The Management of Hepatic Metastasis in Colorectal Cancer

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Abstract

We report a 65-year-old male with rectal cancer who received three hepatic operations and chemotherapy at Tainan Hospital, and the recent advances in hepatic colorectal metastases are also reviewed. Neoadjuvant chemotherapy includes FOLFOX or FOLFIRI with either bevacizumab or cetuximab. There may be a role for adjuvant chemotherapy, but further study is needed. Other options, such as hepatic arterial infusion, have been studied in clinical trials. Preoperative PET/CT is indicated only in the presence of potentially surgically curable M1 disease.（J Intern Med Taiwan 2010; 21: 26-31）

Key Words：Target therapy, Hepatic colorectal metastases, PET/CT

A 65-year-old male came to Tainan Hospital for a rectal mass located 15 cm above the anal verge with nearly total obstruction. Transverse loop colostomy was performed initially for stool diversion and then chemoradiation therapy (CCRT) with 5-FU and leucovorin was given. Initially, only the CA199 value was elevated to 53.69 U/mL (normal range ＜37 U/mL). Three months after CCRT, pre-operative evaluation including colonoscopy and abdominal computed tomography (CT) were performed, and revealed that the rectal mass had shrunk markedly; however, one newly developed hepatic mass about 1 cm at the S6 segment was seen. Low anterior resection and S6 partial hepatectomy were performed (Figure 1). The pathology report showed rectal adenocarcinoma with liver metastasis under R0 resection. A FOLFOX (folinic acid/5-fluorouracil/oxaliplatin) regimen was then infused. The CA199 value was still high after 3 cycles of chemotherapy. Abdominal CT showed newly formed liver metastases at the S5, S6 and S8 segments (Figure 2). Position emission tomography (PET/CT) was then performed, and the results were compatible with the abdominal CT results. Partial S5, S6, S8 segmental hepatectomy with R0 resection and a take down of the transverse loop colostomy were performed in the second operation. After the operation, the CA199 value returned to normal range. Chemotherapy was shifted to a FOLFIRI (folinic acid/5-fluorouracil/

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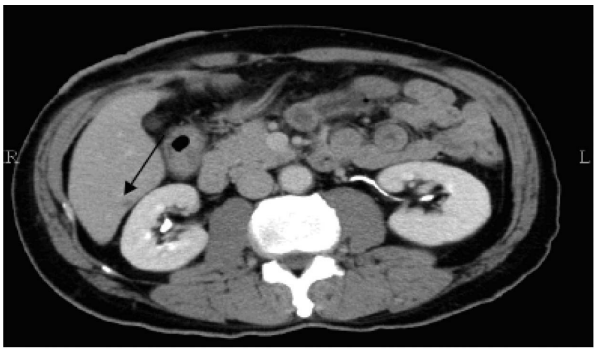

Fig.1. Liver metastatic tumor about 1 cm at S6 segment (arrow).

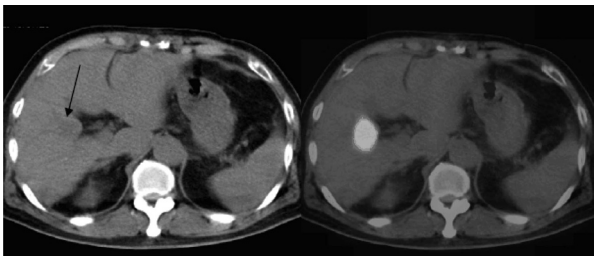

Fig.2(A). The 2nd time liver metastasis. Left, abdominal CT showed S5 metastases (arrow), which was compatible with the right-side lesion on PET/CT.

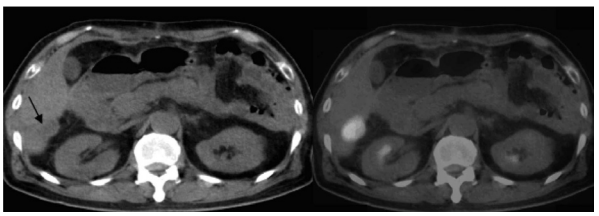

Fig.2(B). The 2nd time liver metastasis. Left, abdominal CT showed S6 metastasis (arrow), which was compatible with the right-side lesion on PET/CT.

irinotecan) regimen with 12 cycles. Six months after the second operation, the CEA value was elevated to 5.4 U/mL (normal range ＜5 U/mL). Abdominal CT revealed a S2 hepatic lesion only. PET/CT showed the S2 lesion and another unsuspected new lesion less than 1 cm in size between the S5 surface and the right kidney (Figure 3). FOLFOXFIRI (folinic acid/5-fluorouracil/oxaliplatin/irinotecan) was infused once. Direct DNA sequencing of the main tumor confirmed a K-ras mutation. The

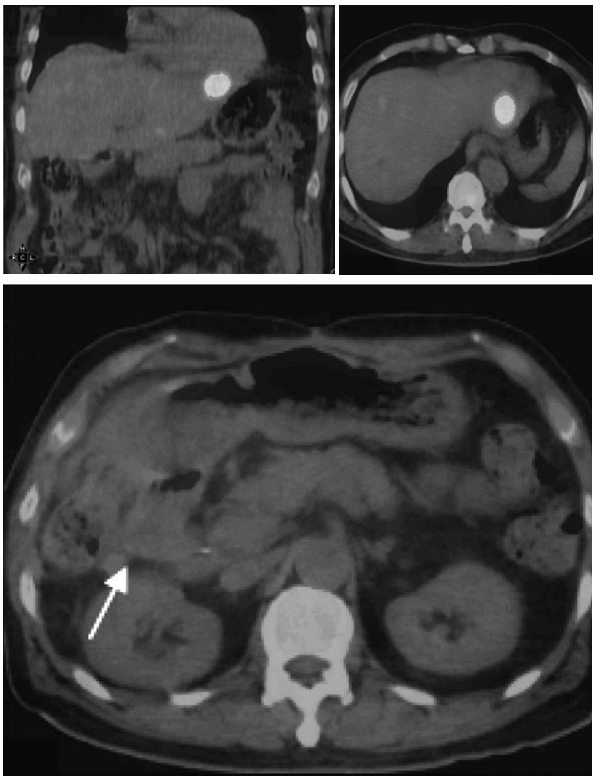

Fig.3. The 3rd time liver metastasis. The upper panel hot spot is the S2 hepatic recurrence. The lower panel is the S5 hepatic surface lesion (arrow).

patient then received a third partial hepatectomy; the pathology results revealed S2 and S5 hepatic metastases with R0 resection. At this writing, 5 months after the third operation, the patient is receiving bevacizumab and FOLFOX regimens and is free of tumor.

Due to the new developments in treatment, recent advances in the management of hepatic metastases in colorectal cancer are reviewed below.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with over a million new cases diagnosed each year[1]. Approximately 20-25% of patients with CRC will have liver metastasis at diagnosis[2], and as many as 60% of patients who develop metastases will have liver metastases[3]. On average, 5-year survival for these patients is 2-8% without surgical resection[4,6], although with impro-

ved detection and treatment options, rates of death from CRC are decreasing[3]. Therapeutic options are limited. Even when a complete clinical response is achieved with chemotherapy, it is not the equivalent of a complete pathologic response and does not obviate the need for curative surgery. Surgery remains the treatment of choice for patients with resectable hepatic colorectal metastases; approximately 25-35% of patients who qualify for complete surgical resection will be alive at 5 years[7]. Unfortunately, recurrences occur in two-thirds of patients within 2 years after resection for liver metastases, but if repeat hepatic resection is feasible, the survival clock could be turned back. However, the majority (80-90%) of patients with hepatic metastases are poor candidates for surgery due to unfavorable location, size, or number of metastases; insufficient liver reserve; or extrahepatic disease[4]. These patients generally receive palliative chemotherapy aimed at alleviating and controlling symptoms, improving quality of life, and improving survival.

In historical series of unresectable patients, the median survival was 6-9 months with very few survivors at 5 years, and none recorded at 10 years. In contrast, studies with long-term follow-up have demonstrated 10-year survival rates of 22-24%[8,9], and several authors have reported survival periods of greater than 20 years following hepatic resection [10-12]. The emphasis is increasingly placed on the likelihood of achieving negative surgical margins while maintaining adequate liver reserve, as opposed to other criteria such as the number of liver metastases present. With the increasing number of reports of success, it is important to review the recent advances in hepatic colorectal metastases.

Neoadjuvant systemic chemotherapy

When preoperative therapy is planned, the National Comprehensive Cancer Network (NCCN) panel recommends that a surgical re-evaluation should be planned within 8-10 weeks after initiation of preoperative therapy.

FOLFIRI had been reported to enable 32.5% of patients with initially unresectable liver metastases to undergo liver resection[13]. FOLFOX4 has also been reported to enable 40% of patients to become resectable liver metastases[14].

Bevacizumab, a monoclonal antibody neutralizing vascular endothelial growth factor, has been administered in combination with chemotherapy for the neoadjuvant treatment of colorectal hepatic metastases. The objective responses of 41 patients (73%) were reported in a phase II study[15]. To deal with the potential of wound healing complications, the NCCN panel recommends at least a 6-week interval (which corresponds to 2 half-lives of the drug) between the last dose of bevacizumab and elective surgery. The anti-epidermal growth factor receptor (anti-EGFR) available in Taiwan, cetuximab, has been combined with either FOLFOX6 or FOLFIRI, and 42% of patients who were initially unresectable became resectable after this combination treatment in a CELIM study[16]. According to the American Society of Clinical Oncology Provisional Clinical Opinion, all patients with metastatic CRC who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in an accredited laboratory. If a KRAS mutation in codon 12 or 13 is detected, then those patients should not receive anti-EGFR antibody therapy as part of their treatment[17]. A recent study has shown that the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab resulted in significantly shorter progression-free survival and an inferior quality of life[18]. Cetuximab and bevacizumab should not be combined outside of a clinical trial. Current evidence suggests that no chemotherapy backbone is preferred over another in combination with targeted agents[19].

To date, the true benefit of neoadjuvant

chemotherapy prior to surgical resection, with respect to progression-free survival or overall survival, is unknown. However, pre-hepatectomy chemotherapy appears to be safe and is an important part of the multidisciplinary approach to this disease[20].

Adjuvant systemic chemotherapy

Portier et al. published a study randomizing 173 patients with completely resected hepatic metastases from CRC to observation or 6 months of adjuvant 5-fluorouracil/folinic acid[21]. Despite what is considered a suboptimal chemotherapy regimen, there was a trend towards increased overall survival in the chemotherapy group, with 5-year overall survival of 51% vs. 41%, p=0.13.

There may be a role for further systemic chemotherapy in these completely resected patients. However, a well-designed prospective randomized trial is presently lacking.

There are concerns about liver damage following chemotherapy. Oxaliplatin-based chemotherapy has been known to cause vascular lesions, and steatohepatitis is linked to irinotecan treatment, although studies have shown that mortality was not increased with either of the regimens. Bevacizumab-related complications could also be decreased if the operation was performed 5 weeks after the medications [19].

Hepatic arterial chemotherapy (HAI)

A hepatic arterial infusion pump could be inserted by the radiologist or inserted while the patient is receiving hepatic surgery. Although improved hepatic disease-free survival has been demonstrated, overall survival is minimally affected and recurrence of metastatic disease at distant sites is still a major problem[22]. Overall survival of 16 months for patients with second-line hepatic arterial infusion with a HAI oxaliplatin (100 mg/m^2 2 hours) regimen combined with a modified LV5FU2 regimen has been reported[23]. The overall survival of second-line treatment with a FOLFOX6 intravenous regimen was 10.8 months[24], based on historic reports. Though survival with the HAI regimen seems longer than that with the intravenous regimen, the HAI group enrolled 44 patients who had presented with colonic primary and synchronous liver metastasis and the FOLFOX6 intravenous regimen group enrolled 60 patients, 22 with rectal cancer and 19 with more than 2 metastatic sites. With these two different patient groups, reaching a conclusion as to which is the better treatment is difficult. HAI seems promising, but further head-to-head comparisons are needed. Significant toxicity related to hepatic arterial infusion pump chemotherapy in the form of biliary sclerosis has been reported[25].

Radio frequency ablation/cryosurgery in combination with hepatic resection

Radio frequency ablation (RFA) is not a substitute for hepatic resection. Hepatic resection continues to be the gold standard currently. Though there are no randomized studies comparing these 2 modalities, single institutional experience has repeatedly demonstrated that the outcomes of RFA are inferior to those of hepatic resection. The MD Anderson Cancer Center group reported that for "solitary" colorectal liver metastases, resection was associated with longer 5-year survival rates than RFA, including disease-free (50% vs. 0%, respectively; P=0.001), and OS (71% vs. 27%, respectively; $P<0.001$) rates[26].

Positron emission tomography/computed tomography (PET/CT)

Sobhani I et al.[27] reported that recurrences were detected after a shorter time (12.1 vs. 15.4 months; P=0.01) in the PET/CT group, in which recurrences were also more frequently (10 vs two patients) cured by surgery (R0) among 130 CRC patients

randomized to conventional CT or PET/CT. In our experience, PET has altered our management of liver resection. But for multiple small nodules in lung metastases less than 1 cm, conventional CT had better detection rates than PET/CT. PET/CT has been reported to alter surgical plans by about 23-43%, compared with conventional CT[28-33]. PET/CT has also been reported to miss tumors less than 1 cm in size more frequently[26]. PET/CT should be used in the management of patients with recurrent CRC who are being considered for potentially curative surgery.

The NCCN panel recommends that post-treatment PET scans are not routinely performed for surveillance of patients with resected early-stage CRC or to detect metastatic disease in the absence of other evidence of such disease.

Conclusion

The last decade has seen a revolution in the application of novel therapies leading to an aggressive approach to the management of colorectal liver metastases. It is important for the oncologist and surgeon, as well as the pathologist, to cooperate closely to detect metastatic lesions earlier and make the best profit for the patients.

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大腸直腸癌合併肝臟轉移的最新療法

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摘　要

我們報告一位65歲的直腸癌合併肝臟轉移的患者來署立台南醫院接受治療，前後一共歷經三次切肝手術和多次化學治療，並探討此類患者治療之最新進展。Neoadjuvant 化學治療可用 FOLFOX 或者 FOLFIRI，亦可考慮合併標靶藥物如 bevacizumab 或是 cetuximab。術後化學治療有可能是必要的，但仍需更多證據來支持，其他如肝動脈注射化療仍在實驗階段。而正子攝影的檢查目前是建議使用在有開刀可能性的患者身上。