Abstract Colorectal cancer (CRC) is the second most common cause of cancer death in Spain. Fifty percent of patients will develop colorectal liver metastases (CLM) during the course of the disease. Less than 20% of patients with CLM are initially resectable and for them 5-year disease-free survival (DFS) is about 20–25%, with a high recurrence rate. CLM is a heterogeneous disease. From a clinical point of view, four main groups can be differentiated: initially resectable, not optimally resectable, unresectable that could be resectable and unresectable that never will be likely to be resected. Treatment of CLM must be established, always, in a multidisciplinary team discussion with an analysis of prognostic factors and resectability. For patients with resectable CLM, the EORTC trial 364 demonstrated that chemotherapy plus surgery is better than surgery alone. Consequently most patients should be treated with perioperative chemotherapy based on oxalipatin, and if resection has been done without chemotherapy, they should receive adjuvant chemotherapy after R0 resection. Based on oncological factors, the 5-year survival rate after resection of CLM ranges from 60% to only 14% with a poor score. If a patient has more than one of the poor prognostic factors he should probably be referred for preoperative (induction) chemotherapy. Only a minority of patients with CLM are amenable to surgery; therefore, efforts have been made to increase the percentage of patients who could be candidates for resection. Studies, mostly retrospective, have confirmed the ability of neoadjuvant chemotherapy (conversion chemotherapy) to render some metastases resectable. The regimens we must use depend on the KRAS mutational status and the toxicity profiles of drugs in the context of each patient. In k-ras mutated tumours we can use bevacizumab combined with standard chemotherapy or concomitant administration of the three active agents (FOLFOXIRI) in suitable patients. In k-ras wild-type patients, the combination of cetuximab and FOLFIRI-FOLFOX improved response rates and resection rate in phase III–II trials. With a lower level of evidence, panitumumab is an alternative combined with FOLFOX. Bevacizumab is also an alternative as it does not depend on KRAS status. Radiotherapy is becoming an alternative in selected patients, where surgery is not an alternative. For the majority of patients, who will never be resectable, the continuum of care with chemotherapy will be the paradigm for their management.

Keywords Colorectal liver metastases · Surgery · Chemotherapy · Radiotherapy

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in Spain. Approximately 22,000 new cases are diagnosed each year, of which 13,075 will die [1, 2].
Colorectal liver metastases (CLM) is a heterogeneous disease in which four main groups can be differentiated on clinical grounds: initially resectable, not optimally resectable, unresectable that could be resectable and unresectable that will never be likely to be resected [3] (we will not talk about this group in this article). Treatment of CLM must always be established in a multidisciplinary team discussion with an analysis of prognostic factors and resectability [4–10].

**What is the role of chemotherapy in patients with liver metastases?**

The use of perioperative chemotherapy in patients with CLM is established in two clearly defined treatment settings. The first of these is in the preoperative, neoadjuvant setting to render initially unresectable metastases resectable and the second in either the adjuvant or neoadjuvant settings to reduce the risk of recurrence in patients with resectable metastases.

Initially resectable metastases with good prognostic factors

For patients with initially resectable disease, with good prognostic factors, one approach is immediate surgical resection and another is perioperative chemotherapy.

For patients who are resectable, the advantages of neoadjuvant chemotherapy may be to decrease the tumour size, control of micrometastatic disease and to assess the activity of chemotherapy in order to identify a group of patients who may benefit most from liver resection, namely the responders [11].

*The perioperative approach [12]*

In the EORTC trial 364 patients with resectable liver metastases (1–4 metastases) were randomised to six cycles of oxaliplatin, folinic acid and 5-fluorouracil (FOLFOX4) presurgery and six cycles postsurgery vs. surgery alone. The endpoint was an improvement in disease-free survival (DFS), which was not significant when all patients were included (7.3%, \(p=0.058\)). In eligible patients, the DFS increased from 28 to 36% at 3 years (\(p=0.041\)), which increased further to a 9.2% difference (\(p=0.025\)) when only resected patients were analysed. Postoperative complications were slightly more common in the chemotherapy group (25 vs. 16%, \(p=0.04\)). This study demonstrated an increase in DFS with a tolerable increase in toxicity for the treated group. Further studies need to answer the question of whether improvement of results was due to pre-treatment, posttreatment or both. The combination of targeted agents with cytotoxic therapy has shown high response rates and thus warrants assessment in the perioperative setting. At present the EORTC 40051 BOS (Biologies, oxaliplatin and surgery) trial is assessing perioperative chemotherapy with FOLFOX6 and cetuximab with or without bevacizumab in patients with resectable hepatic metastases from CRC.

**Adjuvant systemic treatment after liver resection**

Nearly 70% of patients that have been resected will develop a recurrence and the majority of recurrences occur in the first two years after resection [13, 14]. A Canadian and European Intergroup compared bolus 5-FU/leucovorin with surgery alone in 107 patients after liver resection and showed no increase in overall survival (OS) or DFS [15]. A French trial [16] randomised 173 patients after liver resection to bolus 5-FU/folinic acid or no further therapy. After adjusting for negative prognostic factors, there was a significant DFS advantage for the chemotherapy group (\(p=0.028\)). With a median follow-up of 84.7 months, the median survival was 62 and 46 months, respectively, for the treated and control patients (\(p=0.13\)). In a meta-analysis [17] of these two studies, the median progression-free survival (PFS) was 27.9 and 18.8 months (\(p=0.058\)) and median survival was 62.2 and 47.3 months (\(p=0.095\)) for the chemotherapy and control groups, respectively. In the multivariate analysis, adjuvant chemotherapy was significantly associated with improved PFS (\(p=0.026\)) and improved OS (\(p=0.046\)). The study of Ychou et al. [18] randomised 151 patients to bolus/infusional 5-FU/leucovorin or folinic acid, fluorouracil and irinotecan (FOLFIRI) after liver resection. With a median follow-up of 42 months, the median DFS was not significant: 21.6 and 24.7 months for the 5-FU/leucovorin and FOLFIRI groups, respectively (\(p=0.47\)). Several non-randomised retrospective series have shown a benefit for the group of patients that received adjuvant treatment after liver resection [19].

**Adjuvant hepatic arterial infusion (HAI) after liver resection**

The majority of recurrences after liver resection occur in the liver. Therefore, there has been interest in adjuvant HAI in this setting. An increase in DFS was observed in three of four randomised studies with the use of HAI plus systemic therapy after liver resection [20]. Most of the studies were too small to demonstrate an increase of OS. This technique has not been used widely, possibly due to technical issues with regard to delivery of the therapy, but the results are good enough to know its value.

In summary, the administration of chemotherapy, with 5FU/leucovorin after resection of liver metastases, tends to improve prognosis and DFS. Irinotecan added to 5FU/leucovorin did not improve results. Newer studies with better drugs are ongoing.

So which of these two options is better in patients with resectable, good prognosis CLM? The answer to this question could be answered with a prospective randomised phase III trial comparing preoperative chemotherapy to adjuvant chemotherapy. Until we have these results, most patients should be treated with perioperative chemotherapy, with a total duration of 6 months, based on oxaliplatin che-