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REVIEW ARTICLE

Topics related to neoadjuvant chemotherapy for resectable liver metastases from colorectal cancer

Shanbao Ke[1], Shufang Zhan[2], Hongbo Zhu[3], Danfang Yan[4]

[1]Department of Radiation Oncology, Henan Province People's Hospital, Zhengzhou University, Zhengzhou 450003, Henan Province, China; [2]Department of Oncology, Henan Provincial Chest Hospital, Zhengzhou 450003, Henan Province, China; [3]Department of Anus and Intestine Surgery, Run Run Shaw Affiliated Hospital, School of Medicine, Zhe Jiang University, Hangzhou 310016, Zhejiang Province, China; [4]Department of Radiation Oncology, No. 2 Hospital, Zhejiang Medical, Hangzhou 310006, Zhejiang Province, China

Summary

Metastases to the liver from colorectal cancer (CRC) are common, and only a minority of patients are candidates for upfront surgery at the initial diagnosis. Carefully selected patients can achieve long-term survival from surgery with curative intent. Unfortunately, the risk of recurrence remains substantial after liver resection. In order to reduce the risk of relapse and improve the outcomes, the role of neoadjuvant chemotherapy has been assessed for resectable colorectal liver metastases (CRLM) with an improvement in progression-free survival (PFS). In particular, this approach seems to be more beneficial for resectable patients with risk factors associated with unfavorable prognosis. However, controversies still remain as to whether neoadjuvant chemotherapy would bring long-term survival benefit for patients with resectable CRLM, along with the main challenge in identifying those who can benefit greatly from this approach due to lack of well documented selection criteria for patient stratification. In addition, no evidence directly addresses whether targeted agents such as cetuximab and bevacizumab should be offered with chemotherapy in the preoperative setting of resectable patients, despite that these aggressive strategies could result in high response rates. To offer the reader an insight into these complex and unresolved issues we will give an overview of three hot topics related to neoadjuvant chemotherapy for initially resectable CRLM.

Key words: *colorectal liver metastases, hepatic resection, neoadjuvant chemotherapy, risk factors, targeted agents*

Introduction

Liver is the most frequent site of hematogeneous metastasis from CRC [1]. Liver metastases which develop in approximately 50% of the CRC patients during the course of their disease [2,3] are the main cause of mortality [4]. Radical excision of liver metastases could result in significant improvement in long-term survival with 5-year survival reported to exceed 70% [5,6] and offers a potential chance for cure [7]. However, unfortunately, only about 20% of patients with this disease are candidates for upfront surgery with curative intent at the time of detection [8], and what's more notable is that not all patients with resectable liver metastases benefit from surgery with nearly 50% of them developing recurrence either in the remaining liver or to extrahepatic sites after re-

Correspondence to: Shufang Zhan, MD. Department of Oncology, Henan Provincial Chest Hospital, 1 Weiwu Rd, Jinshui District, Zhengzhou 450003, Henan Province, China.
Tel: +86 18037790277, Fax: +86 057186044817, E-mail: ykzsf123@163.com
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section of hepatic metastases [9]. To minimize the likelihood of relapse whilst improving the curative rate of initially resectable CRLM [10,11], the role of neoadjuvant chemotherapy in the management of this disease has been evaluated in clinical studies [11-13], but failed to be clearly defined with the main controversy persisting in whether it would bring survival benefit. The primary challenge is to identify those who can benefit significantly from neoadjuvant chemotherapy, since neither National Comprehensive Cancer Network (NCCN) nor European Society for Medical Oncology (ESMO) consensus guidelines in the management of resectable CRLM have give a clear answer to this question up to now. Clinical trials to assess targeted agents either anti-epidermal growth factor receptor (EGFR) antibodies or anti-vascular endothelial growth factor (VEGF) antibodies in combination with neoadjuvant chemotherapy for resectable liver metastases from CRC have also been carried out [14-17]. However, the efficacy of these molecular targeted agents in the preoperative setting for this subset of disease still remains uncertain.

With special attention paid to the recent updates of current mainstream guidelines, the purpose of this article was to give an overview of three hot and controversial topics relevant to neoadjuvant chemotherapy for the management of patients with primarily resectable CRLM, namely: (1) whether neoadjuvant chemotherapy will lead to a survival benefit in patients with resectable CRLM; (2) how to identify those patient who can maximally benefit from neoadjuvant chemotherapy; and (3) neoadjuvant chemotherapy combined with targeted agents: pro or con), and to give the reader an insight into these complex and unresolved issues.

When neoadjuvant chemotherapy will lead to a survival benefit in patients with resectable CRLM?

Actually, within the last two decades, with the approval of effective cytotoxic and biologic agents for CRLM, the use of neoadjuvant and/or adjuvant chemotherapy for resectable CRLM has become an attractive strategy. The most famous, prospective randomized EORTC 40983 study (EPOC) evaluating perioperative chemotherapy with 6 cycles of FOLFOX4 (folinic acid-fluorouracil-oxaliplatin) both pre- and post-operatively in patients with resectable CRLM demonstrated a remarkable improvement in progression-free survival (PFS) [11], while updated data did not achieve a statistically significant benefit in overall survival (OS) after a median follow-up of 8.5 years. However, the trial was not designed nor powered to demonstrate a benefit in OS [18]. In 2012, an exploratory retrospective analysis of the results of EPOC study was published, and indicated that a significant portion of patients enrolled in the study had relatively favourable prognosis: 50% of the patients had only a solitary liver metastasis, and nearly 50% of the patients had not lymphatic spread of the primary cancer and up to 70% of the patients had CEA level <30 ng/ml, thus would obtain little benefit from perioperative chemotherapy [19]. In addition to the selection bias, few patients enrolled in the perioperative arm completed the protocol chemotherapy, and the rate of surgical resection was lower than expected and 59% of patients in the perioperative group received second-line therapy compared to 77% of those in the surgery-alone group [18]. Consequently, these limitations resulted in no significant benefit in OS of perioperative chemotherapy in patients with resectable CRLM. It is worth noting that almost 80% of the patients completed the preoperative chemotherapy while only 52% of them finished the postoperative cycles, which reflected that neoadjuvant chemotherapy contributed more to the outcomes.

To further assess the benefits of neoadjuvant chemotherapy for patients with resectable CRLM, multiple attempts have been made with many retrospective trials having been performed. The results from a large multicenter retrospective study were published favoring chemotherapy administered after but not before hepatic resection for patients with resectable synchronous CRLM [20]. Similarly, Adam's research revealed that preoperative chemotherapy did not achieve a benefit in terms of OS or PFS for patients with metachronous solitary liver metastasis from CRC, only to add complications, but improved survival with postoperative adjuvant chemotherapy was observed [21]. An additional recent retrospective analysis involving 466 patients with resectable CRLM published by Zhu et al. found that not all patients could gain a survival benefit from neoadjuvant chemotherapy [22].

Results were also reported from a recent systematic review assessing preoperative chemotherapy and suggested that neoadjuvant chemotherapy in the routine management of clearly resectable lesions was not beneficial because of lacking clear benefit on survival [23], contrary to the findings of a previous study where upfront chemotherapy was recommended by an international panel for the majority of CRLM patients, irrespective of the initial resectability status of patient metastases [24]. Moreover, a meta-analysis of 642 patients with

CRLM from 3 randomized clinical trials published in 2012 comparing perioperative chemotherapy in conjunction with surgery alone showed that perioperative chemotherapy could improve PFS and disease-free survival (DFS), but not OS [25]. In 2015, another meta-analysis assessing 10 clinical trials with 1896 patients similarly found a benefit of perioperative chemotherapy in DFS, but not in OS [26]. In addition, a recently reported systematic review also failed to detect an improvement in OS with neoadjuvant chemotherapy in resectable CRLM [27], which was consistent with the findings of previous studies discussed above.

How to identify those patient who can maximally benefit from neoadjuvant chemotherapy?

This question has not yet been settled with difficulties in correctly selecting appropriate candidates. Over the last twenty years, several clinical risk-scoring systems (CRS) that would predict risk of relapse and prognosis after surgery of CRLM have been developed to provide risk stratification in guiding patient selection [1,28-36]. For instance, the most commonly used and validated scoring system was described by Fong et al. [1]. In this retrospective study, clinical, pathological and outcome data for 1001 patients undergoing hepatic resection for metastatic CRC were evaluated. Five independent prognostic factors including number of hepatic tumour >1 cm, largest tumour >5 cm, node-positive primary, DFS within 12 months from primary to metastases, and carcinoembryonic antigen level >200 ng/ml were combined to form a preoperative score system with one point being assigned for each factor. Patients with a score more than 3 considered to be high-risk groups of recurrence had poor prognosis compared with those with a score of 2 or less considered to be low-risk groups for relapse. However, it is important to note that these CRS only define clinicopathological characteristics and their validity as prognostic indicators in modern chemotherapy is not definitively validated due to the selection bias related to treatment approaches as well as patient samples in design of the previous trials, thus would be of limited utility in clinical practice [37]. Recently, few studies aimed to build a new prognostic scoring model with molecular factors taking into account patients with resectable hepatic metastases from CRC were published, and detected significant and independent prognostic value of molecular factors [35,36,38], particularly when combined with CRS [36].

Although there are no powerful and excellent prognostic risk score systems, based on these CRS, multiple studies have been carried out to identify factors associated with a high risk of failure. A review published by Jone et al. indicated that preoperative chemotherapy was beneficial for patients with high risk of recurrence or borderline resectable CRLM, but immediate surgery rather than upfront neoadjuvant chemotherapy should be administrated for patients with easily resectable disease [10]. Similar results were found in a retrospective study conducted by Zhu et al. which pointed out that only those with more than 2 independent risk factors achieved a survival benefit from neoadjuvant chemotherapy [22]. Furthermore, a recent study investigating the effect of neoadjuvant chemotherapy on OS in patients with resectable CRLM who were stratified by the Fong score [1] published in 2015, also detected a superior OS in neoadjuvant chemotherapy which was exclusive to patients with high-risk of recurrence [39]. In addition, more recently, a systematic review and meta-analysis focusing on the role of neoadjuvant chemotherapy for primarily resectable CRLM further confirmed the above results [40]. Based on these studies, it could be said that the higher the likelihood of recurrence, the more the benefit the neoadjuvant chemotherapy would drive.

Given current guidelines for the management of resectable CRLM, neoadjuvant chemotherapy has been recommended as a treatment option by the NCCN panel over the past 14 years [41], although the evidence for the efficacy of this approach remains insufficient. Furthermore, the ESMO consensus guidelines in 2016 for that portion, for the first time, put forward a proposal for taking into account both 'technical' (surgical) and 'oncological' (prognostic) criteria to optimize treatment decision-making in the selection of upfront surgery and systemic perioperative therapy [42]. Despite the fact that there is still a lack of convincing and perfect criteria for providing prognostic information, the Fong score [1] discussed above is the preferred option proposed by the ESMO panel. In brief, the easier the surgical resection and the better the prognosis, the less the need for neoadjuvant chemotherapy. However, it needs to be emphasized that neither NCCN nor ESMO consensus guidelines, both of which recommend neoadjuvant chemotheray for most patients with resectable CRLM, give a very clear definition for identifying those who can benefit from this treatment option.

In summary, there is still no validated evidence to consider chemotherapy administered prior to surgery as a standard of care in the man-

agement of resectable CRLM, although most Western countries favor this approach [43]. The EORTC 40983 trial [11] and most of retrospective studies failed to convincingly demonstrate a long-term survival benefit in patients treated with neoadjuvant chemotherapy. More prospective trials are eagerly needed on this topic to confirm the best prognostic scoring system for decision-making. Anyhow, neoadjuvant chemotherapy for resectable CRLM should be seriously considered with both technical and prognostic criteria taken into consideration.

Addition of targeted agents to neoadjuvant chemotherapy: Pro or Con

Recent data regarding the efficacy of neoadjuvant chemotherapy in PFS for the treatment of resectable colorectal hepatic metastases has prompted some to assess the effectiveness of adding targeted agents into chemotherapy in the preoperative setting.

Anti-EGFR antibody: Cetuximab

Currently, the only randomized NEW EPOC trial aimed to detect a further improvement in efficacy of cetuximab in combination with chemotherapy in the preoperative setting in patients with RAS wild-type resectable liver metastases from CRC, found an obvious reduction in PFS by 6.4 months in this strategy instead [14].

Aiti-VEGF antibody: Bevacizumab

The role of bevacizumab plus chemotherapy in the preoperative management of resectable CRLM is less certain than the role of cetuximab, that is, the benefits of this approach have not yet been validated for this disease, with no prospective, randomized and controlled clinical trials having been reported, regardless of high objective response rate having been detected in some small, single-arm phase II studies [16,44]. Bevacizumab may increase bleeding during surgery and delay wound healing [45,46]. Caution should be given to the complications and a safe interval between the last administration of bevacizumab and surgery (at least a 6-week gap) when considering the use of bevacizumab [47].

Overall, there is no powerful evidence available at present in terms of the benefits of targeted agents in combination with chemotherapy before hepatic resection in initially resectable colorectal disease. So, confronted with this unresolved issue, what should we do in clinical practice? Perhaps we can get some insight from the following guidelines. It was not until 2016 that the EMSO consensus guidelines recommended targeted agents incorporated into neoadjuvant chemotherapy for patients with technically resectable CRLM and one or more risk factors associated with unfavourable prognosis. As for this recommendation, a widespread consensus was reached among the panel (>75%) despite the low-level evidence [42]. Interestingly, an update of the version 1.2017 NCCN guidelines on neoadjuvant treatment in primarily resectable CRLM showed that targeted agents were removed as treatment options [48], which was opposite to the EMSO panel's recommendation. However, perhaps based mainly on regarding resectable CRLM as a distinct subset of stage IV metastatic disease rather than evidence-based, for more than a decade, the NCCN panel has always recommended the use of target agents in the preopetative setting for this disease to the 2017 version of these guidelines [41]. With respect to such update, this should be taken seriously. The definition of resectability described in the NCCN guidelines is confined to resection that is technically feasible, without giving consideration to the oncologic factors that could predict "biological resectability", and what's more, from an evidence-based point of view, the criteria for resectability are not well defined and mostly rely on clinical assessment and surgical experience in clinical practice. Thus, the recommendation of ESMO consensus guidelines on neoadjuvant treatment strategy for resectabe liver metastases from CRC should be considered to be more scientific and reasonable.

Conclusions

The decision for optimal treatment strategy in the preoperative setting for initially resectable liver metastases from CRC is complex and remains controversial by and far. Further work is urgently needed to better assess the role of neoadjuvant chemotherapy with or without targeted agents in this subset of disease. Currently, because of the absence of convincing and standard prognostic scoring system for selecting candidates for neoadjuvant chemotherapy with or without targeted agents, carefully consideration should be given to the selection of patients with resectable CRLM who can benefit significantly from these strategies with risk of recurrence and tumor biology as well as technologic criteria taken into account.

Conflict of interests

The authors declare no conflict of interests.

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