RESEARCH ARTICLE

# Effect of Portal Vein Chemotherapy on Liver Metastasis after Surgical Resection of Colorectal Cancer

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## Abstract

**Objective: To explore the effect of portal vein chemotherapy on liver metastasis after surgical resection of colorectal cancer. Methods: Patients fulfilling the eligibility criteria were assigned to receive either surgery plus 1-week continuous infusion of 5-FU (study group) or surgery alone (observational group). Patients in the study group received portal vein chemotherapy, whereby 5-FU (1000 mg/d) and heparin (5000 IU/d) infusion was initiated from the day of surgery and lasted for 7 consecutive days. Liver metastasis was monitored during five years follow-up postoperatively. Results: Sixty four patients were recruited and assigned to the study group (12 with colon and 20 with rectal cancer) or the control group (10 with colon and 22 with rectal cancer). Liver metastasis rate was 12.5% in study and 25.0% in observational group, the difference being significant (P<0.01). Conclusion: Portal vein chemotherapy could be an effective treatment in preventing liver metastasis after surgical resection of colorectal cancer.**

**Keywords:** Portal vein - colorectal cancer - liver metastasis - chemotherapy - prevention

*Asian Pacific J Cancer Prev,* **13 (9)**, 4699-4701

## Introduction

Colorectal cancer is a common cause of morbidity and mortality, and is resectable in approximately three quarters of patients (Ohman et al., 1985; El-Basmy et al., 2012). But up to half will subsequently develop an incurable recurrence and the overall 5-year survival is only around 60% (Ohman et al., 1985; El-Basmy et al., 2012). Approximately 50% of patients diagnosed with colorectal cancer will develop synchronous or metachronous metastasis to the liver at some point during the development of the disease (Stangl et al., 1994; Leonard et al., 2005). Only a small fraction of patients will have discrete, isolated metastasis resectable for cure. Thus, effective adjuvant treatment is essential to prevent liver metastasis. Many efforts have been attempted in this setting, adjuvant portal venous chemotherapy is an option to prevent the development of colorectal liver metastasis with some encouraging results (Taylor et al., 1979). Taylor et al. further suggested that 5-fluorouracil (5-FU) could be effective as an adjuvant therapy if infused via the portal vein (PVI) (Taylor et al., 1985). In a trial on 244 patients, initiated in 1975, they reported, after a median follow-up of 50 months, a statistically significant improvement in survival in patients treated with 5-FU portal vein chemotherapy (1000 mg/day, with heparin infused continuously for the first 7 postoperative days) compared to patients receiving surgery alone. A meta-analysis, based on individual patient data, specifically addressed a comparison between liver infusion chemotherapy and no post-operative treatment, in which, ten trials and 3499 patients were included (Liver Infusion Meta-Analysis Group, 1997). In conclusion, PVI led to a modest but statistically significant improvement in survival, even after exclusion of the promising initial trial on this therapeutic approach (RR=0.89; 95% Cl 0.84 to 0.94).

We conduct this comparative follow-up study to test the hypothesize that Chinese patients in Jiangsu with colorectal cancer will also benefit from therapy and liver metastasis could be prevented by inserting a catheter into the portal vein at the end of laparotomy, and 5-FU administered as a continuous infusion for 7 days after surgery.

## Materials and Methods

*Patients Selection*

The inclusion criteria were: (1) no evidence of distant metastasis or residual tumor following surgical resection(Dukes' A,B ,and C); (2) histologically confirmed and surgically excised colorectal adenocarcinoma; (3) karnofsky performance status of 60 or more; (4) age less than 75 years; (5) adequate hematological (white blood cell count > $3.5\times10^9$ and platelet count > $80\times10^9$), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine level < 1.5 times the

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upper normal limit); (6) no pre-existing or concomitant malignant neoplasms or pre-operative chemotherapy and radiotherapy. Intraoperative palpation and intraoperative ultrasound were used to confirm hepatic metastasis from colorectal cancer (Foley et al., 1998). Patients fulfilling the eligibility criteria were assigned to receive either surgery plus 1-week PVI of 5-FU (study group) or surgery alone (observational group).

*Treatment*

Patients assigned to study group received continuous portal vein infusion of 5-FU (1000 mg/d) and heparin (5000 IU/d), the infusion was initiated from the day of surgery and aderministered for 7 consecutive days. Access to the portal vein was achieved by insertion of a catheter into the right gastroepiploic vein. Patients were observed by investigators daily during portal vein infusion. Routine blood and liver function tests were performed every other day.

*Statistical analysis and research experience*

The primary endpoint of the current study was liver metastasis, and the secondary endpoint was postoperative complications. Rates of liver metastasis between two groups were compared by the log-rank test. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al.,2012).

## Results

Sixty four patients were assigned to study group (12 were colon cancer and 20 rectal cancer) or observational group (10 were colon cancer and 22 rectal cancer). Rate of liver metastasis was caculated according to 5 years follow-up data, and compared between two groups by log-rank test, which is 12.5% (4/32) in study and 25% (8/32)in observational group with statistical significance ($P<0.01$).

*Postoperative complication*

One patient experienced abdominal distension and nausea during portal vein chemotherapy. No other complication,eg.,haemorrhage, cytopenia, liver function impairment and delayed healing of incision occurred. All patients completed scheduled chemotherapy.

## Discussion

Although progress in systemic chemotherapy, regimens including fluorouracil (5FU) with or without oxaliplatin are still considered with limited effectiveness in preventing the recurrence of colorectal cancer (Cihan et al., 2011). Hence, a continuous infusion of cytotoxic drugs into liver via PVI, for at least a few days during the immediate postoperative period, has been proposed. Nonrandomized studies of PVI, with thiotepa or mechlorethamine, were conducted in the 1950s but were abandoned because of concerns about toxicity (Holden et al., 1962). The first randomized trial to test cytotoxic PVI of 5-FU was initiated in 1975. Patients were randomly assigned to either surgery alone or to surgery plus a 1-week continuous infusion of 5-FU via a catheter that was inserted into the portal vein (Taylor et al., 1985). Early results from this trial were encouraging (Taylor et al., 1979), and, subsequently, further randomized trials were conducted in 1980s (Gray et al., 1992; ), and suggested a reduction of about one third in the risk of death for patients allocated to liver infusion of 5-FU (Gray et al., 1991). However, a randomized study inculded 753 colorectal cancer patients receiving either surgery alone (arm 1), surgery plus postoperative PVI of 5-FU 500 mg/m$^2$ for 24 hours and seven consecutive days given on the first day (arm 2), or surgery and the same chemotherapy regimen administered by peripheral venous route (arm 3) suggested that 5-year disease-free survival were 65% (arm 1), 60% (PVI, hazard ratio 1.18, p=0.23), and 64% (arm 3, hazard ratio 1.04, p=0.76); the 5-year overall survival was 72% (arm 1), 69% (PVI, hazard ratio 1.21, p=0.2), and 74% (arm 3, hazard ratio 1.03, p=0.86), respectively (Laffer et al., 2008). A significant accumulation of early deaths were observed in PVI group (p=0.015). This randomized study provides evidence that short-term perioperative chemotherapy does not improve disease-free and overall survival in patients with potentially curative colorectal cancer.Thus,conclusion on PVI for colorectal cancer patients postoperatively are controversial,especially regarding impact on the liver metatistasis is not clear. This is the background why our study is conducted.Our study suggested that liver metastasis rate was 12.5% in study and 25.0% in observational group that is significant difference between two groups suggesting that PVI chemotherapy could be an effective treatment in preventing liver metastasis after surgical resection of colorectal cancer. One explanation might be that hepatic metastasis is a major cause of failure after surgery for colorectal cancer. Because during surgery, tumor cells could disseminate from cutting points of blood vessels to intestinal canal or lymphatic vessels, and surgical compression could push cancer cell to reach portal vein system through mesenteric vessels and then invade the liver, causing liver metastasis (Hayashi et al., 1999). It is reported that plenty of portal venous blood supply for metastatic hepatic carcinoma via percataneous hepatic portography, especially at a port where tumor developed fast (Hayashi et al., 1999). Therefore, it is hypothesized that blood supply from portal vein could play an important role in maintaining tumor growth, and chemotherapy via the portal vein should have great therapeutic value in treating liver metastasis from colorectal cancer.

Our study demonstrated that portal vein chemotherapy could be an effective treatment in preventing liver metastasis after surgical resection of colorectal cancer. However our result did not show the impact on overall survival and need to be confirmed by randomized controlled clinical trials with large sample size and long-term follow-up.

## Acknowledgements

Dr. Xin-En Huang is supported in part by a grant from Jiangsu Provincial Administrtion of Traditional Chinese Medicine (LZ11091), and in part from a special research fund of Organization Department of Jiangsu Provincial Party Committee,Talent Work Leading Group of Jiangsu Province (333 High-level Personnel Training Project).

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