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Prognostic value of biomarkers in metastatic colorectal cancer patients

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ABSTRACT

Backgrounds: The prognostic value of biomarkers in metastatic colorectal cancer (mCRC) patients with liver metastases remains unclear. We assessed the difference of expression of biomarkers between primary tumors and liver metastases treated with chemotherapy in mCRC patients, as well as the prognostic value of these markers.

Methods: Forty-three mCRC patients with liver-limited disease from January 2007–November 2011 were analyzed. They all received resection of primary tumors followed by oxaliplatin-based chemotherapy. After chemotherapy, they all received hepatic resection. Forty-three paired primary and metastatic tumor specimens were collected to measure the messenger RNA expression of six biomarkers by the Danenberg tumor profile method (thymidylate synthase, dihydropyrimidine dehydrogenase [DPD], excision repair cross-complementing gene1, thymidine phosphorylase [TP], folylpolyglutamate synthase, and regenerating islet-derived family, member 4).

Results: Thirty-six patients' messenger RNA was used for analysis. All markers showed similar expression between primary and metastatic sites. The low-expression group of Danenberg tumor profile and TP in the primary tumor showed significantly higher overall survival than the high-expression group ($P < 0.001$ and $P = 0.033$), but for DPD and TP in liver metastases, there were no significant differences of overall survival between the two groups. The ratios of marker expression in liver metastatic site to that in primary site of DPD and TP were significantly higher in chemo-responders than in non-chemo-responders ($P = 0.034$ and $P = 0.022$).

Conclusions: Biomarkers' expressions in liver metastases were similar to those in the primary tumor. DPD and TP in the primary lesion may be a prognostic factor in chemotherapy-naïve mCRC patients with liver-limited disease, but those in liver tumor were not. Further validated analysis to our results would be warranted.

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1. Introduction

Colorectal cancer is one of the most common causes of cancer-related mortality worldwide, and the liver is the most common, and often the only, metastatic site [1,2]. Surgical resection of colorectal liver metastases (CLM) is considered the only curative therapy, but most metastatic colorectal cancer (mCRC) patients with CLM have unresectable disease [3,4]. It is important to develop the strategy of chemotherapy based on the expression of biomarkers to improve the survival of CLM patients.

One of the concerns about biomarkers for CLM patients is to reveal the differences of marker expression between primary lesion and liver metastatic lesion. Some reports have described that the messenger RNA (mRNA) expression levels of several biomarkers (thymidylate synthase [TS], dihydropyrimidine dehydrogenase [DPD], thymidine phosphorylase [TP], and others) in the primary site and the liver metastatic site were similar or showed a positive correlation if laser-captured microdissection was used [5,6]. However, the association of expression of these markers between primary tumor site and metastatic site is not fully understood.

In this study, we selected six specific genes as follows: TS, DPD, TP, excision repair cross-complementing gene 1 (ERCC1), folylpolyglutamate synthase (FPGS), and regenerating islet-derived family, member 4 (REG4). TS, DPD, and TP are involved in the metabolism of fluoropyrimidines, and there are many reports about these markers in colorectal cancer [7–17]. ERCC1 is an excision nuclease within the nucleotide excision repair pathway that plays a major role in repairing platinum-induced DNA adducts [18]. There are some reports that ERCC1 might predict the efficacy of oxaliplatin-combined chemotherapy and that expression of ERCC1 was associated with prognosis of colorectal cancer, but their predictive and prognostic value is still unclear [11,16,19]. Folate-metabolizing enzyme FPGS is involved in the metabolism of folic acid [14] and REG4, which is a member of the REG family that acts as an antiapoptotic factor through the AKT signaling pathway [20,21]. Using these biomarkers collected from the same patients' primary tumor tissues and liver metastatic tissues, we assessed the difference of their expression between primary site and liver metastatic site treated with chemotherapy in CLM patients retrospectively. We also assessed the prognostic value of markers collected from two different sites of the same patient.

2. Methods

2.1. Patients

Forty-three mCRC patients with resectable liver-limited disease from January 2007–November 2011 were assessed. mCRC patients who had extrahepatic disease and who had unresectable liver metastases were excluded from the analysis. Resectability was decided based on the size of the remnant liver volume (>30%) and expected function after the removal of all metastases, regardless of the number and size of the liver metastases. If metastases infiltrated (1) all hepatic veins, (2) both hepatic arteries and 3 both portal vein branches, these patients were defined as unresectable. Patients who received chemotherapy within 12 mo of diagnosis of mCRC with liver-limited disease were also excluded from the analysis.

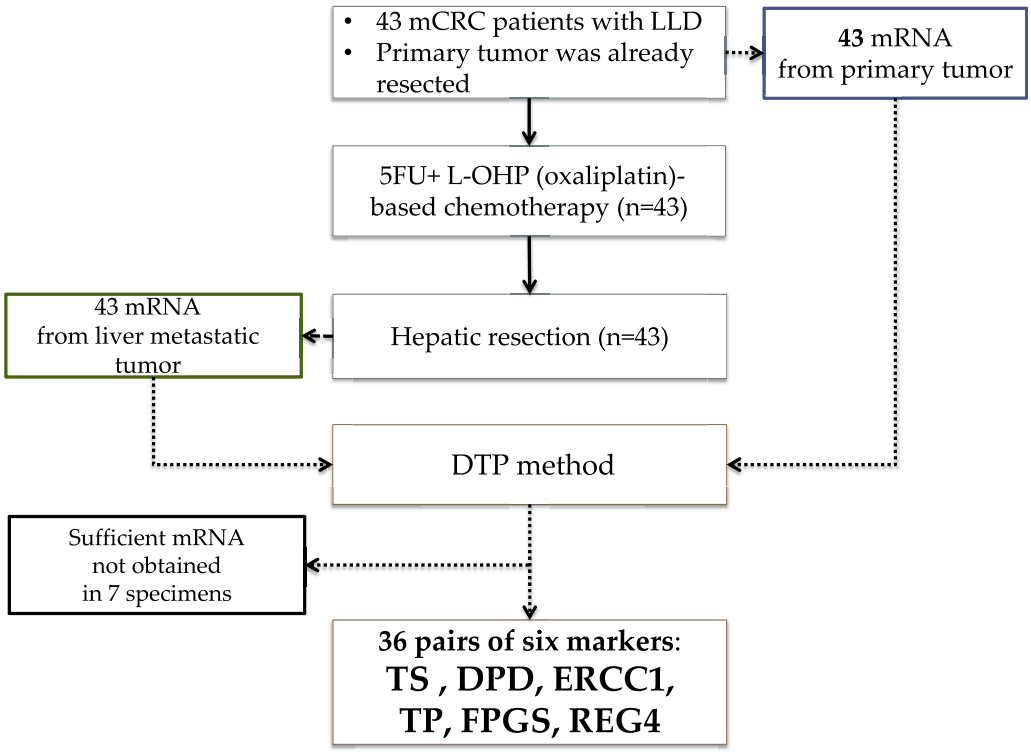

Fig. 1 – Patients' flow. LLD, liver-limited disease. (Color version of the figure is available online.)