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EDITORIAL

Complete clinical response of liver metastasis after chemotherapy: To resect or not?

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Abstract

This paper aims to update the therapeutical strategies in liver metastasis with complete clinical response (CCR) after chemotherapy and to determine if surgery is always necessary after CCR. The aim of chemotherapy is to achieve a good clinical response rather than CCR of liver metastasis. The CCR of liver metastasis after chemotherapy cannot be considered synonymous with a cure. The resection of the hepatic segment where there was hepatic metastases with CCR after chemotherapy theoretically prevents recurrence, improves survival and makes it possible to confirm whether there has been a complete pathological response. However, the medical literature about this topic is scarce and sometimes contradictory.

Key words: Metastasis; Liver; Clinical response; Chemotherapy; Surgery

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COLORECTAL CANCER RELATED HEPATIC METASTASES

Colorectal cancer (CRC) is the second leading cause of death from cancer and the third most commonly diagnosed neoplasm in men and women. In 2010, there were an estimated 142 570 cases in the USA, with a mortality of 51 370. The incidence rate in 2006 was 45.5 cases/100 000 inhabitants, accounting for 9% of cancer-related mortality[1-3].

Approximately 50% of patients with CRC develop synchronous or metachronous hepatic metastases (HM)[1,2,4-6]. However, although hepatic resection is the most effective treatment for CRC-related HM, only 10%-25% of patients who present such HM are initially candidates for a hepatectomy[1,2,4,5,7-11]. A higher survival rate is achieved in patients who present a resectable HM (median of 36 mo and 5 years survival of 21%-58%) compared with those who have an unresectable HM (median of 15 mo)[1,2,9,10].

Two key findings have led to a change in the oncological treatment of HMs: the appearance of new drugs (irinotecan and oxaliplatin) and biological agents that are more effective than standard chemotherapy (CHT), and the use of CHT prior to hepatic resection[1,7,9,10,12].

CHT is currently used preoperatively in patients with CRC-related HM in two scenarios: patients with initially unresectable disease that we try to make resectable, which is achieved in 10%-40% of cases, obtaining a 5 years survival rate of 35% following surgery; or, which is occurring more frequently in resectable patients, to reduce the tumor size in order to avoid liver surgery in patients with progressive disease and to control micrometastases

that were not detected preoperatively, thus improving the survival rate[1,4-15]. The use of preoperative CHT causes more damage to the hepatic parenchyma (steatohepatitis, sinusoidal lesion, *etc.*) but does not increase the morbidity and mortality of hepatic resections[2,12,14]. Currently there is not enough evidence or medical data to recommend routine neoadjuvant chemotherapy in resectable HM.

Preoperative CHT can lead to a variable reduction in the size of the HM in response to this treatment, as shown by imaging tests, usually multi-phase computed tomography (CT) scanning, following the response evaluation criteria in solid tumors (RECIST)[2,16,17]. Magnetic resonance imaging scanning seems to improve the information that CT provides regarding the clinical response of the HM following CHT[5]. Complete disappearance of the HM is known as a complete clinical response (CCR) after CHT and is associated with a higher survival rate[4,5,8,10,14,16,17]. CCR, which is an exceptional situation with standard CHT, has increased as a result of the efficacy of new chemotherapy regimens and now stands at 6.5% of treated HM[4,6,9,10]. CCR cannot, however, be considered synonymous with a cure[5,13] and it has also been reported that there are discrepancies of up to 30% in terms of CCR between the radiological data and intraoperative findings[13].

CCR must be differentiated from the so-called complete pathological response (CPR) after CHT, which is the disappearance of any nests of neoplastic cells when the histology of the hepatectomy specimen is examined in areas where there was a HM prior to treatment with CHT[4,5,13]. The incidence of CPR ranges from 4%-11% of all resected HM previously treated with CHT and this rate is as high as 35%-50% in HM that have presented CCR[9,10,14,18]. Several authors have proposed classifications to quantify the pathological response achieved after CT based on the percentage of viable cells and the degree of fibrosis in the HM[7,9,19]. Thus, Chun *et al*[15] have tried to establish a correlation between CT findings and the degree of pathological response achieved by CHT which seems to be better than the RECIST.

CCR and CPR do not always coincide. In other words there are patients for whom the imaging tests show CCR without CPR and vice versa[4,5,13]. A failure to show up on the PET scan after CHT does not imply CPR either, as 85% of the lesions that normalised the SUV on the PET scan present viable cells. This SUV normalisation may be due to the reduction in the size of the HM or to altered glucose metabolism in the tumor cells[4,11].

Achieving CPR in HM seems to be significantly related to overall and disease-free survival, such that patients whose HM show CPR can achieve 5 years survival rates of 65%-76%[4,9,15,18]. It has also been shown that there is a direct correlation between the degree of pathological response and survival[7,15]. Therefore, some authors believe that the degree of pathological response will become a prognostic factor in the future[4,7,9,15]. The factors that favour CPR include: age below 60 years, metastases measuring less than 3 cm, number of metastases greater than 4, CEA < 5 or < 30 ng/mL (according to series) and clinical response (reduction in tumor size) after CHT[5,6,9]. There is no clear correlation between the different CHT drugs used and CPR[4,13], although the use of bevacizumab seems to increase the CPR rate, especially in lesions measuring less than 4 cm[1,9,10,12,14]. Increasing the number of CHT cycles does not result in a greater CPR, although it does produce more damage to liver tissue, especially with more than eight cycles of CHT which results in an increase in postoperative hepatic failure and other complications[14].

Having defined the concepts of CCR and CPR, the clinical problem consists of what to do in the case of CCR of a HM, as CPR will be determined postoperatively. The information available in the literature regarding the clinical management of HM with CCR is limited and somewhat contradictory. As an example, we can cite the fact that Benoist *et al*[5] observed that microscopic residual tumor was found in the hepatic parenchyma in 80% of the HM studied, where macroscopically there was no lesion but there had been a previous HM, and found a 1 year recurrence rate of 73% in non-resected HM with CCR. Tanaka *et al*[13] treated 55 HMs with CCR; 28 were resected and no viable cells were found in the surgical specimen and no recurrences occurred, whereas 11 recurrences (40%) were observed after a mean of 14 mo in the area where the HM had initially been in 27 who were not resected. van Vledder *et al*[6] achieved a worse survival rate in patients with HM with CCR who were not treated, as they were not found at laparotomy. However, in contrast, Elias *et al*[18] reported that 70% of patients with HM with CCR did not present recurrence in locations where the HM had previously been. This discrepancy in the data is probably due to the different CHT treatments carried out (arterial, intravenous, chronomodulated, *etc.*) and the different drugs used[13].

With such disparate data, the fundamental question that a surgeon faces when treating a patient who presents with CCR is whether or not to operate and whether all the areas corresponding to previous HM should be resected. The most widespread trend in cases that were resectable prior to CHT is to carry out the resection, as this makes it possible to confirm whether there is CPR, avoids the risk of local recurrence and seems to be related to a higher survival rate[1-6].

The intraoperative detection rate for HM that have presented CCR ranges between 31% and 55%[5,6,13]. The absence of lesions during surgery makes it difficult for the surgeon to know which areas should be resected and to achieve a sufficient margin as, although ultrasound changes that may help to identify the problem area have been described (area of hyper-reflectivity), the HM is not palpable and does not show up on intraoperative ultrasound imaging[4-6]. It is therefore sometimes necessary to perform hemihepatectomies or anatomical resections in order to include previously affected areas that are no longer palpable[6].

We must therefore insist that oncologists should refer patients prior to CCR, as there are problems with locating the HM during surgery and also more cycles of chemotherapy (> 8 cycles) increase the sinusoidal lesion without increasing the CPR rate[5,13,14]. The therapeutic recommendation is a short course of CHT (2-3 mo) followed by radiological re-evaluation; if there is a response or resection is now feasible, surgery can be performed, whereas if there is no response or resection is not yet feasible, the CHT regimen can be changed to seek a better response[5,6,13,14]. It has been suggested that lesions in difficult locations could be marked percutaneously to ensure that we are then able to delimit the area to be resected[6].

Another point for discussion is what to do with initially unresectable patients in whom CCR is achieved. If we should always remove all lesions due to the possible existence of microscopic metastatic areas and they were not operated on because it was not technically possible, we cannot resect all previous areas of HM despite the CCR[5,13]. In this respect, some authors argue that it is best to continue with more chemotherapy, whereas others recommend to resect as many areas that previously had HM as is feasible[5,13].

CONCLUSION

The recent data does not let us conclude if neoadjuvant chemotherapy should be considered in every patient with HM (resectable or non resectable). In non-resectable HM, clinical benefit is obvious, but in resectable patients randomized clinical trials are needed to answer this correctly.

About CCR, we can conclude that: (1) The aim of CHT is to achieve a good clinical response rather than CCR of a HM; (2) The CCR of an HM after CHT cannot be considered synonymous with a cure; and (3) The resection of the hepatic segment where there was an HM with CCR after CHT theoretically prevents recurrence, improves survival and makes it possible to confirm whether there has been CPR. Finally, the CCR of HM should be avoided because it usually makes it difficult for surgeons to know which area should be resected for HM.

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