Review Article

Angiographic Considerations in Patients Undergoing Liver-directed Therapy

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The rapid evolution and increasing complexity of liver-directed therapies has forced the medical community to further advance its understanding of hepatic arterial anatomy. The anatomy of the mesenteric system, and particularly the hepatic arterial bed, has been demonstrated to have a high degree of variation. This is important when considering presurgical planning, catheterization, and transarterial hepatic therapies. Although anatomic variants have been well described, the characterization and understanding of regional hepatic perfusion is also required to optimize endovascular therapy and intervention. Although this is true for patients undergoing bland embolization or chemoembolization, drug delivery, and hepatic infusional pump therapy, it is particularly true for intraarterial brachytherapy. The purpose of this review is to provide historical perspective in angiographic aspects of liver-directed therapy, as well as a discussion of normal vascular anatomy, commonly encountered variants, and factors involved in changes to regional perfusion in the presence of liver tumors. Methods of optimizing the safety and efficacy of liver-directed therapies with use of percutaneous techniques will be discussed. This review is based on the experience gained in treating more than 500 patients with transarterial liver-directed therapies. Although the principles described in this article apply to all liver-directed therapies such as chemoembolization and administration of drug-coated microspheres, they apply particularly to intraarterial brachytherapy.

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Abbreviations: DSA = digital subtraction angiography, GDA = gastroduodenal artery, MAA = macroaggregated, SMA = superior mesenteric artery, TACE = transarterial chemoembolization

THE majority of data pertaining to regional chemotherapy and variant anatomy was established in the 1990s with the advent of intraarterial chemotherapeutic pumps placed intraoperatively with presurgical angiography performed before the procedure (1–8). Consequences of inadvertent delivery of chemotherapeutic agent to nontarget vessels had resulted in skin irritation (with falciform artery embolization) and gastric mucosal inflammation and necrosis (with treatment of right gastric artery distribution) in as many as 40% of patients, in addition to gall bladder ischemia/necrosis (with cystic artery treatment) and small bowel necrosis (with supraduodenal and/or retroduodenal artery treatment) (1,9,10). Extensive review of the current literature regarding surgically implanted intraarterial infusion pumps has demonstrated interesting results that bear relevance to proper identification of normal anatomy and anatomic variants (5–8). The purpose of this article is to provide a comprehensive review of hepatic arterial anatomy as it relates to regional therapy.

In the case of intraarterial brachytherapy (ie, "radioembolization") with administration of yttrium 90 microspheres such as TheraSpheres (MDS Nordion, Ottawa, ON, Canada) or SIR-Spheres (Sirtex Medical, Lane Cove, Australia), it is well-known that the generation of oxygen free radicals is one of the triggering points for apoptosis response (11). This relationship has been postulated to relate to the relatively low concentration of superoxide desmutase within cancer cells, limiting their ability to compensate in an environment rich in free radicals (12). Therefore, for intraarterial brachytherapy, optimal perfusion and blood flow is required to generate oxygen free radicals. Radiation combined with embolization-induced hypoxia is less desirable (12).

In contrast, peroxidase free radical formation and retention in chemoembolization is potentiated by an isch-

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emic environment, with relatively higher local doses of chemotherapeutic agents and peroxidase free radicals after embolization (13,14) translating into a need to provide a static and ischemic environment to maximize exposure to therapeutic agents and promote ischemic necrosis. These theories bear relevance to transarterial chemoembolization (TACE), bland embolization, and intraarterial brachytherapy, as the need for stagnant blood flow and direct vascular embolic effect is greater in TACE than in intraarterial brachytherapy (15–17). The preservation of flow to the target area, and hence oxygenation, should in theory increase the response to therapeutic radiation.

The further evolution of TACE, intraarterial brachytherapy, drug and nanoparticle delivery systems, as well as gene therapy will continue to evolve and arm the interventional radiologist with an armamentarium against liver tumors. As techniques and procedures trend toward more profound tumoral response, identification of variant anatomy, aberrant flow, and shunt vascularity, as well as optimization of therapy, become mandatory. The purpose of this review is to introduce the reader to the principles and concepts of optimization of vascular anatomy through proper technique, identification, embolization, and localization of arterial supply as it pertains to hepatic tumors. Identification of anatomic variations and a better understanding of regional perfusion patterns may lead to decreased complications and more effective therapy, as well other secondary benefits such as decreased contrast material administration, radiation exposure, and procedure time. Although this article will not constitute an exhaustive review of the literature, it will provide a guideline to the principles of regional therapy and hopefully generate further interest in the field. For the purposes of this manuscript, the term "therapeutic agent" will refer to the chemotherapeutic agent and embolic material (ie, particles) in TACE, particles alone in bland embolization, ^{90}Y microspheres in intraarterial brachytherapy, and drug-coated microspheres and/or floxuridine in infusional therapies.

HISTORICAL CONSIDERATIONS: INTRAARTERIAL PUMPS

The development of intraarterial chemotherapy infusion for hepatic involvement of malignancy has undergone significant evolution during the past four decades (18). Initially developed as an operative procedure, placement of chemotherapy infusion pumps provided a segue to the development of intraarterial-based single-dose chemotherapy that is now known as TACE.

The characteristic of all liver tumors to preferentially parasitize hepatic arterial vascularity has become the foundation of intraarterial chemotherapy (19). The benefits of such administrations have been well-documented and rely heavily on the ability to target hepatic arterial inflow, and as a result, higher concentrations to the regions of interest. Hepatic arterial infusion began with the surgical placement of intraarterial pumps. Standard surgical techniques in patients with normal anatomy would include cholecystectomy, ligation of the gastroduodenal artery (GDA), dissection of the common hepatic artery 1 cm proximal and distal to the insertion of the GDA, ligation of the right gastric artery, and placement of the pump catheter into the GDA stump, with the tip placed at the GDA/common hepatic artery bifurcation. Confirmation of liver perfusion would then be achieved through injection of methylene blue or fluorescein (5,7).

The technique for placement of intraarterial infusion pumps is complex and involves placement of the catheter in the correct position and proper identification of vessels that may feed the extrahepatic viscera. Despite meticulous surgical dissection and exposure, misperfusion or inadequate perfusion has been reported to occur in as many as 45% of cases, with the highest incidence of complications related to inexperience and the presence of anatomic variation (6). Unfortunately, other complications have also been well-documented, including pump pocket placement–related complications, catheter malposition, and nontarget organ infusion (1,5,6,8,10).

In the case of variant anatomy, a variety of methods have been attempted, including placement of dual-lumen pumps, ligation of the normal vessel, ligation of the variant vessel, and placement of the catheter in a location other than the GDA/common hepatic artery bifurcation. As concluded by Allen et al (6), when surgical placement of the catheter tip in a vessel other than the GDA was performed, a significantly higher complication rate (28%) was noted. In addition, patients with multiple variant vessels experienced an even greater rate of complications (23%) compared with those with single vessel variations. In practical terms, the higher rate of complications in variant anatomy further emphasizes the need to understand the vascular flow of the vessels as best demonstrated through conventional angiography and digital subtraction angiography (DSA). More importantly, this literature provides a framework the interventional radiologist may use to optimize perfusion of target areas and minimize potential pitfalls and complications.

ANGIOGRAPHIC TECHNIQUE

Alternate methods of conventional angiography have been developed to investigate aberrant or variant anatomy of the mesenteric arteries. Implementation of computed tomography (CT), magnetic resonance imaging, and ultrasound for the identification of first- and second-order variants have proven effective for the identification of large variant vessels (9,20–22). However, with consideration toward surgical and intraarterial interventions, smaller vessels well beyond the spatial limitations of the existing imaging modalities exist and, if they are not identified, it may lead to dire consequences. Complications as a result of embolization of chemotherapeutic and/or embolic materials have been well-documented to result in unplanned/unexpected necrosis in undesirable arterial beds, such as the cystic artery and gastrointestinal, cutaneous, and phrenic capillary beds (6,23–28).

As part of their workup, all patients should have a triple-phase CT to assess the tumor vasculature, overall tumor load, and patency of the portal vein. Standard mesenteric angiography that should be performed initially in patients undergoing liver-directed therapy should include the following: