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Role of chemotherapy in resectable liver metastases from colorectal cancer: food for thought from pooled evidence

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Surgical resection is the only option of cure for patients with metastatic colorectal cancer; however, the risk of recurrence after metastasectomy is as high as 75% with the liver being the most frequent site of relapse.[1 2] Improving the cure rate is a core question in oncology nowadays.

Randomised trials analysing the potential use of chemotherapy in the post-metastasectomy setting disclosed that adjuvant chemotherapy improves disease-free survival but not overall survival.[3–5] Consequently, routine post-metastasectomy chemotherapy is not recommended. Since clinical trials suffered from small sample sizes, a meta-analysis of all available randomised evidence was recently performed. Despite nearly 500 patients being included, only a positive trend for an overall survival advantage was observed from the use of adjuvant chemotherapy.[6]

In the perioperative setting, the EORTC 40983 trial investigated the role of perioperative FOLFOX compared with metastasectomy alone. Final results with long-term follow-up did not show an overall survival advantage from the use of perioperative chemotherapy.[7]

Overall almost 900 patients had been randomised across trials in both perioperative and postoperative settings, without establishing a statistically significant overall survival benefit for the use of systemic chemotherapy.

Is there a room for further investigation?

To better scrutinise this topic, we pooled the available randomised evidence both from the perioperative and postoperative trials: 846 patients were analysed (420 randomised to chemotherapy vs 426 to surgery alone), yielding an overall survival relative hazard=0.833 (95% CI 0.689 to 1.006, p =0.057) (figure 1). Surprisingly, the upper bond of the 95% CI was close to 1, similarly to the p value of statistical significance (p 0.05), with no between-study heterogeneity. We believe these data hint that there is a justifiable need for further randomised trials evaluating a possible role for active combination chemotherapy regimens among patients with resectable colorectal liver metastases.

Is there a possibility that statistical significance from cumulative randomised evidence will be reached in the future? Since no between-study heterogeneity was observed and considering studies' coherence (all studies showed better trend for overall survival), there is a high probability that a small but statistically consistent survival benefit will be documented for the use of chemotherapy (any setting considered preoperative/postoperative/perioperative) compared with metastasectomy alone in the management of patients with resectable liver metastases. This will probably happen in 2023 or 2024 when the CHARISMA trial (actually randomising 234 patients to preoperative XELOX vs surgery alone) and the JCOG0603 trial (actually randomising 300 patients to post-metastasectomy mFOLFOX vs surgery alone) will be closed for analyses.[8 9]

CHARISMA and JCOG0603 trials are also of great importance since the investigational regimens evaluated represent active combination chemotherapy, rather than the single-agent fluoropyrimidine monotherapy used in previous randomised studies in the post-metastasectomy setting.

Indeed, since the role of post-metastasectomy chemotherapy is to eliminate micrometastases, it was argued that the use of oxaliplatin-based combination regimens might be of greater benefit. However, following surgical extirpation of liver metastases many patients are frail and not eligible for combination chemotherapy regimens. Moreover, the EORTC 40983 study did not show an overall survival advantage from the combinational regimen in the perioperative setting. For those reasons, the use of combination regimens cannot be currently

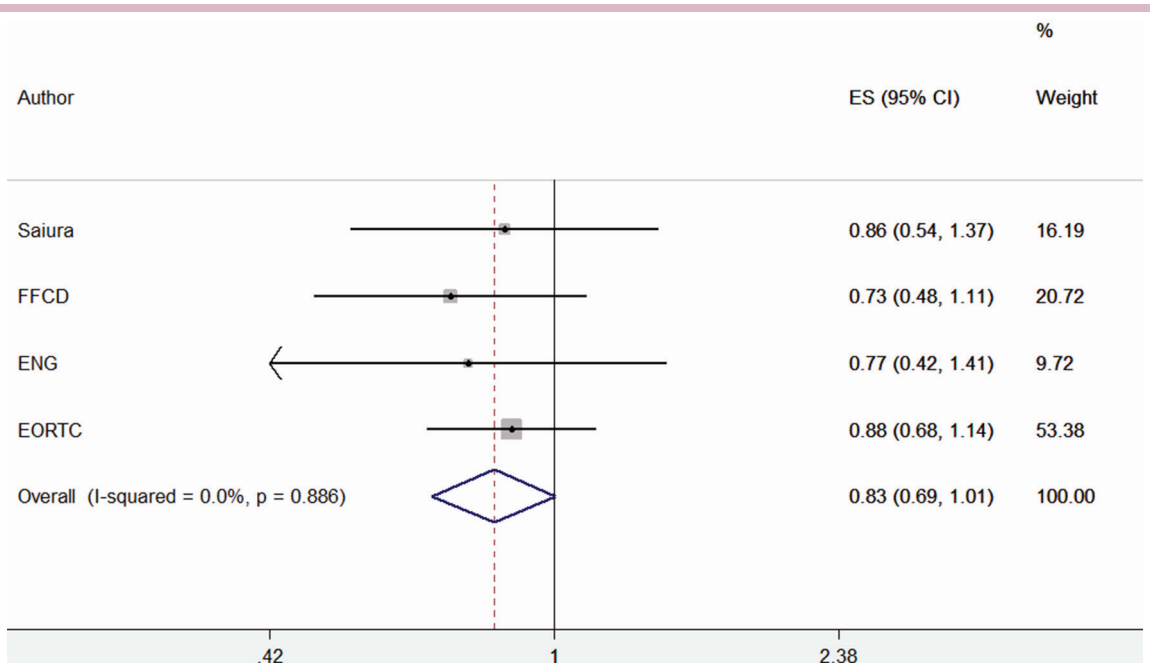

Figure 1 Relative hazard for overall survival in randomised trials evaluating post-operative chemotherapy in resected stage IV colorectal cancer patients.

recommended and the final results from the JCOG0603 and CHARISMA trials are eagerly awaited by the scientific community.[8 9]

What is noteworthy is that without having demonstrated survival benefit for the use of chemotherapy versus metastasectomy alone many trials use chemotherapy regimens in their control arms (FOLFOX vs XELOX, use of chemotherapy with or without biological agents). We believe that these trials have a principal methodological flaw that limits the relevance of any findings, a problem that could have been avoided if appropriate control arms were selected.[10–12]

The problems above lead to loss of resources (human and economic) and loss of potential therapeutic options for patients. Sixteen years after the publication of the first trial,[3] a firm conclusion on the role of systemic chemotherapy in resectable metastatic colorectal cancer cannot be provided. Underpowered trials generated low-level evidence leading to weak guidelines. In the absence of firm evidence, many physicians across the world administer post-metastasectomy chemotherapy while others do not. Although we understand the urge to provide patients with the most active therapies, only evidence-based medicine makes the point: treating the right patient with the most effective modality, when needed.

Considering the enormous accrual difficulties encountered in post-metastasectomy trials and the long survival follow-up required in this setting,[6] the scientific community (physicians, health authorities, academia and industry) has to take the necessary concerted actions in order to enrol patients in well-designed and informative trials.

From the beginning of accrual in the Federation Francophone pour la recherche des Cancers Digestives study in December 1991,[4] 27 years have already elapsed without a clear message on the value of post-metastasectomy chemotherapy.

We owe our patients a scientific team effort to generate the evidence and highlight the most effective therapy.

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