon has to deal with is to proceed decide what to resect first liver or colon and/or when to undertake simultaneous surgical resections of both. The perfect solution seems to be a single stage colon and liver operation. The advantage of the one stage procedure could be less psychological stress for the patient, lower financial cost and shorter hospitalization time. On the other hand the advantages of the staged procedure are that there is no accumulation of the risks of liver and bowel resections at the same time. Neoadjuvant chemotherapy may be given before liver resection, and an extended hepatectomy or demanding bowel resection could be performed with the full attention of the surgical team focused on the liver or bowel disease, although, the key point for decision-making is the patient's safety (1). According to the reported initial experience with simultaneous versus staged resections, a French multicenter study showed an operative mortality of 7% for simultaneous 2% for staged surgery (31), while in a single center US study the mortality was 12% for simultaneous and 4% for staged resections (32). Several studies reported simultaneous operations performed without mortality, however patients were selected by experienced hepatobiliary surgeons and the major hepatectomies were avoided in elderly patients the same as in those with demanding colorectal surgery (33-36). In addition, since the surgical mortality rate is significantly higher when surgery of extensive hepatic resections is combined with colorectal resection (37), this approach should be only performed in carefully selected patients.

The standard staged operative treatment recommendations

in the literature suggest resection of the primary tumor followed by chemotherapy for 3-6 months and second stage of surgical treatment that includes liver surgery. The problem with this approach lies in the fact that liver metastases determine survival more intensive than the primary colorectal tumor. Chemotherapy can sometime not be performed after the surgical treatment of the primary tumor, especially when complicated by anastomotic leak or dehiscence, which occurs in 6-12% of patients (38,39). In cases of advanced rectal cancer usually a long term of radio-chemotherapy of 5 weeks is recommended and the second stage of operative treatment is planned 6-10 weeks following the neoadjuvant therapy. Therefore the patients do not receive a therapy of liver metastases for almost 15 weeks, which brings to the progress of liver metastatic disease (40). On the other hand some experimental studies have reported the rapid growth of metastases after removal of primary tumor (41,42). The underlying mechanism for those experimental results could be the loss of primary tumor-induced inhibition of angiogenesis in the metastases, which supports the founding of the increase of vascular density in humans after resection of primary tumor (43).

The reverse surgical approach onto the surgical treatment of colorectal liver metastases known as "liver-first" approach is reported as feasible and safe procedure with promising results, although it brings along the risk of bowel obstruction following the growth of primary tumor, which can be avoided by Hartmanns procedure (39,44). Results from the Liver Met Survey, involving 13,334 patients from 330 centers in 58 countries who underwent surgery for liver metastases, reported a better survival outcome in patients who undergo first resection of liver metastases than in those who do not (45). A recent systematic review of studies published in 1999-2010 confirmed these results and revealed 5-year survival rates for patients with liver metastases in the range of 16-74% (median, 38%) after liver resection (46).

The main idea of the "liver first" approach was to avoid the time loss between the operative therapy of primary tumor and the oncological therapy. Since the patients with rectal cancer often require a complex oncological therapy (chemotherapy, radiotherapy, and a complex pelvic operation), they could be the most proper candidates for such an approach (47). Despite liver-first patients usually have a greater hepatic disease burden and undergoing major resection more often, the reverse strategy was found safe and had long-term outcomes comparable to those of the other approaches (48).

How to achieve resectability without chemotherapy?

A large number of liver metastases should not be an absolute contraindication to surgery combined with chemotherapy provided that resection can be complete, with preservation of a functioning liver remnant of 25-30% (49). However, the problem is the loss of the proper functioning remnant volume of normal liver tissue, which presents an absolute contraindication for surgical resection. Advances in interventional radiology, particularly PVE in which the hypertrophy of normal liver tissue is provoked in order to ensure the proper remnant volume (50) and radiofrequency thermal ablation (RFA) widened the indications for surgical treatment of patients with colorectal cancer and liver metastases. In patients planned for major hepatectomies and with an otherwise normal liver, preoperative PVE is recommended when the ratio of the remnant liver to total liver volume is estimated to be less than 30%, whereas in patients with neoadjuvant chemotherapy this ratio is considered to be 40% (51,52). PVE is a safe procedure, but manipulation of the embolic material to the main portal vein or into branches that supply the future remnant liver remains a risk (1). RFA was initially anticipated for local treatment of hepatocellular carcinoma but has recently found application for the management of colorectal liver metastases, where its indications are still under doubt. Critical review of the results of RFA shows that it must be restricted in cases with a maximum of 3 lesions with the size of the biggest lesion less than 3 cm (53). Another limitation for the use of RFA in the management of colorectal liver metastases is the anatomic location of the lesion near big vessels, which increases the risk of incomplete ablation due to reduced heat effect that is used (54). A great indication of RFA is actually recurrence after resection, detected as small lesions, so it is possible not to interrupt chemotherapy (55).

A novel method in liver surgery that can solve the problem of remnant volume is the associating of liver partition and portal vein ligation (ALPPS) firstly reported 3 years ago (56). In ALPPS approach, the portal vein ligation associated with in situ splitting is able to induce enormously accelerated hypertrophy (57). The neovascularization and persistence of interlobar perfusion are prevented by performing parenchymal dissection and complete devascularization of segment IV (56). The nearly total parenchymal dissection induced a median hypertrophy of 74%, which is markedly above the range that can be achieved by portal vein ligation or PVE alone (58,59).

Conclusions

Surgical R0 resection still remains the only curative therapeutic tool in patients with colorectal cancer and liver metastases. The proper diagnostic algorithm is ultimate. The indications for surgical treatment are enlarged by the progress in neoadjuvant chemotherapy, diagnostic imaging, interventional radiology procedures especially the usage of PVE and radio frequent ablation. On the other hand the surgical techniques still develop producing the new pathways of treatment such as "liver-first approach" in the context of 2-stage operative therapy and ALPPS for the ensuring the remnant liver volume. Simultaneous liver and colorectal operations are feasible at carefully selected patients but should be avoided in cases of major hepatectomies, in elderly patients, and in patients with too complex intraoperative asset of colorectal tumor. The 2-stage hepatectomies as well as the "liver first" approach seem to become the new treatment strategies that improved the prognosis in patients in whom an R0 resection can be achieved with curative intention. The multidisciplinary treatment therapeutic approach in patients with colorectal cancer and liver metastases is essential to make the proper treatment plan and achieve the best results.

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