

### Intraarterial Cancer Chemotherapy, Arterial Occlusion, and Tc-99m Macroaggregated Albumin Perfusion Scintigraphy

Intraarterial infusion of anticancer drugs has been used to produce an increase in local tumor effect coupled with a reduction in systemic drug toxicity. In this method of treatment, cytotoxicity within the tumor is dependent on drug concentration and duration of exposure. Concentration depends on the amount of blood flow to the tumor, the intratumoral disposition of the drug and the required metabolic alterations of the chemotherapeutic agent (1). Duration of exposure relates to the rates of blood flow and of drug uptake and elimination. Lower systemic toxicity will be obtained if a substantial amount of the drug is removed during the first pass through the infused region. Drugs such as methotrexate and the fluorinated pyrimidines, which have rapid blood clearances, achieve higher concentrations when given directly into a tumor (2,3). Also, antineoplastic drugs that require no metabolic activation, such as cisplatin, have greater antitumor activity when given this way than do agents such as cyclophosphamide, which require biotransformation within the liver (4). Various clinical studies have supported the pharmacologic advantages of regional chemotherapeutic infusion. At our institution arterial infusion has been effective in prolonging survival in hepatic cancer, melanomas, bone and soft-tissue cancers, and carcinomas of the bladder (5). However, the survival gains have been of the order of months, not years, and ways are needed to enhance the dichotomy between increased tumor effect and reduced systemic toxicity to improve therapeutic results.

One method of achieving this goal is intraarterial infusion of chemotherapeutic agents combined with occlusion of the arterial supply to the tumor. In addition to the direct effect of ischemia on the tumor, arterial occlusion prolongs the transit time of the drug through the tumor's vascular bed, thus increasing the contact time of the drug with the tumor cells. Preliminary results suggest that this can improve therapeutic results in metastatic liver cancer. In 55 patients with hepatic metastasis from colo-rectal cancer, treated in our institution with hepatic arterial infusion (HAI) of floxuridine (FUDR) and mitomycin C, the group of 31 patients treated with HAI alone had a median survival of 8 mo from the initiation of treatment, as opposed to the group of 24 patients treated with HAI and hepatic artery occlusion, which had a median survival of 15 mo (6). Polyvinyl alcohol foam particles, gelatin sponge fragments, and stainless steel coils are among the materials used for hepatic-artery embolization. The selection of an embolic agent depends on whether the desired occlusion is to be proximal or peripheral and whether it is to be temporary or permanent. The degree of peripheral embolization is related directly to the size of the particles used (7). Side effects of hepatic-artery embolization that occur in most cases, the "postembolization syndrome," include abdominal pain, nausea, vomiting, and low-grade fever, usually of 2 to 7 days' duration. Besides the complications related to angiography, others secondary to HAI of chemotherapeutic agents may occur. Since all or part of the blood supply to the stomach, duodenum, gallbladder, and pancreas may originate from the hepatic artery, alteration in perfusion patterns in the hepatic artery may increase toxicity to the gastrointestinal tract.

Infusion of 2 mCi Tc-99m MAA in a 0.5-ml solution into the arterial catheter at flow rates that approximate the chemotherapeutic infusion rate has become popular, since it provides a map of regional perfusion at the capillary level, one not provided by contrast angiography. These studies permit therapists to optimize catheter position for infusion chemotherapy by recognizing displaced or misplaced catheters, assessing changing arterial flow patterns during intraarterial chemotherapy, visualizing tumor vascularity, and recognizing arteriovenous (AV) shunting within the tumor bed as manifested by the presence of lung activity following intraarterial injection (8). Regional arterial perfusion to a specific area may change as a result of physiologic or other mechanisms, e.g., changes in the diameter of the arterioles distal to the catheter tip will change distribution in the perfused region, allowing more blood or infused chemotherapeutic agent to enter dilated blood

vessels and, correspondingly, less to narrowed blood vessels (9). Progressive arteritis and subsequent occlusion of vessels due to endothelial proliferation and thrombosis after repeated courses of chemotherapy may also cause changes in the perfusion pattern. Transient narrowing of vessels may be due to trauma to the vessel wall during catheterization, resulting in spasm. When arterial catheters are placed proximal to a bifurcation, a streaming effect occurs that causes perfusion changes with slight changes in the catheter tip position (laminar flow). Extrahepatic uptake of the MAA infused into the hepatic-arterial catheter may be due to placement of the catheter tip proximal to branches leading to other abdominal structures, to clotting or tumor encasement of the hepatic artery, with backflow into the mesenteric and splenic arteries, or to flow into extrahepatic collaterals that may be formed after surgical ligation of the gastroduodenal or splenic arteries. Intrahepatic collaterals have been observed following both surgical ligation and coil embolization of the hepatic artery, and some of these collaterals develop promptly (10).

The paper by Ziessman et al. in this issue presents an innovative method of producing arterial occlusion, using intraarterial degradable starch microspheres (DSM), 40–50  $\mu\text{m}$  in diameter, to occlude hepatic arterioles transiently (11). These have been combined with Tc-99m MAA to study the effect on perfusion. The use of a radioactive tracer may be of particular value when starch microspheres are used, since investigations at our institution have revealed that a contrast medium alters the degradation rate of DSM, at least in the dog kidney (personal communication, L. Schulman, S. Wallace). A most interesting finding is that in patients who first had a drop in percent shunt index (PSI) to the lung with DSM, then had a rise with further embolization. It is hypothesized that at first DSM goes to tumor vessels, where flow is greatest and some shunting is already occurring. Further embolization blocks normal liver vessels, which leads to the opening of collaterals and produces more shunting. A number of questions are raised by the finding, since not all patients showed this interesting phenomenon, nor did all respond identically to increased doses of microspheres. Did those who did not respond have different tumors from the group with an initial drop of PSI—e.g., were their tumors more or less vascular? Were there changes in DSM distribution after embolization—e.g., was laminar flow changed with embolization? Was there any change in portal flow with hepatic-artery occlusion? Or, perhaps more important, will DSM increase chemotherapeutic drug levels in the tumor or only in normal liver? Will the ischemic environment created by DSM alter the uptake, degradation, and antitumor effect of a given chemotherapeutic agent? The answer to these questions almost certainly varies with the agent used, the nature of the tumor and its blood supply, and how much DSM is used. Zeissman's data suggest that, at least in some patients, degradable starch microspheres may increase contact time of chemotherapy in the liver, but that there may be an optimal dose that should not be exceeded, lest the advantage of reduced toxicity associated with the technique be lost due to increased shunting. With regard to this latter point, Kaplan et al. (12) recently reported findings supporting the existence of hepatic AV communications in some patients before therapy, and they found that pulmonary activity of  $\geq 20\%$  injected dose predicts an increased incidence of gastrointestinal toxicity. Further work will perhaps provide answers to some of the other questions we have posed. In any event, the advantage of the radionuclide method for investigating this important area of cancer research is well illustrated by the work of the Michigan group, who are to be complimented on their well-designed study and interesting report.

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## Southeastern Chapter Society of Nuclear Medicine 24th Annual Meeting

**October 26-29, 1983**

**Hyatt Orlando**

**Kissimmee/Orlando, Florida**

The Southeastern Chapter of the Society of Nuclear Medicine will hold its 24th Annual Meeting October 26-29, 1983 at the Hyatt Orlando in Kissimmee, Florida.

The program will include continuing education and scientific programs. Fifteen hours of AMA Category I credit will be available. VOICE credits will be available for technologists.

The topic for this meeting is "Nuclear Magnetic Resonance Imaging: Its Clinical Utility and correlation with Other Imaging Modalities." It is intended to review the state-of-the-art in multiple imaging modalities including ultrasound, x-ray computed tomography, digital radiography, and nuclear magnetic resonance imaging. The emphasis will be on nuclear magnetic resonance imaging and its clinical utility and correlation with other imaging modalities.

The objectives of this program are to:

1. Present an overview of the physical principles and technology of nuclear magnetic resonance imaging.
2. Discuss the pathophysiological significance of NMR images and data.
3. Consider the role and place of NMR imaging with other imaging modalities.
4. Provide a forum for the scientific interchange among scientists and clinicians who are leaders in the field both in the United States and in Europe.
5. Provide a meaningful scientific program in an area of great national interest.

Commercial exhibits will be open October 27 and 28. Registration begins at 1:00 p.m., October 26.

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