Repetitive hepatic arterial infusion chemotherapy (HAIC) using an implanted hepatic arterial port system has been reported to be a useful therapeutic modality in patients with advanced hepatocellular carcinoma (HCC)\(^1\),\(^9\). As interruption of HAIC due to complications such as catheter infusion hole migration, hepatic artery damage, port-catheter system occlusion, and problems around the hepatic arterial port or the puncture site, is closely associated with a poor prognosis\(^6\), they must be avoided so that treatment can be completed.

The catheter-fixation method aims at preventing catheter infusion hole migration and hepatic artery damage by inserting an indwelling catheter with a side-hole into the gastroduodenal artery (GDA)\(^6\),\(^10\). The side-hole is directed at the common hepatic artery (CHA) and the distal tip of the indwelling catheter is fixed with the GDA using coils and/or glue\(^{19}\). This fixed catheter tip (FCT) method has been used widely in Japan and Europe.

Hamada et al reported a new hepatic arterial port that features a coaxial catheter comprised of a 2.9-Fr microcatheter (Sniper; Clinical Supply, Gifu, Japan) and a 5-Fr catheter (Frosty catheter;...
Clinical Supply). Use of the hepatic arterial port using the coaxial method makes it easier to position an indwelling catheter in stenotic or tortuous arteries. While this method has yielded high technical success rate in a small series of patients, there is no information available on long-term outcomes.

Since January 2004 implantation of hepatic arterial ports using the coaxial method via the femoral approach has been the standard procedure at our institution. In the current study we retrospectively evaluated the long-term functioning of our implanted hepatic arterial port system using the coaxial method in 176 patients with HCC.

**MATERIALS AND METHODS**

This retrospective study was approved by the Institutional Review Board of our hospital; informed patient consent was waived.

**Patients**

Between January 2004 and July 2009 we attempted to implant a hepatic arterial port using the coaxial method in 202 consecutive HCC patients (169 men and 33 women; age range 26-84 years; mean age 63.4 years). In all patients the liver lesions were judged to be unresectable with this factor limiting survival. All patients provided prior written informed consent for treatment and the interventional procedures. Inclusion criteria in our study were patients who had undergone hepatic arterial port implantation for HAIC to treat unresectable HCC. Exclusion criteria were (a) no verifiable outcome after hepatic arterial port implantation using the coaxial method at our institution, (b) disuse of the hepatic arterial port due to deterioration of the patient’s general condition immediately after implantation, (c) previous hepatic arterial port implantation, (d) implantation of a hepatic arterial port using a fixed catheter tip, (e) interruption of HAIC due to side effects elicited by chemotherapy and (f) HAIC performed at another institution. Ultimately, 176 patients (149 men and 27 women, age range 26-84 years, mean age 63.3 years) were included in this study.

Based on follow-up studies carried out until March 2011, of the 176 patients 9 (5.1%) underwent subsequent hepatic surgical excision, 1 (0.1%) manifested post-operative GDA occlusion, and 8 (4.5%) presented with stenosis of the celiac artery (CA), CHA, or proper hepatic artery (PHA).

**Method for the hepatic arterial port implantation using the coaxial method**

With the patient under local anesthesia, we inserted a 3.5-Fr or 4-Fr introducer sheath (S-one sheath: Clinical Supply) via a unilateral femoral artery. Then we acquired celiac and superior mesenteric arteriograms through the 3.5-Fr or 4-Fr angio catheter (Selecon PA catheter: Clinical Supply) to assess the hepatic vascular anatomy. We studied the location of neoplasms and vascular invasion by the tumors on CT scans acquired during hepatic arteriography (CTA) and arterial portography (CTAP).

In patients with multiple hepatic arteries we did not unify the hepatic blood flow redistribution by coil embolization. Rather, we placed the indwelling catheter in the hepatic artery that dominantly fed the lesion after transcatheter arterial chemoembolization (TACE) of the other arteries using a microcatheter (Microferret-18: William Cook Europe, Bjaeverskov, Denmark or Masters Parkway; Asahi Intec, Nagoya, Japan, Parkway C3: Asahi Intec). We used a suspension comprised of a mixture of cisplatin powder (Randa: Nippon Kayaku, Tokyo, Japan, and IA-call; Nippon Kayaku, Tokyo, Japan) and iodized oil (Lipiodol Ultrafluid: André Guerbet, Aulnay-sous-Bois, France); the ratio was 10 mg cisplatin to 1 ml oil. The embolic materials were gelatin sponge particles (Gelform: Pfizer, Tokyo, Japan, and Gelpart: Nippon Kayaku, Tokyo, Japan). Extrahaepatic feeding arteries, i.e. the inferior phrenic-, adrenal-, and renal capsular arteries were embolized using the same TACE technique.

Before implanting the catheter through the CHA we embolized the accessory left gastric artery (LGA), the right gastric artery (RGA), and the GDA with microcoils (Tornado & Nester: Cook Europe, Bjaeverskov, Denmark or Masters Parkway; Asahi Intec, Nagoya, Japan, Parkway C3: Asahi Intec), using a microcatheter to prevent the perfusion of anti-cancer agents into extra-hepatic organs.

The microcatheter was inserted through the 3.5-Fr or 4-Fr catheter and advanced to a predetermined position in the target artery to facilitate stable positioning of the 2.9-Fr indwelling microcatheter (outer diameter of the proximal and the distal shaft, 2.9-Fr and 2.5-Fr) featuring the side-hole. The indwelling microcatheter was made of polyamide elastomer; its surface was polymer-coated. Then we aligned the tip of the micro-guidewire to the tip of the microcatheter and withdrew the micro-guidewire into the common or proper hepatic artery to the predetermined site of the side hole. This procedure was under fluoroscopic guidance and the distance between the location of the side hole and the catheter tip was measured. Using surgical scissors we then manually created a side-hole in the catheter at the desired location (distance from the side-hole to the tip 0.5-7.0 cm, mean distance 1.8 cm), making sure that the hole was large enough to permit the efflux of the injected fluid.

We placed the 3.5-Fr or 4-Fr angio catheter at the abdominal aortic bifurcation and inserted a
hepatic artery were patent and the target lesions were perfused adequately. The port was flushed and filled with 2 or 3 ml of heparin solution (100 IU/ml) at the end of each chemotherapy session and once every 2 months during the follow-up period.

Evaluation of our port-catheter system

Cumulative rate of hepatic arterial port functioning

The study endpoint was the occurrence of a primary interruption, the completion of HAIC or patient death. The follow-up period started at the completion of hepatic arterial port implantation. To assess the cumulative rate for possible HAIC and the predictable cumulative rate of hepatic arterial port functioning we used the Kaplan-Meier method. The cumulative rate for possible HAIC was estimated, taking as an endpoint possible factors leading to the discontinuation of HAIC via the primary hepatic arterial port, including patient death, lost follow-up, change hospital, complications and complete remission of tumors. The predictable cumulative rate of hepatic arterial port functioning was also estimated defining the endpoint as the discontinuation of HAIC due to complications related to the hepatic arterial port.

Technical success rate

We defined technical success as the successful implantation of the port-catheter system and confirmation by angiography via the port as the final step of implantation of good distribution of the chemotherapy agents to target areas in the liver.

**Hepatic arterial infusion chemotherapy (HAIC)**

HAIC was started within 2 weeks after hepatic arterial port implantation. Chemotherapy was with low-dose cisplatin and 5-fluorouracil, 5-fluorouracil plus interferon, or low-dose cisplatin and 5-fluorouracil plus gemcitabine. The latter drug was delivered systemically.

Before each course of HAIC, and if we suspected port- or other malfunctions, we obtained angiograms and CT arteriograms via the hepatic arterial port to confirm that the catheter and hepatic artery were patent and the target lesions were perfused adequately. The port was flushed and filled with 2 or 3 ml of heparin solution (100 IU/ml) at the end of each chemotherapy session and once every 2 months during the follow-up period.

**Fig. 1. Technique**

A. The indwelling microcatheter is introduced via the 5-Fr catheter in the celiac trunk after coil-embolization of the gastroduodenal artery (GDA) and the right gastric artery (RGA). A side hole in the catheter facilitates perfusion of the common- or proper hepatic artery.

B. Arteriogram obtained via the implanted catheter shows good distribution of the anticancer agent to the entire liver from the side-hole (arrow) and cessation of flow in the GDA, RGA, and accessory left gastric artery due to the presence of the coils (arrowheads).

0.032 inch guide wire (Fixed Core Wire Guide Saft-T-J Curved; Cook Medical Inc., Bloomington, IN) into the contralateral femoral artery through the angio catheter due to be exchanged for a 5-Fr heparin-coated catheter (Terculca Port; Clinical Supply). We removed the 3.5-Fr or 4-Fr introducer sheath and the 3.5-Fr or 4-Fr angio catheter and inserted the 5-Fr heparin-coated catheter using an over the guidewire technique.

Based on the target artery, we then placed the tip of the 5-Fr heparin-coated catheter into the celiac- or superior mesenteric artery (CA, SMA). Next we inserted the indwelling microcatheter over the 0.014-inch guide wire into the hepatic artery and adjusted the position of the side-hole to target the CHA or PHA through the 5-Fr heparin coated catheter (Fig. 1).

We then connected the indwelling microcatheter and the 5-Fr heparin-coated catheter to the port (Terculca Port; Clinical Supply). Details on connecting the catheters to the port are reported elsewhere. Lastly, we implanted the port into the subcutaneous space below the level of the inguinal ligament.
Time required for implantation of the hepatic arterial port

We recorded the time required in one session from skin incision to closure for the implantation of the hepatic arterial port. The procedural time requirement included the time for diagnostic angiography, TACE, and embolization of arteries supplying the extrahepatic organs.

Complications

Based on the definition of the Society of Interventional Radiology, major complications were defined as implantation-related problems that arose during the follow-up and resulted in the discontinuation of HAIC. These included side-hole migration, occlusion of the port-catheter system (catheter occlusion, disconnection between the catheter and the port, port breakage), and hematoma and/or infection around the port or puncture site.

In our study we did not consider as complications adverse side effects elicited by the administered anticancer drugs because these were not related to our hepatic arterial port implantation method.

RESULTS

Cumulative duration and rate of hepatic arterial port functioning

The median follow-up in 176 patients after hepatic arterial port implantation was 7.7 months (range 0.4 - 68.3 months); 130 patients (73.9%) died in the follow-up period. The median duration of hepatic arterial port functioning was 4.3 months (range 0.4-5.16 months), the cumulative rate for possible HAIC via the primary hepatic arterial port at 6-, 12-, and 24 months was 43.8%, 21.0% and 8.8%, respectively (Fig. 2). The reasons for cessation of HAIC using the primary hepatic arterial port are summarized in Table 1. The predictable cumulative rate of hepatic arterial port functioning at 6-, 12-, and 24 months was 75.1%, 60.9% and 44.6%, respectively (Fig. 3).

Table 1. Reasons for cessation of HAIC using primary hepatic arterial port

<table>
<thead>
<tr>
<th>Reasons</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of HAIC without complications related with the hepatic arterial port</td>
<td></td>
</tr>
<tr>
<td>Patient death</td>
<td>86</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>21</td>
</tr>
<tr>
<td>Complete remission of tumor</td>
<td>3</td>
</tr>
<tr>
<td>Refusal of treatment</td>
<td>2</td>
</tr>
<tr>
<td>Cessation of HAIC due to complications related with the hepatic arterial port</td>
<td></td>
</tr>
<tr>
<td>Catheter dislocation</td>
<td>15</td>
</tr>
<tr>
<td>Hematoma and/or infection around the port or puncture site</td>
<td>14</td>
</tr>
<tr>
<td>port-catheter system occlusion</td>
<td>10</td>
</tr>
<tr>
<td>Damage to the hepatic artery</td>
<td>10</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>4</td>
</tr>
<tr>
<td>Leak of the anti-cancer agent around the implanted port</td>
<td>2</td>
</tr>
<tr>
<td>Intermittent claudication due to severe stenosis of external iliac artery</td>
<td>1</td>
</tr>
</tbody>
</table>

Technical success rate

Implantation of the hepatic arterial ports succeeded in 175 of the 176 patients (99.4%). We placed the ports through the CA in 172- and the SMA in 3 patients. The single implantation failure was due to severe stenosis at the origin of the replaced right hepatic artery (RHA) from the SMA.

Time required for implantation of the hepatic arterial port

The total time required for the procedure was 121 ± 27 min (mean ± SD, range 58-185 min) in 175 patients. The procedure time also included TACE in 75 patients and embolization of arteries supplying extrahepatic organs in 150 patients.
Complications
As shown in Table 1, we encountered complications in 56 of the 175 patients (32%) who underwent successful port implantation. These were attributable to infusion hole migration (n=15, 8.6%), hematoma and/or infection around the port or puncture site (n=14, 8.0%), damage to the hepatic artery (n=10, 5.7%), port-catheter system occlusion (n=10, 5.7%), catheter infection (n=4, 2.3%), leakage during HAIC of the anti-cancer agent around the port due to loosening of the needle (n=2, 1.1%), and intermittent claudication during the follow-up period due to severe stenosis of the external iliac artery (n=1, 0.6%). In 45 of the 56 patients manifesting these complications we removed the port under local anesthesia. The reasons for removal of the primary hepatic arterial port are summarized in Table 2.

Table 2. Reason for removal of hepatic arterial port

<table>
<thead>
<tr>
<th>Complications</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter dislocation</td>
<td>15</td>
</tr>
<tr>
<td>Hematoma and/or infection around the port or puncture site</td>
<td>11</td>
</tr>
<tr>
<td>Port-catheter system occlusion</td>
<td>8</td>
</tr>
<tr>
<td>Damage to the hepatic artery</td>
<td>5</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>4</td>
</tr>
<tr>
<td>Leak of the anti-cancer agent around the implanted port</td>
<td>1</td>
</tr>
<tr>
<td>Intermittent claudication due to severe stenosis of external iliac artery</td>
<td>1</td>
</tr>
</tbody>
</table>

DISCUSSION
In our literature search we found 4 reports that documented experience with hepatic arterial port implantation in more than 100 patients. However, unlike our study, none of the earlier reports that used the coaxial method for implantation of a hepatic arterial port system involved more than 100 patients. Hamada et al assessed the long-term outcome in 64 patients who underwent port implantation using a combination of the coaxial- and the FCT method. They reported that the mean length of HAIC possible via the port system was 14.1 months (range 1-56 months), and that the cumulative rate for HAIC possible via this route was 93%, 72% and 38% at 6-, 12-, and 24 months, respectively. In our series the median length of HAIC was 4.3 months (range 0.4-51.6 months) and the cumulative rate for HAIC possible via the hepatic arterial port was 43.8%, 21.0% and 8.8% at 6-, 12-, and 24 months, respectively. Our results were worse than those in their reports because the prognosis of participants was considered to be poor due to advanced HCC. The hepatic arterial ports in patients with death, best supportive care, refusal of treatment or tumor remission were still available. The longer the survival time of participants, the longer the hepatic arterial port would need to be available. Therefore, we estimated the predictable cumulative rate of hepatic arterial port functioning containing only the complications related to the hepatic arterial port in endpoint. The predictable cumulative rate of the hepatic arterial port functioning was 75.1%, 60.9% and 44.6% at 6-, 12-, and 24 months, suggesting that adding catheter tip fixation to the coaxial method resulted in slightly higher cumulative rates. We also assume that the difference between their and our results may be attributable to the larger number of patients in our series and to our higher rate of complications involving infusion hole migration, hematoma and/or infection around the reservoir port or puncture site.

With the FCT method, the reported rate of infusion hole migration was 2.8-5.4% in our current series and in patients reported by Venturini et al and Kuroiwa et al who did not use the FCT method, this rate was higher at 8.6%, 8.8% and 10% respectively (Table 3).

The incidence of problems involving the port or the puncture site was higher in ours than in the previously-reported series. We considered that this was due to three factors. First, as most of our patients presented with underlying liver cirrhosis, the incidence of hematoma and/or infection involving the port and puncture site was higher. Second, in the early and middle stage of this study, we may not have paid enough attention to the port and the puncture site. Third, in the early part of the study we used a 4-Fr sheath for

Table 3. Large studies in implantations of reservoir systems for hepatic arteries

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Patient number</th>
<th>Type of the implanting catheter</th>
<th>Catheter-fixation method</th>
<th>Technical success rate %</th>
<th>Catheter infusion hole migration %</th>
<th>Hepatic arterial damage %</th>
<th>Catheter-port system occlusion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deschamps et al. 2010</td>
<td>93</td>
<td>5-Fr non-tapered</td>
<td>Yes or No</td>
<td>94</td>
<td>12</td>
<td>Not described</td>
<td>11</td>
</tr>
<tr>
<td>Yamagami et al. 2008</td>
<td>166</td>
<td>5-Fr tapered</td>
<td>Yes</td>
<td>100</td>
<td>5.4</td>
<td>6.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Seki et al. 2006</td>
<td>131</td>
<td>5-Fr non-tapered</td>
<td>Yes</td>
<td>79</td>
<td>3.0</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>Venturini et al. 2004</td>
<td>204</td>
<td>5-Fr non-tapered</td>
<td>No</td>
<td>100</td>
<td>8.8</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Tanaka et al. 2003</td>
<td>426</td>
<td>5-Fr tapered</td>
<td>Yes</td>
<td>99.8</td>
<td>2.8</td>
<td>Not described</td>
<td>0.1</td>
</tr>
<tr>
<td>Kuroiwa et al. 2001</td>
<td>90</td>
<td>5-Fr non-tapered</td>
<td>No</td>
<td>98</td>
<td>10</td>
<td>1.1</td>
<td>11</td>
</tr>
<tr>
<td>Our study</td>
<td>176</td>
<td>2.9-Fr microcatheter</td>
<td>No</td>
<td>99.4</td>
<td>8.6</td>
<td>5.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>
diagnostic angiogram, whose outer diameter was larger than of the 5-Fr indwelling catheter. As our study progressed we implemented meticulous observation of the port and the puncture site. This considerably reduced the development of hematoma and/or infection at those sites. Also, we started using a 3-Fr sheath rather than the 4-Fr sheath used in the earlier part of the study.

According to Tanaka et al the cumulative patency rate of the hepatic artery in 425 patients treated with the FCT method using a 5-Fr tapered catheter was 91.0%, 81.4%, and 58.1% at 6 months, 1 year and 2 years, respectively. We posit that their results reflect a lower incidence of infusion hole migration, of hematoma and/or infection around the port or puncture site, and of port-catheter system occlusion.

The rate of port-catheter system occlusion in our series was higher than in earlier studies that used 5-Fr implanted catheters (Table 3). The small diameter of the catheter we used increased the risk for catheter occlusion due to thrombosis. Moreover, in other series, the catheters were made of polyurethane or silicone while the microcatheter we implanted was made of polyamide elastomer, a material whose appropriateness for long-term implantation has not yet been demonstrated and whose nature may invite catheter occlusion.

Methods for the implantation of hepatic arterial port systems using the coaxial method must be improved and the incidence of catheter infusion hole migration and of port-catheter system occlusion must be reduced. In most of our cases we placed the microcatheter tip in the CHA or PHA; catheter migration was encountered less often when the tip was placed in the right- or left hepatic arteries. If the microcatheter is implanted in a more peripheral hepatic artery, the incidence of infusion hole migration may be reduced. Implanted microcatheters made of materials other than polyamide elastomer may lower the rate of port-catheter system occlusion. For example, polyurethane 2.7-Fr implanting microcatheters have become commercially available (Piolax W spiral catheter, Piolax Medical Devices, Inc., Yokohama, Japan).

Our technique for hepatic arterial port implantation yielded a high technical success rate, it is simple and can be adapted to variations in the anatomy and condition of the hepatic artery. The reported success rate for hepatic arterial port implantation ranges from 79 to 100% (Table 1); in our study it was 99.4%, and acceptable under a variety of anatomical conditions. Our technique does not require a change to an indwelling catheter over a guide wire placed in the hepatic artery, nor does it necessitate puncture of a contralateral femoral artery.

Hepatic arterial port implantation using the coaxial method makes use of conventional angiographic techniques used for TACE of liver tumors.

The time required by Tanaka et al for catheter implantation via the subclavian artery was 75.9 ± 41.2 min; this did not include the time required for diagnostic angiography. Irie needed a mean of 115 min for implanting the catheter via the femoral artery. Our procedure time of 120 ± 27 min was similar or shorter, and included TACE in 75- and embolization of arteries supplying extrahepatic organs in 150 patients.

Our rate of hepatic artery damage was lower than in earlier series (5.7% vs. 6.0-12%, Table 1). Takeuchi et al attributed the induction of hepatic artery damage to mechanical stimulation of the inner wall of the hepatic artery due to the movement of the catheter tip and tube, and to the toxicity of the delivered anticancer agents. The degree of mechanical stimulation may be closely associated with the diameter of the catheter and the host vessel.

Our study has some limitations. First, it was retrospective, noncomparative, and non-randomized. Second, the hepatic arterial ports were implanted by different interventional radiologists and their techniques were somewhat different. The complication rate and the time required for system implantation may reflect these differences.

CONCLUSION

The predictable cumulative rate of hepatic arterial port functioning using our method was 75.1%, 60.9%, and 44.6% at 6-, 12-, and 24-months, respectively. Our high technical success rate was not affected by anatomical variations. The incidence of port-catheter system occlusion and catheter dislocation was higher in our method than in conventional methods. Although our technique represents another option to treat patients in whom conventional techniques cannot be applied, technical improvements and the development of suitable catheter materials are necessary to overcome catheter infusion hole migration and port-catheter system occlusion.

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