Annals of Oncology 19: 847–851, 2008
doi:10.1093/annonc/mdm528
Published online 20 November 2007

Hepatic arterial infusion of chemotherapy: the role of diagnostic and interventional radiology

A. Ganeshan[1], S. Upponi[1], Lye-quen Hon[2], D. Warakaulle[3] & R. Uberoi[1]*

[1]*Department of Radiology, John Radcliffe Hospital, Headley Way, Oxford;* [2]*Department of Radiology, The Royal Hallamshire Hospital, Glossop Road, Sheffield;* [3]*Stoke Mandeville Hospital, Mandeville Road, Aylesbury, UK*

Received 7 September 2007; revised 12 October 2007; accepted 15 October 2007

Hepatic arterial infusion of chemotherapy (HAIC) delivers higher local drug concentration to unresectable liver tumors with fewer significant systemic side-effects. It has been shown to produce better response rates than systemic chemotherapy and remains an important treatment option in patients with advanced, inoperable primary or maetastatic hepatic tumors. Traditionally, catheters for HAIC were inserted surgically under general anesthesia. The advancement and expansion of interventional radiology have made it possible for catheter-port systems to be inserted percutnaeously under local anesthesia with no significant increase in morbidity. A comprehensive review of the literature, techniques and complications of percutanoeus placement of catheter-port systems for HAIC is presented in this article.

Key words: chemotherapy, colorectal cancer, HAIC, hepatic arterial infusion

introduction

Regional hepatic arterial infusion of chemotherapy (HAIC) takes advantage of the first-pass effects of cytotoxic agents, delivering higher local drug concentration to unresectable liver tumors with fewer significant systemic side-effects. The theoretical basis for treating liver tumors with HAIC is that hepatic neoplasms receive ∼95% of their blood supply from the hepatic artery unlike normal hepatocytes, which are perfused primarily by the portal vein [1]. HAIC has been shown to produce better response rates than systemic chemotherapy despite little final impact on survival time, mainly due to the development of extrahepatic metastases [2, 3]. Nevertheless, HAIC remains an important treatment option in patients with advanced, inoperable primary or metastatic hepatic tumors as it can be delivered on an outpatient basis and can lead to an improvement in quality of life in many patients [4].

To achieve long-term administration of cytotoxic agents to the liver, hepatic arterial catheters were initially placed surgically under general anesthesia. These hepatic arterial catheters were connected to s.c. ports to allow easy and repetitive infusion of chemotherapy directly to liver tumors. Surgically implanted hepatic catheters have considerable complication rates. Moreover, the repair and replacement of malfunctioning port systems often require further surgery. The advancement and expansion of interventional radiology facilities and techniques have made it possible for catheter-port systems to be inserted percutnaeously under local anesthesia. Compared with the surgical approach, radiologic implantation of hepatic catheter-port systems is a quick and simple procedure with no significant increase in morbidity [5]. The aim of this article is to provide a comprehensive review of techniques and complications of percutaneous placement of catheter-port systems for HAIC.

**Correspondence to:* Dr R. Uberoi, Department of Radiology, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK. Tel: +44-1865-220816; Fax: +44-1865-220801; E-mail: raman.uberoi@orh.nhs.uk

hepatic arterial anatomy

Hepatic arterial anatomy is complex and shows a great deal of variation. Anatomical variation is also observed with the remaining branches of the celiac trunk. The standard anatomy is defined as the common hepatic artery dividing into the gastroduodenal artery and the hepatic artery proper, with the latter separating into two branches distally: the right and left hepatic arteries. An aberrant hepatic artery may arise from a source other than the common hepatic artery, and has been found in 40% examined cadavers [6]. An accessory hepatic artery is defined as an addition to the one that is normally present. A replaced hepatic artery is a substitution for a normal hepatic artery which is absent. The standard hepatic anatomy is only seen in 55% of cases [7]. The numerous other variations of hepatic blood supply were classified by Michels [6] into 10 types with minor variation in each type. Similarly, a great deal of anatomical variation is also observed with the remaining divisions of the celiac artery.

Precise placement of the catheter tip position is pivotal to optimizing the hepatic chemoinfusion treatment with reduced extrahepatic cytotoxic side-effects. An accurate assessment of hepatic arterial anatomy is therefore required before inserting an HAIC. A comprehensive detailed hepatic arterial assessment is routinely carried out with the use of noninvasive CTA or MRA techniques. Findings from this investigation are then confirmed with the diagnostic digital subtraction angiogram (DSA) study at the beginning of the HAIC insertion procedure.

patient preparation and analgesia

Percutaneous HAIC catheter insertion is carried out under local anesthesia. Pretreatment hydration with i.v. normal saline is advised >6 h before the procedure. A sterile technique is used. Lidocaine 1% 10–15 ml is often used to anesthetize the arterial puncture and portocath s.c. pocket sites. Long-acting analgesic agents such as fentnyl or morphine are reserved if local anesthesia is found to be inadequate to control pain relief. Use of benzodiazepines such as midazolam is reserved for anxious patients. All medications other than the local anesthesia are administered by a trained nurse who also monitors the patient's heart rate, oxygen saturation and electrocardiogram recording on a regular basis during the procedure. Conscious sedation or antibiotic prophylaxis is not routinely administered before the procedure.

vascular access route

Various percutaneous access routes to the hepatic artery have been described in the placement of HAIC catheters. The subclavian, hypogastric, femoral and brachial arterial have all been used [8–11]. The left subclavian and femoral artery approaches are used most commonly.

With the subclavain approach, the left subclavian artery is often used as it minimizes motion in the region through which the indwelling catheters must pass, resulting in a lesser possibility of catheter migration. In addition, patients can be fully ambulatory with no activity restriction. The subclavian vessels are accessed using the Seldinger method under US or fluoroscopic guidance. It is advisable to puncture the artery over a rib to avoid pneumothoax. A very distal puncture of the vessel can, however, lead to difficulty in advancing the guide wire because the artery descends dorsally at the distal portion of clavicle. Advancement of catheters can also be problematic and be technically unsuccessful if there is significant tortuosity of the artery. Increased aortic totuosity can also be problematic with the axillary and brachial approaches.

Cerebral infarction has been described as a serious complication that occurs in patients with HAIC catheters inserted via subcalavian and brachial routes [12]. Catheter redundancy in the aortic arch increases the risk of stroke in patients with subclavian catheters for HAIC infusion by increasing the formation of mural thrombus around the catheter [13]. Therefore, minimizing catheter redundancy in the aorta is important to reduce the frequency of cerebral infarction in patients when using these approaches. The increased risk of cerebral complications means that the brachial, axillary and subclavian arteries are not the access points of first choice.

The common femoral arterial approach is technically easier than the subclavian method as the vessel is superficial and less tortuous and remains the most popular vascular access route for the majority of endovascular procedures. In addition, this route obviates the risk of catheter-related stroke. Catheter migration due to the mobility of the hip joint initially made this access route less popular as patients were immobilized during the treatment period. With the increased use of catheter fixation techniques and the use of stiff copolymer fluorine–acryl–stryrene–urethane–silicone-coated catheters, however, this is no longer a major concern [14]. US and fluoroscopic guidance are used to puncture the femoral artery, and the right common femoral artery is often preferred.

placement of catheter

After puncturing access point using a Seldinger technique, a 5-French catheter is inserted and advanced to the celiac and SMA vessels, and visceral arteriography is carried out to assess the arterial supply further. The final position of the catheter tip is usually determined according to the vascular anatomy of each patient and location of hepatic tumor masses. Common locations of the catheter tip are the gastroduodenal artery, right hepatic artery, hepatic artery proper or common hepatic artery. A frequent complication of infusion of chemotherapy agents through hepatic arterial catheters is reactive gastric or duodenal mucosal lesions caused by irritation, resulting from the infusion of chemotherapeutic agents into these adjacent organs through arteries originating from the common hepatic artery including the gastroduodenal artery and the right gastric artery [15]. Distal selective embolization of the accessory hepatic, anterior and posterior superior pancreaticoduodenal, gastroduodenal and right gastric arteries are carried out with microcoils to prevent these side-effects. In addition, duodenal arterial branches, anastamotic branches to the dorsal pancreatic artery and omental branches may also be embolized to prevent gastrointestinal mucosal ulceration especially if these vessels were dilated and visible during the angiographic study. Access to the right gastric artery can be technically challenging. If direct access proves impossible, the vessel may be embolized by approaching it through the left gastric artery [16].

fixation of the catheter

Position of the catheter tip is pivotal to successful selective chemotherapy treatment. Frequent catheter dislodgement and hepatic artery occlusion were noted as major limitations of the radiologic implantation of conventional catheters, where an end-hole catheter is simply inserted into the common or proper hepatic artery. Migration of the catheter tip from a preferred position occurs in ∼6%–18% of cases and can lead to treatment failure and increased cytotoxic side-effects [10, 17, 18]. Mechanical trauma caused by the catheter tip on the arterial wall along with migration is believed to be an important cause of arterial thrombosis. To prevent these complications, catheter placement using the fix catheter tip method is often used. With this technique, a side hole is made in the indwelling catheter and is located at the common hepatic artery ostium (Figure 1). The tip of the indwelling catheter is placed in the gastroduodenal artery. A microcoil is then inserted via a microcatheter advanced inside the indwelling catheter beyond the side hole to close the end hole of the catheter. The microcatheter is introduced through the side hole of the indwelling catheter into the

Figure 1. The end hole of the hepatic arterial infusion of chemotherapy catheter is fixed in the gastroduodenal artery after embolization of the distal end of the artery. The side hole of the catheter is positioned to allow infusion of chemotherapy into the hepatic artery proper. (A) Gastroduodenal artery. (B) Catheter in the common hepatic artery. (C) Hepatic artery proper (Anthron® catheters, Courtesy of Virso Medical Ltd).

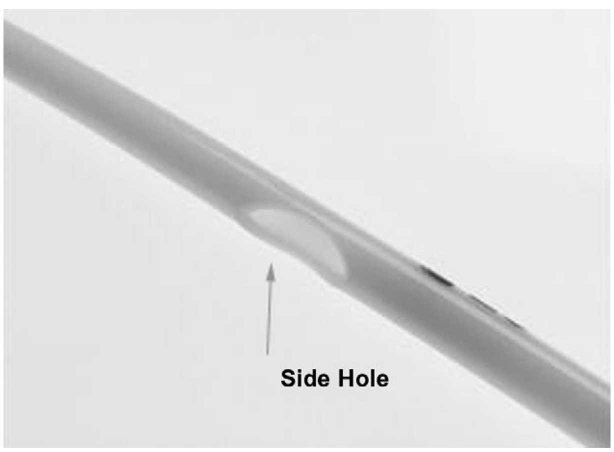

Figure 2. A close view of the catheter to illustrate the position of the side hole; presence of side holes allow chemoinfusion into the hepatic artery proper, while the catheter tip is fixed in the gastroduodenal artery (Anthron® catheters, Courtesy of Virso Medical Ltd).

gastroduodenal artery outside the catheter. The gastroduodenal artery is then embolized with microcoils through the microcatheter (Figure 2). A combination of *n*-butyl cynoacrylate (Histoacryl-Blue; Braun, Melsungen, Germany) and iodized oil (Lipodol; Laboratorie Gurbet, France) can be added through the microcatheter for sufficient embolization and to fix the catheter more firmly [19]. This technique is, however, inadequate when the gastroduodenal artery is small or absent. Also, removing the catheter at the end of the therapy or in cases of catheter dysfunction can be troublesome. W-spiral self-retaining indwelling catheters that can be fixed without the usage of embolic materials have been introduced recently to overcome these serious complications [20]. The W-spiral is a soft spiral catheter whose outer surface is coated with polyvinylpyrolidone with an anticoagulant feature. 3D-shaped memory metals made of nitinol are spirally arranged to facilitate the self-retaining function.

subcutaneous pocket formation and catheter connection

An incision ~3 cm in length is made in the skin distal to the puncture site at the anterior surface of the thigh, starting from the cutaneous puncture site and running medially and laterally along the inguinal fold. A s.c. pocket is then formed under local anesthesia, wherein the port reservoir is to be placed.

After fixing the angiographic catheter tip in gastroduodenal artery, the proximal end of the catheter is cut off adjacent to the puncture site. To create the connection between the angiographic catheter and port reservoir, a metal cannula is introduced into the lumen of the angiographic catheter. The tip of the silicone catheter end from the port is subsequently inserted into the metal connector. The skin incision is sutured with sutures.

postprocedure care

Patients are observed for 3 h on a day case ward. During the first 2 h of the observation period, patients are mainly bed restricted. Pulse, blood pressure and any evidence of groin hematoma or bruise are observed every 15 min during the period of bed rest. In the absence of any significant complications, patients are then mobilized gradually during the final hour of the observation period before discharge. Before the initiation of HAIC, a flow confirmation study is recommended with flow scintigraphy, computed tomography angiography or DSA to assess the passage of cytotoxic agents in relation to the tumor lesion. Regular flushing of the catheter with 10 ml of saline solution at the end of the chemotherapy cycle is advised to maintain catheter patency. No routine anticoagulation or antibiotics are used to reduce thrombosis or infective complications. Assessment of the port site for hematoma, bleeding, infection and catheter dislocation on a regular basis is, however, vital.

complications

The catheter-port system is associated with various complications after radiologic implantation. Bruising and formation of a small hematoma at the puncture and port pocket site remain the commonest complication. Catheter dislocation is a major problem with percutaneous catheter insertion and occurs in between 2% and 44% of cases [10, 17, 18]. The frequency of dislocation is higher with axillary or brachial artery access [21, 22]. Catheter fixation techniques with the use of braided polyurethane angiographic catheters have been shown to reduce catheter dislocation significantly [14]. Thrombotic occlusion of the catheter and the hepatic

 doi:10.1093/annonc/mdm528

artery are also seen with precutaneous catheter placement. Catheters with small diameter have higher occlusion rates [23]. Use of the brachial, axillary and subclavian arteries as access sites has been associated with increased rates of stroke and should be avoided if possible [12, 24]. The material and thickness of the indwelling catheters and the relation between the size of the catheter and the lumen of the target vessel as well as toxic effects of the cytotoxic agents play an important role in arterial thrombosis associated with percutaneous catheter placement [17, 21, 23, 25]. Lytic therapy with tissue plasminogen activator can be useful in cases of acute arterial or catheter thrombosis [17, 21]. Prophylactic use of anticoagulation is not generally considered to reduce these complications significantly. Infection is an important complication with the permanently implanted catheter system and occurs up to 25% of cases [26]. It can be caused by use of inappropriate hygienic measures and be avoided by employing aseptic techniques when inserting or accessing the implantable port system. Early usage of appropriate antibiotics can also reduce the rate of catheter failure due to infective complications [27].

interventional versus surgical methods of inserting HAIC catheters

Interventionally implanted port-catheter system for HAIC has evolved into a promising alternative to surgically implanted devices. There are only a limited number of studies comparing the surgical and interventional insertion of HAIC catheters [28, 29]. It has been shown that the length of hospitalization (1.8 versus 8.2 days) and the mean analgesic requirement (2 versus 9.7 doses) postprocedures are lower in the interventional group compared with its surgical counterpart [28]. Comparative studies of both techniques show that percutaneous interventional catheter insertion has a higher port implantation success rate (100% versus 95%), catheter patency rate (77% versus 50%) and longer port duration (19 versus 14 months) than the surgical implantation of port-catheter system [29]. There is a higher rate of device-related complication with the interventional technique compared with the surgical approach (63% versus 40%), and catheter dislocation due to poor fixation techniques contributes significant proportion of these complications [29]. With the improvement of catheter fixation techniques, these complications are likely to become less frequent in the future. Furthermore, the majority of these device-related complications have shown successfully be corrected by interventional revisions with a rate device-related treatment interruption of 17% which compares favorably with the surgical technique [29].

conclusion

HAIC remains a valuable treatment option for patients with advanced nonsurgical hepatic primary or metastatic tumors. Recent advances in interventional radiological techniques avoid the use of surgical placement and allow the minimally invasive placement of hepatic arterial catheters percutaneously under local anesthesia. Diagnostic and interventional radiology play a vital role in establishing vascular access, monitoring for complications and assessing the outcome of HAIC treatment regimes.

references

1. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954; 30(5): 969–977.
2. Goldberg JA, Kerr DJ, Stewart I, McArdle CS. A comparison of regional and systemic chemotherapy for hepatic metastases. Eur J Surg Oncol 1990; 16(5): 464–467.
3. Cohen AM, Kemeny NE, Kohne CH et al. Is intra-arterial chemotherapy worthwhile in the treatment of patients with unresectable hepatic colorectal cancer metastases? Eur J Cancer 1996; 32A(13): 2195–2205.
4. Allen-Mersh TG, Earlam S, Fordy C et al. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. Lancet 1994; 344(8932): 1255–1260.
5. Grosso M, Zanon C, Mancini A et al. Percutaneous implantation of a catheter with subcutaneous reservoir for intraarterial regional chemotherapy: technique and preliminary results. Cardiovasc Intervent Radiol 2000; 23(3): 202–210.
6. Michels NA. Blood Supply and Anatomy of the Upper Abdominal Organs. Philadelphia, PA: Lippincott 1955; 152–154, 256–259.
7. Chuang VP, Wallace S. Hepatic arterial redistribution for intraarterial infusion of hepatic neoplasms. Radiology 1980; 135(2): 295–299.
8. Oi H, Kishimoto H, Matsushita M et al. Percutaneous implantation of hepatic artery infusion reservoir by sonographically guided left subclavian artery puncture. AJR Am J Roentgenol 1996; 166(4): 821–822.
9. Ikebe M, Itasaka H, Adachi E et al. New method of catheter-port system implantation in hepatic arterial infusion chemotherapy. Am J Surg 2003; 186(1): 63–66.
10. Strecker EP, Boos IB, Ostheim-Dzerowycz W et al. Percutaneously implantable catheter-port system: preliminary technical results. Radiology 1997; 202(2): 574–577.
11. Wirtanen GW. Percutaneous transbrachial artery infusion catheter techniques. Am J Roentgenol Radium Ther Nucl Med 1973; 117(3): 696–700.
12. Hirota T, Yamagami T, Tanaka O et al. Brain infarction after percutaneous implantation of port-catheter system via the left subclavian artery. Br J Radiol 2002; 75(898): 799–804.
13. Hirota T, Yamagami T, Tanaka O et al. Catheter redundancy in the aortic arch increases the risk of stroke in left subclavian arterial port-catheter systems. J Vasc Interv Radiol 2005; 16(4): 471–476.
14. Kuroiwa T, Honda H, Yoshimitsu K et al. Complications encountered with a transfemorally placed port-catheter system for hepatic artery chemotherapy infusion. Cardiovasc Intervent Radiol 2001; 24(2): 90–93.
15. Doria MI Jr., Doria LK, Faintuch J, Levin B. Gastric mucosal injury after hepatic arterial infusion chemotherapy with floxuridine. A clinical and pathologic study. Cancer 1994; 73(8): 2042–2047.
16. Yamagami T, Nakamura T, Iida S et al. Embolization of the right gastric artery before hepatic arterial infusion chemotherapy to prevent gastric mucosal lesions: approach through the hepatic artery versus the left gastric artery. AJR Am J Roentgenol 2002; 179(6): 1605–1610.
17. Wacker FK, Boese-Landgraf J, Wagner A et al. Minimally invasive catheter implantation for regional chemotherapy of the liver: a new percutaneous transsubclavian approach. Cardiovasc Intervent Radiol 1997; 20(2): 128–132.
18. Herrmann KA, Waggershauser T, Heinemann V, Reiser M. Interventional radiological procedures in impaired function of surgically implanted catheter-port systems. Cardiovasc Intervent Radiol 2001; 24(1): 31–36.
19. Yamagami T, Iida S, Kato T et al. Using n-butyl cyanoacrylate and the fixed-catheter-tip technique in percutaneous implantation of a port-catheter system in patients undergoing repeated hepatic arterial chemotherapy. AJR Am J Roentgenol 2002; 179(6): 1611–1617.
20. Tajima T, Yoshimitsu K, Kuroiwa T et al. Percutaneous femoral catheter placement for long-term chemotherapy infusions: preliminary technical results. AJR Am J Roentgenol 2005; 184(3): 906–914.
21. Okuyama K, Tohnosu N, Koide Y et al. Complications and their management in intraarterial infusion chemotherapy. Gan To Kagaku Ryoho 1992; 19(7): 1007–1013.
22. Laffer U, Durig M, Zimmerli W et al. Implantable catheter system for ambulatory parenteral antibiotic chemotherapy. A prospective study. Helv Chir Acta 1989; 56(1–2): 127–131.
23. Strum S, McDermed J, Korn A, Joseph C. Improved methods for venous access: the Port-A-Cath, a totally implanted catheter system. J Clin Oncol 1986; 4(4): 596–603.

24. Seki H, Kimura M, Yoshimura N et al. Hepatic arterial infusion chemotherapy using percutaneous catheter placement with an implantable port: assessment of factors affecting patency of the hepatic artery. Clin Radiol 1999; 54(4): 221–227.
25. Habbe TG, McCowan TC, Goertzen TC et al. Complications and technical limitations of hepatic arterial infusion catheter placement for chemotherapy. J Vasc Interv Radiol 1998; 9(2): 233–239.
26. Huk I, Entscheff P, Prager M et al. Patency rate of implantable devices during long-term intraarterial chemotherapy. Angiology 1990; 41(11): 936–941.
27. Zhu AL, Liu LX, Piao DX et al. Liver regional continuous chemotherapy: use of femoral or subclavian artery for percutaneous implantation of catheter-port systems. World J Gastroenterol 2004; 10(11): 1659–1662.
28. Aldrighetti L, Arru M, Angeli E et al. Percutaneous vs. surgical placement of hepatic artery indwelling catheters for regional chemotherapy. Hepatogastroenterology 2002; 49(44): 513–517.
29. Hildebrandt B, Pech M, Nicolaou A et al. Interventionally implanted port catheter systems for hepatic arterial infusion of chemotherapy in patients with colorectal liver metastases: a Phase II-study and historical comparison with the surgical approach. BMC Cancer 2007; 7: 69.