Colorectal carcinoma is a common problem in the United States, and the liver is the most frequent site of metastatic disease. Because there is a good pharmacologic rationale for the use of hepatic intra-arterial (HIA) therapy, and because of the disappointing survival observed with systemic chemotherapy, studies of hepatic arterial infusion have been conducted.

### Reviewing the Randomized Trials

In reviewing the randomized studies, Dr. Venook cites American trials separately and asserts that none of them showed an increase in survival with regional therapy. However, two large American studies permitted a crossover from systemic to hepatic arterial therapy.[1,2] This could have increased survival in the systemic arm and served to diminish a potentially significant difference between the systemic and HIA therapy groups. In the Memorial Sloan-Kettering Cancer Center (MSKCC) study,[1] patients on the systemic arm had infusion ports placed at surgery so that they could receive HIA therapy at a later date. The most common reason for not crossing over to HIA therapy was occlusion of the infusion ports.

In this study, 60% of patients on the systemic arm crossed over to HIA therapy. Of these, 26% had a partial response, while 32% had a minor response or stable disease with HIA FUDR after progressing on systemic FUDR. The patients who crossed over to receive hepatic arterial infusion experienced a doubling of survival compared to those who never received HIA therapy: 18 vs 8 months in the MSKCC study and 24 vs 12 months in the Northern Oncology Group (NCOG) study.[2]

The two other American studies were too small to assess survival differences between the arms.[3,4] In one of these studies, 49% of patients in the HIA therapy group received inadequate treatment. Thus, the six completed randomized studies mentioned had three major problems: crossover design in two American studies, inadequate systemic chemotherapy in two European studies, and small numbers of patients in two American studies.

Dr. Venook then touches on the meta-analyses of HIA therapy vs systemic therapy that have been performed.[5,6] An increase in survival in the hepatic arterial group was observed if all studies were included. However, no increase in survival was seen if the two European studies in which inadequate systemic therapy was administered were excluded. In a meta-analysis, it is desirable to include only prospective randomized studies utilizing adequate therapy. However, if this were done in the case of systemic vs HIA therapy, one would be left with small studies, and it would be difficult to make conclusions about survival.

Dr. Venook offers several reasons why an improvement in response rate does not translate into improved survival. He makes the point that colorectal cancer is a systemic disease, and therefore, regional therapy should not affect survival. In autopsy data, however, Weiss noted that 46% of patients dying of colorectal cancer had metastases limited to the liver.[7]

It is also clear that a significant proportion of patients with colorectal carcinoma die of progressive hepatic disease despite the presence of disease in other organs. Toxicity and surgical complications may affect survival with HIA, but until we have a study without a crossover design that has an adequate number of patients, we will not be able to answer the question about whether there is a survival advantage for HIA.

### Potential Areas of Improvement

A strong part of this review focuses on potential areas of improvement, including the standardization of surgical techniques and the optimization of delivery of chemotherapy to the liver in an attempt to reduce toxicity and increase response rates.

The review of surgical issues is excellent. Certainly, this type of treatment requires a team approach.
First, the radiologist has to carefully define the arterial supply, so that the surgeon knows where the vessels to the duodenum and stomach are located and also whether there are any replaced or accessory arteries.

The surgeon must devascularize the stomach and duodenum and ensure adequate perfusion of the liver. There is a learning curve, with fewer complications arising after surgery performed by more experienced surgeons. In a review by Campbell et al, inexperienced surgeons had a technical complication rate of 37% vs 7% for experienced surgeons.[8]

The nuclear medicine physician must read the perfusion scans accurately and make sure that there are no small areas of extrahepatic perfusion; obviously, the large areas of missed perfusion are easier to identify.

The medical oncologist must carefully follow the patient's liver function tests and must be cognizant of the need for dose modifications dictated by changes in liver function. The types of modifications that we use at MSKCC are summarized in Table 1.

The multidisciplinary approach may be difficult to implement in some centers, but it is important for this type of therapy in order to maximize benefit and reduce both the financial costs and medical risks of hepatic infusional chemotherapy.

**CALGB Study Will Address Survival Issues**

During the last 20 years, there has been no change in the survival for metastatic colorectal carcinoma. More than 2,000 patients have been randomized to 5-FU plus leucovorin vs 5-FU alone. A meta-analysis of these studies demonstrated a median survival of 11 months and a 2-year survival of less than 20% for both treatment groups.[9]

Recently, new drugs have been developed for the treatment of colorectal carcinoma: irinotecan (Camptosar), a camptothecan derivative; tomudex, a new thymidylate synthase inhibitor; and oxalaplatin, a new platinum. All of these drugs produce response rates similar to those obtained with 5-FU and leucovorin. In many studies of these new agents, survival is similar, with only 20% of patients alive at 2 years. Whether combinations of these agents will increase survival is yet to be tested.

In three recent studies of HIA using FUDR plus leucovorin, FUDR plus dexamethasone, and FUDR plus leucovorin and dexamethasone, the median survivals were 23, 23, and 27 months, respectively.[10-12] The 2-year survival rates in these studies were 61%, 44%, and 47%, respectively.

Because of this apparent survival advantage of HIA chemotherapy compared to systemic chemotherapy, a new randomized study was initiated by the CALGB to ascertain whether these results can be reproduced. The CALGB study will address many issues that were not answered in the earlier trials:

- Does HIA therapy improve survival, as compared with adequate systemic therapy?
- Is there a difference in quality of life between the two treatments?
- Is there a difference in financial cost over the entire course of treatment?
- Is hepatic arterial infusional chemotherapy a more effective treatment than systemic chemotherapy for patients with metastatic colorectal carcinoma limited to the liver?

The CALGB study will not allow a crossover, will have a large number of patients, and will utilize the best available chemotherapy in each arm. Hopefully, with the cooperation of many centers, this trial will provide us with the answers to these questions.

**References:**


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