Update on Hepatic Intra-Arterial Chemotherapy

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The use of hepatic intra-arterial (HIA) chemotherapy is based on the pharmacologic principle that the regional administration of certain drugs can lead to higher drug concentrations at the site of a tumor. This has been studied most extensively in patients with liver-only colorectal metastases. Four large randomized studies have failed to demonstrate a survival advantage of regional treatment over systemic chemotherapy, although two meta-analyses confirmed an improvement in response rate and suggest a trend toward improvement in survival. Two randomized studies have shown improved survival in patients treated with HIA chemotherapy, as compared with those given supportive care, and quality of life also appears to be superior in HIA chemotherapy recipients. The treatment employed in all of the randomized studies was hindered by substantial hepatobiliary toxicity and many surgical complications. Improved surgical techniques and newer chemotherapy combinations appear to have improved phase II results with HIA therapy, leading to a randomized trial now being conducted by the Cancer and Leukemia Group B (CALGB). The role of HIA chemotherapy in adjuvant settings and in other diseases has not been as well-studied, and such uses remain appropriate only for very selected patients. Ultimately, the regional advantage gained by the HIA route may prove to be most advantageous for the delivery of newer biologic agents.


Introduction

About 140,000 people in the United States were diagnosed with colon or rectal cancer in 1996, and 40% of those patients will ultimately die of metastasis from that disease.[1] The liver is the dominant metastatic site in the majority of these patients, and more than 80% of patients with hepatic metastases succumb to liver failure.[2]

Despite the fact that metastatic colorectal cancer is usually a systemic disease, in some patients, the liver is the only site of metastasis. This is evidenced by the fact that, with careful patient selection, resection of isolated hepatic metastases can result in long-term disease-free survival. For example, resection of up to three colorectal cancer lesions in patients without evidence of extrahepatic colorectal tumor leads to a 5-year survival of approximately 25%.[3,4]

The incorporation of intraoperative ultrasound of the liver into the staging evaluation, as well as the application of prognostic factors, such as carcinoembryonic antigen (CEA), lesion size, and stage of the primary tumor, may permit the identification of a group of patients who would enjoy an even better survival.[5] Unfortunately, although about one-third of patients with hepatic metastases appear to have liver-only tumor, in no more than 10% of these patients is the tumor amenable to curative hepatic resection.

The regional delivery of chemotherapy to patients with liver tumors is not a new concept. Even though colorectal metastases appear to migrate to the liver via the portal vein, macrometastases in the liver derive more than 80% of their blood supply from the hepatic arterial circulation; in contrast, normal hepatocytes are supplied primarily by the portal circulation. Therefore, the administration of chemotherapy into the hepatic artery allows for the selective delivery of drug to the tumor with relative sparing of normal hepatocytes.[6] The pharmacology behind this strategy is well-defined[7]: depending on a drug's clearance and toxicity profile, a marked increase in the area under the curve (AUC) may be achieved. If a dose-response relationship for that drug and that disease exists, this could then translate into proportionally greater efficacy.

The regional behavior of colorectal cancer metastatic to the liver and favorable drug pharmacokinetics led to extensive clinical investigation of hepatic intra-arterial (HIA) chemotherapy in the 1970s and '80s, initially via percutaneously placed catheters. The introduction of a totally implantable pump system made this an ambulatory treatment. Encouraging, if not inflated, response rates ranging from 29%[8] to 88%[9] were reported and engendered numerous randomized protocols comparing systemic vs HIA chemotherapy. Despite these studies, the optimal dosing and
role of HIA therapy in the management of colorectal liver metastases remain unclear. This review will summarize and critique the randomized studies and will address the technologic and surgical advances that have now better defined the technique necessary for the safe, successful administration of HIA chemotherapy. A series of phase II trials will be reviewed, and the design of a Cancer and Leukemia Group B (CALGB) randomized study assessing this modality will be described. Although the focus of this review is on liver metastases from colorectal cancer, a brief description of HIA therapy in other malignancies will also be presented.

**HIA Chemotherapy in Untreated Patients**

### Results of Randomized Trials

Four major prospective trials comparing systemic fluoropyrimidine chemotherapy vs HIA floxuridine (FUDR) chemotherapy delivered via the implanted pump in untreated patients with liver-only colorectal metastases were completed in the early 1980s ([Table 1](#)). In all, 375 patients were enrolled in these randomized studies. In each study, the response rate to HIA chemotherapy was superior to the systemic counterpart. However, in none of the studies did this translate into a survival improvement for the HIA approach.

Two European trials conducted during the late 1980s randomly assigned patients to either best supportive care or HIA FUDR. The studies of Rougier et al[14] and Allen-Mersh et al[15] both demonstrated a survival advantage of HIA therapy, but most of the control patients did not receive systemic chemotherapy, raising the concern that these patients, at least by American standards, received suboptimal treatment.

The latter study,[15] done in the United Kingdom, was conducted with particularly rigorous quality control: Every pump was implanted by the same surgeon (Allen-Mersh). A thorough quality-of-life analysis, administered by dedicated nurses, demonstrated a prolongation of normal-quality survival, with respect to physical symptoms, anxiety, and depression, in patients treated with HIA chemotherapy, as compared with those given best supportive care.

The data of all of these trials have been subjected to two different meta-analyses. Each meta-analysis confirmed the trends that were apparent in the individual studies; namely, that response rates were greater with HIA therapy. However, although there was a trend toward an improvement in survival, only when the patients enrolled on the no-treatment control arms were included did the difference reach statistical significance.[16,17]

Why would the substantial improvement in response rate not translate into a survival advantage? There are numerous possible explanations for this:

- **Colorectal cancer is a systemic disease, and thus, even effective regional chemotherapy to liver metastases does not alter patient survival.**

Although colorectal cancer metastatic to the liver is usually a systemic disease, as noted above, selected patients with isolated liver metastases from colorectal cancer can be cured with hepatic resection.[3]

Also, most patients with unresectable liver metastases die of progressive liver dysfunction,[2] and even with effective management of liver metastases, most patients treated with HIA chemotherapy in these studies die from advancing liver involvement.[17] Therefore, the argument that systemic therapy is needed is not necessarily supported by the facts.

- **Hepatobiliary toxicity, including biliary sclerosis, led to the cessation of therapy in many patients.**

Without question, the dose of FUDR in most of the studies--.3 mg/kg/d for 14 days--was too high. This was not appreciated until many patients suffered permanent biliary damage.[18] Therefore, the HIA therapy was overly toxic, and nearly half of the patients stopped treatment for that reason rather than for treatment failure.

- **Surgical complications, including catheter dislodgment and gastrointestinal misperfusion (ie, inadvertent administration of chemotherapy to the stomach or duodenum), made this a very difficult therapy to deliver safely.**

Reflecting the experience of the operating surgeon[19] and the infancy of the technique,[20] surgical
complications in these studies were prohibitive. For example, of 33 patients randomized to HIA therapy in the Mayo Clinic study,[13] HIA treatment was never begun in 5 patients because of surgical complications, was prematurely discontinued in another 5 because of later problems, and was abrogated in 4 others because of gastrointestinal misperfusion.

- **Crossover of patients from systemic to HIA therapy may have masked a survival advantage.**

This may have confounded the findings of the two largest studies,[10,11] since there is evidence that fluoropyrimidine-based HIA chemotherapy produces a response rate better than 30% in previously treated patients.[17,21]

The results of these trials led to one of two interpretations: either the therapy was not worth pursuing or needed to be improved markedly to make it worthwhile. Focusing on potential areas of improvement, investigators concentrated on patients without radiographic evidence of extrahepatic tumor and pursued two avenues: (1) standardizing the surgical technique of pump placement and (2) optimizing the delivery of chemotherapy from the standpoint of toxicity and response.

**Surgical Issues**

**Standardization of Pump Placement**

The goals of pump placement are to enable bilobar hepatic perfusion with chemotherapy and to prevent administration of chemotherapy to the stomach or duodenum (misperfusion). While this sounds simple, the rate of complications in the early experience with this therapy was unusually high and correlated with the experience of the operating surgeon.[19]

The regimentation of the procedure into three basic steps helps clarify the critical issues. The principal factors influencing the safe and optimal use of HIA therapy are listed in Table 2.

The first step is a preoperative angiogram of the arterial supply of the liver. A review of the hepatic arterial anatomy in 550 patients at the University of California, San Francisco (UCSF), has demonstrated conventional anatomy in just 61% of patients. The variations in the other 39% are distributed among 10 different anomalies, making a thorough angiographic evaluation—celiac, then selective hepatic, left gastric, and superior mesenteric arteries—necessary to identify replaced or accessory hepatic arteries prior to surgery.

With the arterial road map in hand, the surgeon takes the next step—exploratory laparotomy. First, an exploration is done to exclude unresectable extrahepatic tumor. The lymph nodes in the porta hepatis, along the common hepatic artery, and at the celiac axis are the likeliest radiographically inapparent sites of extrahepatic tumor. If no contraindication to pump placement is found, a cholecystectomy is performed. The details of vascular dissection and the necessity for total devascularization of the distal stomach and proximal duodenum to minimize the risk of misperfusion are reviewed elsewhere.[22]

The final step is the identification of any variations in the hepatic lobar arterial supply. A search is made for replaced or accessory left or right hepatic arteries These may be ligated and divided without problems. In nearly all cases, the gastroduodenal artery is the vessel of choice for cannulation. In the past, a dual cannulation was done in the face of a replaced right or left hepatic artery, but that appears to be an unnecessary procedure in most patients.[23]

The replaced hepatic artery is temporarily clamped and if no obvious ischemia to the liver ensues, the vessel may be ligated. As long as at least one hepatic artery to either lobe of the liver originates at the take-off of the gastroduodenal artery, hepatic perfusion of the contralateral lobe occurs, often within seconds of ligation of the variant lobar artery. On the rare occasion in which clamping of a replaced hepatic artery produces ischemia to one lobe, that vessel must be side-cannulated using either a tapered catheter and a dual catheter pump or a second device. The intricacies of catheter placement in other arterial circumstances have been reviewed recently by Curley et al.[24]

Once the catheter is situated, the pump is placed subcutaneously and is loaded with heparinized water. The catheter is passed through the abdominal wall, trimmed to an appropriate length, and inserted into the gastroduodenal artery so that its tip lies just at the take-off of the gastroduodenal artery; it is secured with silk ties on either side of the intraluminal lead. Finally, 5 mL of fluorescein is injected into the pump side port, and the liver, stomach, and duodenum are examined with a Wood's lamp to verify bilobar liver perfusion and to exclude misperfusion to the stomach or duodenum. Before initiating HIA chemotherapy, one postoperative step, a technetium-99m-macroaggregated albumin (TcMAA) scan (see Figure 1 and Figure 2), is obtained to ensure that there is no
misperfusion and to assess the adequacy of whole liver perfusion,[25] which represents the physiologic distribution of chemotherapy and is probably important for maximal clinical response.[26]

Postoperative Complications
Early postoperative complications consist of arterial injury leading to hepatic artery thrombosis, incomplete perfusion of the entire liver due to the lack of recognition of an accessory hepatic artery, misperfusion to the stomach or duodenum, and pump pocket hematoma. If the above steps are followed rigorously, these complications should occur in fewer than 5% of patients. Operative mortality should approach that of an open cholecystectomy.

Late complications tend to be more common, and include inflammation or ulceration of the stomach or duodenum, pump pocket infection, and thrombosis of the catheter. When antral or duodenal ulceration occurs, the possibility that chemotherapy misperfusion may be responsible can be evaluated by endoscopy of the stomach and duodenum with concomitant injection of methylene blue through the pump side port.[27] Immediate deep blue staining of the ulcerated site warrants an angiographic search for a vessel responsible for the misperfusion. Once identified, the offending vessel can often be occluded using interventional radiologic techniques.

Optimizing Chemotherapy
As mentioned above, it was apparent early in the initial phase III trials that the dose of FUDR employed--.3 mg/kg/d for 14 out of 28 days--induced severe biliary toxicity. This toxic effect probably was the result of ischemic cholangiopathy,[28] which appeared to reflect the patients' cumulative exposure to FUDR.[20] It should be noted that the FUDR dose reported by Memorial Sloan-Kettering Cancer Center (MSKCC) for all of its studies[29-31]--.3 mg/kg/d for 14 days--actually reflected the total amount of drug placed into the pump, not the dose actually delivered to the patient. (By not taking into account the residual volume in the pump after a 14-day infusion, these studies reported a dose approximately 60% higher than it actually would have been if reported by conventional means.)

Awareness of these shortcomings of the phase III trials led to the exploration of a number of strategies aimed at overcoming treatment-limiting toxicity and maximizing the efficacy of HIA treatment. Four phase II trials evaluating these approaches were conducted in previously untreated patients with colorectal liver metastases (Table 3); these trials are discussed in detail below.

Alternating FUDR and Fluorouracil
One trial conducted at UCSF[17] sought to take advantage of the differing toxicities and pharmacokinetics of infusional FUDR and HIA bolus fluorouracil (5-FU). In this study, one-sixth of the original FUDR dose (.1 mg/kg/d for 7 days) was alternated with HIA bolus 5-FU administered through the pump side port on days 15, 22, and 29 of each 5-week cycle. In none of the 64 patients, 30 of whom had not responded to prior systemic chemotherapy, was alternating FUDR/5-FU treatment limited by hepatobiliary toxicity. The median survival of the previously untreated patients exceeded 2 years. Despite a 50% response rate, progressive liver tumor was the initial site of failure (and cause of death) in the majority of patients.

FUDR Plus Dexamethasone
In a randomized phase II trial performed at MSKCC,[29] dexamethasone was added to FUDR (reported dose, .3 mg/kg/d for 14 days) in an attempt to ameliorate the inflammatory component of the hepatobiliary toxicity. It was hoped that the incorporation of dexamethasone would lead to the delivery of more FUDR, but this did not turn out to be the case, at least over the first 6 months of treatment. However, the combination led to a response rate of 71% and a median survival of 23 months, which was superior to the control arm of FUDR alone. The precise mechanism for this interaction between FUDR and dexamethasone is unclear.

FUDR Plus Leucovorin
In another study from MSKCC,[30] FUDR was modulated by intra-arterial leucovorin in an attempt to increase antitumor activity. Six different regimens were explored in this study (ranging from .25 to .3 mg/kg/d of FUDR and from 15 to 30 mg/m²/d of leucovorin), which was interrupted for a few years because of the substantial biliary toxicity, but was reopened when long-term survivorship was seen in the initial cohort of patients. The incidence of biliary sclerosis was 12%, but the median survival of the 42 patients treated in the second phase was 24.2 months.

FUDR, Leucovorin, and Dexamethasone
By creating a hybrid of the treatment regimens used in the other two MSKCC trials, Kemeny et al hoped to diminish toxicity and increase antitumor activity.[31] The response rate to this hybrid
regimen--FUDR, leucovorin, and dexamethasone--in previously untreated patients was 78% and median survival was 24.8 months. A strict dose-reduction paradigm reduced the incidence of biliary sclerosis to 3%, although dose adjustments or temporary cessation of therapy was necessary in nearly every patient. The liver was the initial site of failure in two-thirds of the patients.

**Combinations of Intra-arterial and Systemic Therapy**

Another obvious approach would be the sequential or concomitant use of intra-arterial and systemic chemotherapies. This, in theory, would address the concern of extrahepatic tumor progression while achieving maximal therapeutic effect in the liver. One attempt at such a therapy--alternating HIA and IV FUDR--was compared to HIA therapy alone in a randomized study.[32] Although the incidence of extrahepatic progression appeared to be lower with the combination of HIA and IV FUDR therapy than with HIA therapy alone--61% vs 33%--overall survival did not differ in the two arms. A pilot study of HIA FUDR alternating with systemic 5-FU and leucovorin has also been conducted,[33] and this regimen is currently being tested at MSKCC in an adjuvant trial following hepatic resection of isolated colorectal metastases. At UCSF, a variety of alternating schedules of HIA and systemic chemotherapy have been saddled by substantial and treatment-limiting hepatobiliary and systemic toxicities.

All of the above phase II data on HIA chemotherapy in previously untreated patients need to be placed in context. The standard approach to patients with unresectable colorectal liver metastases is generally considered to be "low-dose" 5-FU and leucovorin given for 5 consecutive days out of each month.[34] When that regimen has been compared to other schedules or to 5-FU plus modulating agents, the response rate is about 20% with a median survival of 14 months, and is similar regardless of the schedule or modulating agent employed.[35] Indeed, infusional 5-FU may be as good as any of these other combinations. In a meta-analysis of studies of 5-FU and leucovorin, in which about one-third of the participants were considered to have liver-only disease, median survival was less than 12 months.[36]

**Ongoing CALGB Trial**

Clearly, definitive assessment of the role of HIA therapy, as described in the above phase II trials, awaits a noncrossover study that randomizes untreated patients with liver-only colorectal metastases between HIA and systemic treatment. Such a study is underway at selected centers under the auspices of the CALGB. In that study (CALGB #9481), patients are first staged radiographically to verify the absence of extrahepatic tumor. This staging includes a chest x-ray, CT scan of the abdomen and pelvis, and colonoscopy. Only patients with less than 70% of the liver involved by tumor are eligible. Stratification parameters include:

1. extent of liver involvement (less than 30% or 30% to 70%);
2. prior chemotherapy in the adjuvant setting (none, 12 months or more since completion of regimen containing leucovorin, more than 6 months since completion of regimen without leucovorin); and
3. synchronous disease (no or yes).

Patients in this study are randomized either to HIA FUDR, leucovorin, and dexamethasone[31] or to "low-dose" systemic 5-FU plus leucovorin[34] (see Figure 3). Patients found to have extrahepatic tumor at the time of exploratory laparotomy are treated with HIA therapy despite those findings, since to do otherwise would bias the results in this group of patients compared to those who do not undergo exploratory laparotomy. Crossover to the alternative treatment at the time of progressive disease is strongly discouraged. The accrual goal is 340 patients.

As a companion study to this trial, the CALGB will also prospectively assess tumor tissue for a variety of biologic parameters. Overexpression of the p53 nuclear protein[37] and the level of thymidylate synthase in primary tumors[38] appear to correlate with outcome in patients with colorectal cancer. These and other markers will be analyzed to see whether they may help identify good or poor candidates for HIA therapy in the future.

Although survival and a correlation with tumor biology are the primary end points of CALGB #9481, assessment of clinical and economic trade-offs may be more important.[39] This trial will prospectively evaluate differences in quality of life between the systemic and HIA therapies, using the Rand 36-Item Health Status Profile, Memorial Symptom Assessment Scale, and other instruments. Similarly, medical resource utilization will be analyzed at selected centers, enabling an estimate of the cost differential and relative benefits of the two therapies.
HIA Chemotherapy in Previously Treated Patients

The above studies focus on untreated patients with colorectal liver metastases. In clinical practice, however, increasingly more patients with liver-only colorectal metastases have already received systemic 5-FU-based chemotherapy. Patients with metachronous liver metastases usually present with advanced local colorectal cancers and have previously received a "standard" adjuvant chemotherapy containing 5-FU. Other patients have received front-line systemic chemotherapy with similar agents. The approval of irinotecan (Camptosar) for 5-FU-refractory colorectal cancer patients now provides clinicians with a systemic treatment option, although the response rate in such patients is only about 15%.[40]

A few of the above-mentioned HIA studies included previously treated patients. In the alternating FUDR/5-FU protocol[17] and the hybrid FUDR/leucovorin/dexamethasone study,[31] the response rate for patients who had progressed on 5-FU-based systemic treatments was between 30% and 52%, with a median survival exceeding 1 year from the time of pump implantation. These results are similar to a randomized study that compared HIA FUDR with HIA FUDR, mitomycin (Mutamycin), and carmustine (BCNU (BiCNU)) in such patients. In this study, the response rate exceeded 33% and overall survival was 16.8 months from the initiation of treatment.[21] These results suggest that patients with liver-only colorectal metastases that have proved refractory to systemic 5-FU-based chemotherapies may benefit from HIA treatment, as do untreated patients. However, the true utility and cost-benefit of pump placement and HIA therapy can fully be assessed only by a randomized study comparing it to an alternative systemic therapy.

Other Applications of HIA Therapy

Preoperative Administration

Although some patients have impressive clinical responses to HIA chemotherapy, no prospective studies have established any benefit to "neoadjuvant" HIA infusional chemotherapy. Of over 300 patients with unresectable liver metastases treated with "preoperative" HIA chemotherapy at UCSF in the past 8 years, only 3 have been explored for surgical extirpation of residual tumor. One such patient was free of disease 12 months after starting HIA treatment (Figure 4 and Figure 5) but suffered a recurrence within the liver 14 months after resection. Preoperative HIA chemotherapy should be used cautiously or in the context of a clinical study, since biliary toxicity may diminish hepatic reserve and make patients less able to withstand extensive hepatic resections thereafter.

Postoperative Administration

With the observation that the liver is the dominant site of recurrence in patients undergoing potentially curative resection of liver-only colorectal metastases, and given the proven efficacy of adjuvant 5-FU-based chemotherapy in node-positive patients,[41] it was a logical step to apply HIA treatment following metastectomy.

One study testing that hypothesis randomized patients with a solitary hepatic metastasis to resection only vs resection plus HIA FUDR, and also compared resection with or without HIA FUDR in patients with multiple resectable liver metastases.[42] Unfortunately, patient accrual was inadequate to address the utility of adjuvant therapy.

An ongoing Eastern Cooperative Oncology Group study is randomizing fully resected patients to observation vs a combination of HIA FUDR and infusional 5-FU. Accrual now exceeds 100 patients and is nearly complete; results may be available within the next year.

Other pilot studies are exploring the role of HIA FUDR-based chemotherapy in conjunction with partial debulking of liver metastases, either via surgical resection or cryosurgery.[43] Until the results of such studies are known, the use of HIA chemotherapy in that setting should be considered investigational.

Other Diseases

Although most, if not all, cancers metastasize to the liver, colorectal cancer is the exceptional disease that may stay confined to that organ. Regional HIA treatment of patients with liver metastases from other cancers (eg, breast cancer) can certainly induce antitumor activity,[44] but any overall advantage to patients is almost certainly overshadowed by the systemic nature of these diseases.

Some patients with hepatocellular carcinoma are candidates for HIA therapy, and intra-arterial treatment with such agents as FUDR, mitomycin, and interferon-alfa (Intron A, Roferon-A) has achieved response rates as high as 50% in some trials.[45,46] However, these responses are usually not durable, and performance status of the patients treated in such trials tends to be better than
that of the average patient with hepatocellular cancer. Furthermore, long-term percutaneous catheterization of the hepatic artery or laparotomy for the placement of an infusion device may be ill-advised in patients with hepatocellular carcinoma, who may tolerate such invasive procedures poorly.[47] Given such realities and the lack of data on intra-arterial therapy for hepatocellular cancer generated in randomized trials, any benefit is hard to quantify. Thus, HIA therapy is probably appropriate only for rare patients with this cancer or as part of a clinical trial.

**Other Substances**

Hepatic intra-arterial chemotherapy has been done in conjunction with a variety of other substances, such as collagen particles [48] and/or ethiodol.[49] The relative contributions of the chemotherapeutic agents and these substances are not always clear. A thorough discussion of these approaches and their applicability is beyond the scope of this paper.

**Other Chemotherapeutic and Unconventional Anticancer Agents**

It is evident that the pharmacokinetic principles of HIA therapy outlined above lend themselves to a variety of agents. A regional advantage may or may not be expected for other chemotherapeutic agents, depending on the characteristics of the individual drugs. For example, it is not at all clear that irinotecan, an active systemic agent against colorectal cancer, will be useful via the HIA route. Because irinotecan is a prodrug that requires a metabolic step to become the active metabolite, SN-38, and because the dose-limiting toxicity of diarrhea appears to be directly related to the biliary levels of SN-38,[50] HIA administration of this drug may be counterproductive. Only carefully conducted phase I and II trials can address the utility of this or other new agents given via the HIA route.

Unconventional anticancer agents, such as viruses, liposomes, and a variety of gene therapy vectors, may also be better administered via the hepatic artery. The preferential hepatic arterial flow of tumors in the liver may enable a relative "targeting" of the agent. A few clinical studies evaluating such biologics are underway.

One study at UCSF, for example, is accruing patients with unresectable colorectal liver metastases or hepatocellular carcinoma, whose primary tumor tissues have evidence of a mutant p53 gene, as possible candidates for the HIA delivery of a bioengineered replication-deficient adenovirus containing the wild-type p53 gene.[51] Hepatic tumor will then be biopsied to determine the molecular and biologic effects of the administered vector. This is just one example of the phase I and II work that needs to be done before the utility of the HIA approach with agents such as these can be determined.

**Conclusions**

The regional administration of chemotherapy for hepatic neoplasms is based on sound pharmacologic principles and appears to increase the activity of the anticancer agents. The toxicity and complications of the intra-arterial approach have limited its utility, although newer treatment regimens and greater experience with this modality may expand its applications. A randomized study assessing systemic vs HIA chemotherapy in previously untreated colorectal cancer patients with liver-only metastases is now underway. The HIA strategy may also prove to be most useful with newer agents.

**References:**


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