

Euro Cancer 2018: Strategy for colorectal cancer liver metastases - Shinji Osada - Gifu Municipal Hospital.

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In this presentation, the surgical indications for liver metastasis from colorectal cancer (CRC) and its optimal timing will be discussed. Clinically, our treatment policy has been to perform hepatectomy first, if the resection can be done with no limit on size and number of tumors. However, if curative resection is not, chemotherapy is begun first and timing for the possibility of a radical operation is planned immediately. Recurrence was detected after hepatectomy, similar between simultaneous and staged resection, but early detection was higher in simultaneous cases, indicating the staged operation to be better. As a research target focused on hepatocyte growth factor (HGF) and its receptor (c-Met), the signaling pathway might induce cancer progression in the process of liver regeneration after hepatectomy. Actually, c-Met overexpression was closely associated with liver metastases, but its expression was detected to reduce in the metastatic site compared with primary lesions. In addition, pre-treatment of CRC cells with HGF enhanced 5-FU-induced cell death by 63% compared with the control during the expression of signaling pathway by HGF/c-Met activation. E2F is a transcriptional factor of thymidylate synthase (TS), which is important to metabolite 5FU, and the D-type cyclins, which play a critical role in the cell cycle and correlate the activation of E2F. The expression of E2F1 was decreased significantly to 50.5% by HGF with a reduction of cyclin D1 to 52.1%. TS were also decreased in a time-dependent manner to 80.6±2.0% after 24 hours and to 52.7±1.5% after 96 hours. In conclusion, the presence of HGF was found to increase the 5FU-induced death signal, the best procedure for favorable patient prognosis will be a hepatectomy after chemotherapy. The present study also lead to a novel concept in which the hepatectomy-induced high serum level of HGF for liver regeneration allows drug-resistant cancer cells to become sensitive again.

Expansion of multidisciplinary care with advances in surgical procedure and technique in the past decade has resulted in simultaneous resection being the standard treatment of choice because of its safety and efficiency. However, the optimal timing of surgical resection of synchronous metastasis remains controversial, and guidelines regarding the upper limits of operative indications for synchronous metastases have not yet been defined. In addition, neoadjuvant chemotherapy has also been found to be beneficial not only for initially unresectable but also resectable synchronous metastases. After the development of combinations of 5-fluorouracil/folinic acid with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) treatment regimens, a prospective phase II study demonstrated that the response rate was 66% and the maximum resection rate was 82%. Traditional surgical strategies of hepatic resection in accordance with past chemotherapeutic regimens have been used less and less over

the past several years. Therefore, this review will primarily discuss treatments in association with the FOLFOX/FOLFIRI chemotherapeutic regimens. Consideration of the timing of hepatectomy and whether it should be performed.

Introduction:

Hepatic metastatic disease from colorectal cancer (CRC) is significant clinical problem. The liver is dominant metastatic site for patients with CRC and although two-thirds of affected patients have extrahepatic spread as some have disease that are isolated to liver. For patients with isolated liver metastases, regional treatment approaches may be considered as an alternative or in combination with systemic chemotherapy. The available regional treatments for hepatic metastases from CRC include surgical resection, thermal ablation, regional hepatic intraarterial chemotherapy, chemoembolization, radioembolization, and radiation therapy (RT), including stereotactic RT. Among these treatments, surgery remains the gold standard because it is associated with a long-term relapse-free survival plateau, although newer technologies, such as stereotactic RT, may theoretically confer similar long-term benefit to some patients. Although hepatic resection used to be reserved for patients with a maximum of three lesions in the same lobe, if it was possible to achieve 1 cm margins, and those without portal lymph node metastases, these "rules" have been changed in the modern era, particularly with advancements in both surgical technique and systemic therapy. Profound improvements in the outcomes of patients with metastatic CRC over the past 15 years have been attributed to increased use of hepatic resection in appropriately selected patients and more effective chemotherapy. As a result, the criteria for defining which patients are suited for surgical therapy have evolved, and many surgeons take an aggressive stance in the management of hepatic metastases. (See "Systemic chemotherapy for metastatic colorectal cancer: Completed clinical trials".)

This topic review will focus on the integration of resection and systemic chemotherapy in patients with potentially resectable CRC liver metastases. The optimal selection of patients for resection, the timing and order of resection in patients who present with synchronous CRC liver metastases, issues related to surgical margins and repeat resection for recurrent liver metastases; surgical techniques for hepatic resection; results for local ablation, regional chemotherapy and embolization, and RT; surgical management for CRC pulmonary metastases, other locoregional methods which are managing for patients presenting with stage IV CRC i.e. stenting, resection and cytoreductive surgery and intraperitoneal chemotherapy which are addressed elsewhere. Hepatic resection of colorectal cancer liver

metastasis and "Overview of the hepatic resection" and "Non-surgical local treatment strategies for colorectal cancer liver metastases", Hepatic resection techniques, Surgical resection of pulmonary metastases: Outcomes by histology section on 'Col-

orectal cancer' and "Locoregional methods for management and palliation in patients which presents with stage IV colorectal cancer".