Preoperative Embolization

William S. Rilling, M.D.,¹ and Gene W. Chen, B.S.²

ABSTRACT

Preoperative embolization procedures are constantly evolving and allow the performance of, or improve the outcome of, subsequent surgical interventions. Currently, some of the more frequently performed procedures in this group are portal vein embolization (PVE) in anticipation of extended liver resection, preoperative embolization of hypervascular tumors, and chemoembolization of hepatocellular carcinoma (HCC) as a bridge to liver transplantation. The indications, technique, and results of these procedures will be reviewed.

KEYWORDS: Embolization, liver neoplasms, liver transplant, renal cell carcinoma, and bone metastases

Objectives: Upon completion of this article, the reader will be able to discuss the clinical indications for preoperative embolization, specific techniques used, and clinical outcomes.

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Preoperative embolizations are procedures that allow the performance of, or improve the outcome of, subsequent surgical interventions. These procedures are constantly evolving. Many currently performed embolization procedures were initially preoperative procedures that have evolved into stand-alone therapeutic modalities (e.g., uterine fibroid embolization). At present, the most commonly performed preoperative embolization procedures are portal vein embolization (PVE), embolization of various hypervascular tumors and vascular malformations prior to resection, and chemoembolization of hepatocellular carcinoma (HCC) as a bridge to liver transplantation. These three categories are the topic of this article.

PORTAL VEIN EMBOLIZATION

PVE has emerged as a technique to allow select patients to undergo extended hepatectomy. PVE induces hypertrophy of the future remnant liver prior to resection. Although PVE is considered safe and may eventually expand the patient population that can safely undergo extended liver resection, it has been demonstrated that portal vein occlusion induces atrophy of the embolized liver with compensatory hypertrophy of the remaining liver. The exact mechanism of this process is not well elucidated, but both intra- and extrahepatic stimuli are known to induce these changes. One significant stimulus is hepatocyte growth factor, which, in combination with mitogenic factors, allows hepatocytes to expand clonally

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and thereby increase in number as well as mass.¹ This process occurs very rapidly following an appropriate stimulus (liver resection, PVE) in patients with normal liver, with peak mitotic activity occurring at 3 to 4 days and reaching a plateau at 7 to 14 days.² Individuals with diabetes and cirrhosis have a slower rate of regeneration.

The current indications for PVE remain controversial. Although originally reported in the treatment of biliary malignancies, PVE has been applied in a variety of primary and secondary hepatic tumors. In general, appropriate patients are those who will require extended hepatectomy and in whom the future remnant liver is deemed inadequate in size and/or function. Prediction of adequate remnant liver remains difficult. A lower limit of 25% preservation of total hepatic volume in normal liver and 40% in chronic liver disease has been proposed.³

Some authors have raised concerns that PVE may induce tumor growth and increase recurrence rates following resection. Factors potentially contributing to tumor growth associated with PVE include changes in cytokines and growth factors, changes in blood supply (arterial hypertrophy), and delay from diagnosis to resection following PVE. Kokudo⁴ reported a lower disease-free survival rate in 18 patients with colorectal metastases undergoing PVE versus a control group undergoing hepatic resection for colorectal metastases without PV. Overall survival may not be significantly different between the two groups. Additional investigations are needed to determine if these factors adversely affect the long-term outcome following PVE and hepatic resection.

A wide variety of techniques and embolic agents have been used to perform PVE. Access to the portal vein can be obtained percutaneously or via a mini laparotomy with catheterization of the ileocolic vein. Percutaneous access via the lobe to be embolized may minimize the risk of puncture-related complications to the future remnant liver (Fig. 1). Embolic agents that are

used include Gelfoam (Upjohn Co., Kalamazoo, MI), thrombin, cyanoacrylate, polyvinyl alcohol (PVA), coils, and absolute alcohol. A trend toward greater hypertrophy of the remaining liver has been noted with cyanoacrylate and alcohol versus gelfoam Gelfoam and thrombin.⁵ Although it is usually well tolerated, with minimal perturbations in liver function tests and post-procedure symptoms, PVE with alcohol is associated with significant periportal fibrosis and necrosis, and significant changes in liver function tests.

Despite extensive differences in technique and disease processes, reported results and complications with PVE are remarkably consistent. Future remnant liver volumes increased from 19 to 36% pre-embolization, to 31 to 59% postembolization⁴ (Fig. 2). Complication rates of 0 to 10% have been reported; transient hemobilia, small bowel obstruction, and need for re-embolization were the most commonly reported complications. In patients undergoing surgical resection following PVE, complication rates are equal to or less than complication rates reported for major liver resection without PVE.

PREOPERATIVE EMBOLIZATION OF HYPERVASCULAR TUMORS

The resection of hypervascular tumors, particularly renal cell carcinoma (RCC), presents a distinct challenge because the procedure can be associated with large intraoperative blood losses. Renal artery embolization, introduced in the 1970s, has played an important role in the management of unresectable RCCs. In addition to use with tumors that are unresectable, embolization can be performed prior to nephrectomy. It is thought that by decreasing vascularity and inducing the formation of edema adjacent to the infarcted kidney, embolization may facilitate a subsequent surgical intervention. Significant improvements in blood loss have been observed

Figure 1 Preoperative right portal vein embolization in a patient with a large central cholangiocarcinoma requiring extended right lobectomy. (A) Pre-embolization portogram. Percutaneous access has been obtained in a peripheral branch of the right portal vein. (B) Portogram following embolization of the right portal vein with polyvinyl alcohol and coils showing a very small amount of residual flow in the right portal vein and filling of the normal portal vein.

Figure 2 Pre-embolization and postembolization computed tomography scans in the same patient as discussed in Figure 1. The top row shows pre-embolization scans in this patient with a large central cholangiocarcinoma involving the right lobe and extending into segment IV. Scans in the bottom row were obtained 2 weeks after right portal vein embolization and images are at similar anatomic levels to the preoperative scans. There has been significant interval hypertrophy of the left lobe, particularly in segments II and III.

following alcohol embolization of large RCCs prior to nephrectomy.^{6,7} Perhaps more importantly, in a recent series of 474 patients undergoing radical nephrectomy, Zielinski et al⁸ found that preoperative embolization provided significantly improved 5- and 10-year survival rates (62 and 47%, respectively, in the embolized group and 35 and 23%, respectively, in the matched group treated with surgery alone [$p = 0.01$]).⁸ Certain immune responses following embolization may in part explain this survival benefit. Further studies are warranted.

Osseous metastases from RCC behave in a similar fashion to the primary malignancies. Hypervascular metastases to both the axial and appendicular skeleton can be embolized to reduce blood loss during subsequent surgical intervention (Fig. 3). Spinal metastases often present with intractable pain, neurological symptoms, and/or pathologic fracture. Primary treatment modalities include radiation therapy and surgical resection to achieve local tumor control and palliation of symptoms as well as preserve spinal stability and nervous tissues. Transarterial embolization of spinal tumors has been well described as both a palliative measure and a useful presurgical adjunct. Empirically, it has long been

observed that preoperative embolization appears to reduce intraoperative blood loss and improves the surgeon's ability to decompress the spinal cord and maximize tumor resection. Many authors have reported significant decreases in intraoperative blood loss following embolizations of spinal lesions.⁹⁻¹⁵

Magnetic resonance imaging might be useful in identifying spinal lesions that might benefit from preoperative embolization. A recent study of 51 patients evaluated the presence of large flow voids, bright contrast enhancement, and other signs on magnetic resonance (MR) images as predictors of hypervascularity.¹⁶ These authors found a 77% positive predictive value and 21% negative predictive value of MR imaging in determining tumor hypervascularity as proven by subsequent angiography.¹⁶

Multiple authors have suggested that a correlation exists between the extent of devascularization following embolization and subsequent surgical blood loss.^{9-11,16} In the majority of reports, PVA particles, with or without coils, are the embolic agent of choice. Most authors report embolization to be generally well tolerated. Sun⁹ demonstrated no adverse effect of embolization on

Figure 3 Preoperative embolization of a renal cell carcinoma metastases in the proximal humerus. (A) A large hypervascular mass in the right proximal humerus with associated pathologic fracture. (B) Right upper extremity angiogram following embolization of the metastasis with 300- μ m polyvinyl alcohol particles. Very little residual tumor vascularity is noted.

subsequent bone healing. Conversely, one series demonstrated major complications, including permanent paraplegia, transient paraparesis, and aortic dissection, in 4 of 47 patients (9%).¹⁷ The identification and protection of radicular vessels is crucial in avoiding inadvertent embolization of the spinal cord; the radiculomedullary artery and tumor vessels were found to share a common vascular pedicle in 29 of 51 patients (57%) in one series.¹⁶ If a common trunk is visualized, superselective catheterization distal to the origin of the spinal artery can be used to circumvent this situation.

Paragangliomas are rare tumors comprising glomus tumors (jugulare, tympanicum, vagale) and carotid body tumors (CBT). These arise from neuroendocrine tissue and present most commonly in the head and neck region. Although they may metastasize in $\sim$ 10% of cases, local invasion is more common. Surgery traditionally has been the treatment of choice for paragangliomas, however, resections of these tumors can be complicated. In the 1970s, Dent et al¹⁸ reported an average blood loss of 2000 mL during the removal of CBTs. As with other hypervascular tumors, excessive blood loss is often unavoidable; importantly, this may lead to a higher risk of injury to the nearby major blood vessels or cranial nerves. Early attempts to decrease the vascularity of the tumor while maintaining cerebral blood flow included clamping of the common carotid artery following placement of an intraoperative shunt. This approach requires an arteriotomy, proximal and distal control of the vessel, and subsequent repair of the vessel, all of which were found to represent challenges, particularly in larger tumors that tend to surround major vessels traversing the neck.

The first successful preoperative embolization of a CBT was reported in 1980. Since this initial study, numerous authors have reported using embolization as a useful presurgical adjunct for CBTs and other

paragangliomas.^{19–28} Significant reductions in blood loss^{20,22,24,25} and operative time^{20,24} have been observed in multiple series. Embolic agents used most commonly after superselection of feeder vessels are smaller PVA particles (typically 100 to 250 μ m), followed by surgery between 1 to 14 days postembolization.

Embolization is generally a safe procedure. However, identification of dangerous anastomoses and careful manipulation of the catheter and injection of embolic material are crucial to the avoidance of particle reflux to the ophthalmic or cerebral circulation. Most authors report low complication rates; however, serious complications can occur, including stroke, transient aphasia, transient ischemic attack, carotid sinus syndrome, and cranial nerve palsies. The majority of published experiences are retrospective reviews of small to modest size, some of which have not found a benefit from preoperative embolization.^{29,30} In addition, the majority of the reports have examined CBTs primarily; these results might not be generalizable to the other paragangliomas that can involve different structures in the neck, and thus present different operative risks. It is still unclear if there is an optimal tumoral size range for which embolization is most useful, although based on available data, a lower size limit of 3 cm is reasonable.²⁴

CHEMOEMBOLIZATION AS A BRIDGE TO LIVER TRANSPLANT

Orthotopic liver transplant (OLT) has emerged as an effective treatment option for patients with end-stage liver disease and hepatocellular carcinoma. Unlike hepatic resection, a cirrhotic liver with future malignant potential or unrecognized neoplastic lesions is not retained with OLT. Five-year survival rates following OLT for HCC have been reported in the range of

60 to 69%, compared with 35 to 51% in patients who were treated with liver resection alone.^{31,32} As with all treatment decisions regarding HCC, patient selection for OLT is critical for optimal outcome. The recognition that tumor size and staging of disease are important prognostic factors led to the current United Network for Organ Sharing guidelines for OLT in the setting of HCC. According to these guidelines, patients are amenable to undergo OLT if they have a HCC lesion that is < 5 cm, or three or fewer lesions each < 3 cm. Currently, the major impediment to more widespread use of OLT for HCC has been the discrepancy between the availability of organs and patients awaiting transplantation.

Unfortunately, waiting periods of 1 to 2 years for transplantation are common in the United States. As a result, many patients progress without therapy during this delay and might no longer qualify for OLT under current guidelines. In one study, in 6 months 25% of patients awaiting transplantation progressed to the stage that they were no longer transplantation candi-

dates.³³ There is a need for a form of bridge therapy in patients with HCC awaiting transplant. Several strategies have been developed to meet this need, including transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), image-guided percutaneous intratumoral chemotherapy injections, and systemic chemotherapy. TACE is a procedure that typically involves injection of lipiodol (iodized poppy-seed oil with an affinity for hepatomas) and a chemotherapeutic agent into the hepatic artery followed by embolization with particles. TACE is thought to produce both pharmacologic and ischemic injury to the lesion(s) to control tumor growth; long-term survival benefits can also be seen (Fig. 4). In one study of 27 patients with HCC awaiting transplantation, TACE was performed as bridge therapy. After a mean waiting period of 167 days, all 27 patients had successful OLT, and there were no HCC recurrences during a mean follow-up of 29.2 months.¹⁷ Although it seems that TACE is able to induce marked tumor necrosis and

Figure 4 Chemoembolization of hepatocellular carcinoma in a patient awaiting live transplantation. (A) A 3-cm hypervascular mass in segment 7 is consistent with hepatocellular carcinoma. (B) Selective catheterization of a right hepatic artery branch feeding segment 7 with the hypervascular mass identified. Computed tomography scans (C) immediately following and (D) 2 months following selective chemoembolization of the lesion. The patient had subsequent liver transplantation and there was no viable tumor identified in the explanted liver.

control local tumor growth, the effect of TACE on long-term survival is more controversial.³⁴⁻³⁶ One study employed pretransplantation TACE every 2 to 3 months until an organ became available for OLT, and preoperative TACE in another group undergoing liver resection only. Downstaging or total necrosis of tumors occurred in 62% of cases.³⁶ Multivariate statistical analysis suggested that response to TACE was more successful for larger tumors (> 5 cm). More importantly, patients with tumors >3 cm in whom downstaging occurred had a 5-year disease-free survival rate that was significantly better than patients with no response to TACE (71 versus 29%, respectively; $p = 0.01$). A trend toward improved disease-free survival also was noted in patients receiving TACE in whom downstaging occurred when compared with patients who did not receive TACE prior to surgery (71 versus 49%, respectively; $p = 0.09$). It was concluded that a response to TACE should be regarded as a strong argument to proceed to transplantation in patients with larger tumors (>3 cm) who might initially have been considered to be poor candidates for OLT. The survival benefit of TACE before transplantation remains open to debate,^{34,35} and further prospective studies are warranted. In addition, the relative roles of RFA and PEI and other promising treatment strategies for patients with HCC awaiting transplantation remain unproven and currently are being evaluated.³⁷

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