



Current status of treatment for colorectal liver metastases in the United Kingdom

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Hepatectomy is the treatment choice for resectable colorectal cancer (CRC) liver metastases (LM) (CRCLM) according to the national guidelines (1-3). The National Comprehensive Cancer Network guidelines indicate that the treatment for liver-limited metastases depends on the resectability (1). In the European Society for Medical Oncology guideline, a similar statement is made on the treatment of resectable CRCLM, except for the recommendation of perioperative chemotherapy for some populations with resectable CRCLM (2). In the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, hepatic resection is recommended for LMs if all the lesions are curatively resectable (3). The indication criteria for hepatectomy in the JSCCR guidelines are as follows: (I) the patient can tolerate surgery; (II) the primary tumor has been controlled or can be controlled; (III) the metastatic liver tumor can be completely resected; (IV) extrahepatic metastases are absent or can be controlled; and (V) the function of the remaining liver will be adequate (3). The authors of the present study commented in the introduction that outcomes of CRC in the UK are known to be behind those in many economically comparable countries, maybe because of the poorer outcomes in patients with advanced disease at the first visit to hospital. They also indicated that previous studies showed that the resection rates of CRCLM showed significant variation across the English National Health Service (NHS), which indicates the possibility of a considerable variation in the decision-making process to decide the treatment strategy

for CRCLM with or without a specialist liver team. Thus, the aim of the current study was to investigate the rate of hepatic resection for CRCLM across the English NHS.

As a result, authors identified 157,383 patients who underwent a major resection for a colorectal tumor between January 1, 2005, and December 31, 2012. Of the 7,423 (4.7%) patients who underwent 1 or more hepatectomy within 3 years after the primary CRC was resected, 89.9% had 1 resection, 9.3% had 2 resections, and 0.8% had 3 or more resections. Most (90.4%) of the patients received their first hepatectomy after the primary CRC was removed, of whom 6.7% had a synchronous hepatectomy with the primary CRC resection and 2.9% had their first hepatectomy performed before the resection of primary CRC. The liver-first strategy (4), which precedes LM prior to primary resection, is not performed often in the UK.

The percentage of patients who underwent hepatectomy increased between 2005 and 2012. During the last 4 years of the study period, it reached a stable figure up to approximately 5% for all patients with primary CRC resection. On the other hand, the Charlson comorbidity index of the all the patients in the present study increased over time. The proportion of patients with 1 or more comorbidities increased from 22.8% to 25.2% during the course of the study period. Although patients aged >70 years made up 51.4% of those who underwent a CRC resection, they accounted for only 29.4% of those who underwent hepatectomy. In the >70s group, frequency of hepatectomy increased more than doubled over time, from 1.2% in

1998–2004 to 2.8% in 2005–2012. The fact suggests that management patterns may have changed. These data suggest that hepatectomy is expected to be safely performed for patients with complications or elderly patients in recent years.

Patients who underwent primary CRC resection in a hospital with a specialist liver team were more likely to undergo hepatectomy (odds ratio, 1.22; 95% confidence interval, 1.10–1.35). The authors speculated that it is due to a higher frequency of hepatectomy performed synchronously to resection of primary CRC resection in these patients (18%) than in those who received primary CRC resection in a hospital without a specialist liver team in the same hospital (3%). Patients who received the primary CRC resection in a hospital with a specialist liver team onsite were 22% more likely to undergo hepatectomy than those who had to be consulted to other hospitals. This result suggests that referral pathways may not be as efficient as they should be. Patients may lose the access to treatment, depending on their proximity to a hospital with a specialist liver team. In other words it is suggested that proximity to a liver center is as an important socioeconomic deprivation factor in terms of the low likelihood of receiving a liver resection.

The frequency of major hepatectomy (hemihepatectomies and extended hemihepatectomies) was reduced over the study period from 48.2% to 39.9% ($P < 0.001$). The major hepatectomy rate was 36.1% in a hospital with a specialist liver team and 41.1% for patients who underwent primary CRC resection in hospitals without a specialist liver team ($P < 0.001$). For multiple lesions, hepatectomy may be performed at once. However, the theoretical advantage of a policy for preserving the liver parenchyma and major vessels as much as possible was reported in preparation for repeated resections in case of another recurrence (parenchyma-preserving hepatectomy) (5,6). Oba *et al.* reported that repeated hepatectomy is actively performed for recurrence in approximately 70% of cases after resection of CRCLM and that the therapeutic effect of hepatectomy did not diminish regardless of whether it was performed repeatedly (7). The development of major hepatectomy procedures such as liver partition and portal vein ligation for staged hepatectomy (ALPPS) (8) has been reported, although it is limited to the general clinical practice in the UK.

In CRC chemotherapy, targeted therapy with a high tumor shrinkage effect has been performed since the early

2000s. Recently, the treatment of metastatic CRC (mCRC) has remarkably progressed with biological agents. Nowadays, the median survival time of patients with mCRC is more than 30 months. Under such circumstances, identifying the biological agent preferred for treatment, especially as first-line treatment of mCRC in patients with RAS wild-type tumor, becomes more and more important (9). For unresectable mCRC, the preferred treatment should be decided by considering the treatment goal; patients should be treated to attain maximum shrinkage, or to be maintained treatment duration without severe adverse event. For the former, anti-EGFR monoclonal antibody (mab) might be a preferred option in terms of depth of response. For the latter, bevacizumab (BEV) might be preferred for treatment maintenance without severe side effect. Oki *et al.* reviewed clinical trials of the effectiveness of chemotherapy for CRCLM (10). For unresectable liver-limited diseases, a similar treatment strategy can be recommended. LM is of several types. If the LM is bulky and unresectable, tumor shrinkage is needed to convert the LM to resectable. If the LM is disseminated, a pathological effect can prevent recurrence after liver resection. For the former, anti-EGFR mab maybe a better treatment option. For the latter, BEV may be better, considering the characteristics of the mabs (9,11). A preferred treatment option should be considered according to a real clinical case (11).

In the TRICC0808 trial, we showed that mFOLFOX6 plus BEV therapy was followed by a high hepatectomy rate and a high conversion rate (12). In the trial, the rate of chemotherapy-associated adverse events and hepatectomy complications were both acceptable. In the ATOM trial, a randomized phase II study of mFOLFOX6 with BEV compared with mFOLFOX6 with cetuximab (CET) for CRCLM that is upfront unsuitable for resection, we reported that BEV and CET showed similar efficacies in terms of progression-free survival and liver resection rate, although greater tumor shrinkage was observed in the CET group (13).

In this study, the rate of hepatectomy in women was low even when the tumor location was corrected. In CRC, genetic characteristics such as the consensus molecular subtypes are becoming clearer (14). The treatment result of CRCLM may be affected by sex-based genetic background.

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Footnote

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