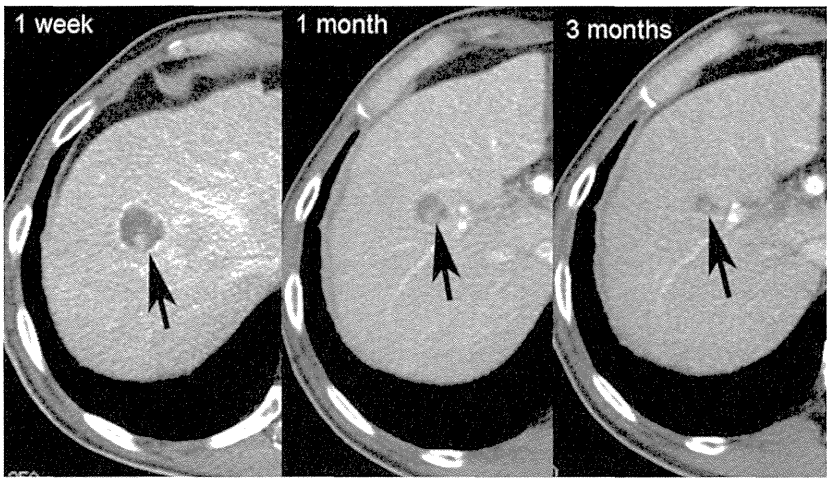

Figure 5. *Follow-up CT 1 week, 1 month, and 3 months after bland TAE show the shrinkage of the tumor (arrows).*

It could be difficult to evaluate the efficacy of treatment after bland TAE for a non-hypervascular tumor because injected microspheres are not visible, and tumor enhancement cannot be seen before or after TAE. CT perfusion images obtained before and after TAE could quantitatively assess the arterial vascularity. In addition, the tumor shrinkage during the follow-up period indicated good tumor control.

In conclusion, superselective bland TAE using 40-μm microspheres could be effective for early-stage HCCs with fine tumor-feeding arteries. This treatment might also be useful for non-hypervascular HCCs refractory to superselctive lipiodol TACE.

Conflicts of Interest

The Authors declare that they do not have any conflicts of interest nor any financial disclosures.

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SPECIAL REPORT

Guidelines on the use of gelatin sponge particles in embolotherapy

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Abstract Gelatin sponge (GS) is one of the most widely used embolic agents in interventional procedures. There are four commercially available GS products in Japan; however, the endovascular use of Gelfoam and Spongel is off-label, and Gelpart can only be used for hepatic artery embolization and Serescue can only be used for hemostasis of arterial bleeding. GS has been used for a variety of clinical indications, mainly tumor embolization and stopping massive arterial bleeding. The optimal size and preparation procedure of GS particles differs slightly for each clinical indication. In addition, there is a risk of ischemic and/or infectious complications associated with GS embolization in various situations. Therefore, radiologists should be familiar with not only the preparation and handling of GS particles, but also the disadvantages and potential risks, in order to perform GS embolization safely and effectively.

Keywords Gelatin sponge · Endovascular use · Embolization · Indication · Complication

Introduction

Gelatin sponge (GS) is a water-insoluble hemostatic agent, composed of bovine or porcine collagen [1]. This agent was first used for hemostasis during surgery in 1945 [2]. In 1967, it was used as an intravascular embolic agent to occlude a cavernous-carotid fistula [3]. Thereafter, GS has been used for this purpose worldwide, particularly in the management of hepatocellular carcinoma (HCC) [4–11], uterine fibroids [12–16], and massive arterial bleeding [16–22].

Now, four main GS products are commercially available in Japan: Gelfoam (Pfizer, Tokyo, Japan), Spongel

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(Astellas, Tokyo, Japan), Gelpart (Nippon Kayaku, Tokyo, Japan), and Serescue (Nippon Kayaku). Gelfoam and Spongel are 2- or 2.5-mm-thick sheets, and different procedures can be performed to obtain ready-to-use occlusive agents. However, the endovascular use of Gelfoam and Spongel as embolic agents is off-label. Gelpart is a spherical form with a 1- or 2-mm diameter, and it is ready to use when mixed with contrast material. Serescue is a 2.5 × 2.5 × 1-cm sheet and is composed of the same material as Spongel. This product became commercially available at the end of 2013 and manual preparation is also necessary before the use. The endovascular use of both Gelpart and Serescue is approved; however, Gelpart can only be used for hepatic artery embolization and Serescue only for hemostasis of arterial bleeding. Therefore, it is very important to understand how to handle GS particles effectively and safely in embolotherapy for several clinical indications and situations. In this article, we describe the general consensus regarding GS embolization in Japan.

Rationale for GS embolization

CQ1: How does GS occlude vessels?

Recommendations

GS particles achieve vascular occlusion due to mechanical packing of the vessel lumen and blood clotting. GS itself can also promote blood clotting.

Specific comments

GS particles injected through a catheter are distally carried away by the arterial blood flow. These are trapped and clustered in vessels with a lumen smaller than the particle size. Blood clotting gradually develops when the blood flow is hindered by mechanical blockage. GS has a hemostatic ability almost equal to that of fibrin when directly adhering to the bleeding surface [2]. GS can also shorten the coagulation time from 9.5 to 6.2 min when added to a whole-blood sample [23].

CQ2. How long can GS occlude vessels?

Recommendations

GS particles can be absorbed within 2–6 weeks, and embolized vessels are fully recanalized thereafter. However, the attenuation of embolized vessels occurs due to arteritis and intimal proliferation. Permanent vascular occlusion can also develop, depending on the amount and compactness of GS particles and intensity of inflammatory reactions.

Specific comments

GS is widely recognized as a temporary occlusive agent; however, it was reportedly found in a vessel wall surrounded by granulation tissues after 7 months [24]. In an experimental study by Sato and Yamada [25], acute inflammatory reactions developed around GS particles immediately after intravascular injection, followed by granulomatous arteritis with a massive infiltration of mononuclear and giant cells within 20 days. The proliferation of fibroblasts into thrombi occurred after 1 week, and then GS was surrounded by a proliferated intima after 2 weeks. Thereafter, GS was gradually resorbed and the occluded lumen became recanalized. However, the attenuation of embolized vessels occurs due to arteritis and intimal proliferation, and permanent vascular occlusion may develop when a dense packing of GS is performed [1, 25, 26].

Indications

CQ3a: Which hypervascular malignant tumors are indicated for GS embolization?

Recommendations

GS embolization contributes to prolonged survival in patients with HCCs (recommended grade A). Tumor embolization using GS can also be used as preoperative management to reduce perioperative blood loss and palliation to improve symptoms related to renal cell carcinomas (RCC) (recommended grade C1).

Specific comments

Two randomized clinical trials that were undertaken in 2002 revealed that transcatheter arterial chemoembolization (TACE) using GS helped to improve the prognosis of patients with unresectable HCCs compared with those receiving conservative treatments [7, 8]. Two meta-analyses also demonstrated the clinical usefulness of TACE in prolonging HCC patients' survival [9, 10]. Given that GS is used in most procedures, TACE using GS helps to improve the prognosis of patients with unresectable HCCs.

Although there is a lack of high-level evidence, GS embolization for RCC has been applied in an attempt to reduce blood loss during nephrectomy, improve symptoms related to unresectable tumors, and stop bleeding from tumors [27, 28]. However, the superiority of GS over other embolic agents, such as ethanol, metallic coils, acrylic microspheres, and polyvinyl alcohol (PVA) particles, has not been proven.

CQ3b: Which bleeding conditions are indicated for GS embolization?

Recommendations

Arterial embolization using GS is effective for postpartum bleeding, gastrointestinal (GI) bleeding, trauma, tumor rupture, and hemoptysis (recommended grade C1). However, there is insufficient scientific evidence regarding the combined use of GS and other embolic agents (recommended grade C2).

Specific comments

The success rates of hemostasis by transcatheter arterial embolization (TAE) using GS for postpartum hemorrhage are very high [29–31]. In addition, embolization has the advantage that fertility may be maintained because of the avoidance of hysterectomy. Menstruation restarts in 93–100 % of patients after GS embolization [29, 31]. GS embolization is also effective for traumatic bleeding, GI bleeding, tumor rupture, and hemoptysis. In patients with ruptured HCC, the survival period was significantly prolonged from 13.0 to 98.5 days when GS embolization was performed in order to stop the bleeding [32].

According to a comparison of the embolic effects of GS, microcoils, and *n*-butyl-cyanoacrylate (NBCA) for traumatic or GI bleeding, the primary hemostatic rate of the NBCA group was significantly higher than that of the GS group (100 and 67 %, respectively, $p = 0.009$), and the rebleeding rate of the GS group (23 %) was significantly higher than that of the microcoil (0 %, $p = 0.048$) and NBCA (0 %, $p = 0.048$) groups. The procedural time in the NBCA group (9 ± 4 min) was significantly shorter than that in the microcoil (37 ± 19 min, $p = 0.001$) and GS (25 ± 10 min, $p = 0.001$) groups [33]. Additionally, in patients with a coagulopathic condition, who have a prothrombin time-international normalized ratio (PT-INR) >1.5, platelet counts <50,000/ml, or an activated coagulation time (ACT) >400 s, GS embolization has risks of incomplete embolization and rebleeding; therefore, the use of NBCA is recommended [33, 34].

With regard to the choice of embolic agents, GS is suitable for diffuse bleeding, and coils are recommended for localized hemorrhage [17]. Additionally, several embolic agents should be appropriately selected according to the size of the target vessel; GS is recommended for small vessels, a combination of GS and coils for medium-sized vessels, and coils for large vessels [35]. In bronchial artery embolization (BAE) using GS for hemoptysis, the primary hemostatic and rebleeding rates in the midterm results ranged from 73 to 99 % and 10 to 55.3 %, respectively [36]. Hahn et al. [37] reported that the midterm results of BAE using GS were inferior to those using PVA particles, although there were no significant differences in the technical and short-term clinical success rates.

CQ3c: Which benign tumors are indicated for GS embolization?

Recommendations

Uterine artery embolization (UAE) using GS for uterine fibroids is effective for relieving bulk-related symptoms (recommended grade B). However, there is insufficient scientific evidence regarding GS embolization for other hypervascular benign tumors, including renal angiomyolipomas (recommended grade C2).

Specific comments

UAE using GS is effective in improving bulk-related symptoms caused by uterine fibroids [12–15]. Katsumori et al. [14] reported that 100 % necrosis of uterine fibroids was achieved in 64.3 % (142/221 cases), 90-99 % necrosis in 33.5 % (74/221), and <90 % necrosis in 2.6 % (5/221) 1 week after UAE using GS. Both the initial success (98 % for menorrhagia and 97 % for bulk-related symptoms) and long-term symptom improvement rates (96.9 % at 1 year, 94.5 % at 2 years, 89.5 % at 3 years, 89.5 % at 4 years, and 89.5 % at 5 years) were similar to those of UAE using PVA particles [13]. A multicenter phase I/II study also indicated that UAE using GS was safe and had equivalent therapeutic effects compared with UAE using other embolic agents [15]. However, it is unclear whether or not fertility can be preserved after UAE using GS, because no pregnant cases have been reported.

With regard to the application of GS embolization for other benign hypervascular tumors, there are a few case reports of GS embolization for hepatocellular adenoma [38]. TAE of renal angiomyolipoma aimed at hemostasis or the relief of bulk-related symptoms has been reported; however, GS is not necessarily used in all patients, and other embolic agents, such as a mixture of ethanol and iodized oil or metallic coils are also combined [39, 40].

CQ3d: Is preoperative GS embolization for hypervascular tumors effective?

Recommendations

TAE with GS can be used for preoperative management of hypervascular tumors in order to reduce perioperative blood loss (recommended grade C1).

Specific comments

It has been reported that preoperative tumor embolization using GS is useful for reducing bleeding and perioperative blood loss for primary and metastatic bone tumors, RCCs, uterine fibroids, glomus tumors, and paragangliomas [28, 41–49]. Preoperative embolization is usually performed within 14 days, mostly within 3 days, before surgical intervention [41–43]. Although most studies are uncontrolled studies or case series, a few high-level evidence-based studies have shown the clinical utility of preoperative tumor embolization using GS. However, the efficacy of preoperative embolization for HCC is controversial, and there is insufficient scientific evidence to conclude whether or not preoperative embolization using GS improves the survival of patients with HCC [50–53]. Although Lu et al. [53] did not identify any advantage of using preoperative TACE for improving either overall or recurrence-free survival in patients with HCCs measuring 2–8 cm in their maximum diameter, they found a survival benefit in a patient group with HCCs >8 cm. This suggests that tumor shrinkage by preoperative TACE can facilitate safe and curative surgical resection, especially in large tumors.

CQ3e: Is GS embolization effective for hypersplenism?

Recommendations

Partial splenic embolization (PSE) using GS is effective in improving thrombocytopenia due to hypersplenism and chronic idiopathic thrombocytopenic purpura (recommended grade C1).

Specific comments

The usefulness of PSE with GS for hypersplenism associated with liver cirrhosis or chronic idiopathic thrombocytopenic purpura has been reported [54–60]. The percentage of embolized splenic tissues strongly influences the therapeutic effects and complications of PSE. No increase of platelets was achieved when areas <50 % of the splenic volume were embolized [55, 57]. In contrast, serious complications, such as splenic abscess, developed when areas >70 % of the splenic volume were embolized [54]. Therefore, the embolization rate should not exceed 70 % of the splenic volume. Although PSE using GS is effective for hyersplenism, a more favorable increase of platelets and white blood cells at 3 years after PSE using PVA was reported compared with PSE using GS ($p < 0.05$) [54]. The size of GS particles used in PSE varies in each report ranging from 1 to 5 mm [54–58], and the optimal size is still unclear. The advantages of metallic coils for PSE are also unknown [61].

CQ3f: Can GS embolization be used for preoperative portal vein embolization?

Recommendations

Preoperative portal vein embolization (PVE) using GS mixed with iodized oil can be performed in an attempt to induce the hypertrophy of the future remnant liver to increase the safety of major hepatectomy; however, there is not enough scientific evidence indicating the advantage of this embolic agent in PVE (recommended grade C1).

Specific comments

Generally, the embolic effects of GS in PVE are insufficient because recanalization of the portal vein is frequently observed [62]. Ohkawa et al. [63] reported that the characteristic of ''non-dissolubility'' could be induced by mixing GS particles and iodized oil. Iodized oil coating GS surfaces can make it difficult for GS to dissolve and reduce recanalization of the portal vein. Kakizawa et al. [64] also reported the usefulness of this embolic agent in PVE. However, the efficacy of this embolic agent has still not been established because another report indicated that recanalization of the portal vein was observed in 1/3 of patients who underwent PVE using the same embolic agent [65]. In addition, the superiority of this embolic material over other embolic agents, such as ethanol, has not been proven.

Complications of GS embolization

CQ4: Which complications may develop after GS embolization?

Recommendations

Anaphylaxis rarely occurs as a reaction to allocollagen of GS. Ischemic and/or infectious complications may develop after GS embolization. The incidences and grades of these complications are influenced by the size of the embolized areas, particle size, and magnitude of embolization. Nontargeted embolization may also occur when GS particles inadvertently overflow into nontargeted vessels.

Specific comments

Spongel and Serescue are composed of bovine collagen and Gelfoam is made up of porcine collagen [1]; therefore, these materials may cause many antibody-mediated reactions. Intraoperative anaphylaxis induced by the gelatin component of thrombin-soaked Gelfoam was reported in

two pediatric patients [66, 67]. Granulomatous arteritis caused by a hypersensitivity reaction against gelatin also develops when GS particles are used as an embolic agent [25, 68].

Several ischemic and/or infectious complications have been reported after GS embolization [13, 16, 17, 69–77]. Liver abscess is a common infectious complication after TACE for HCC. Additional ischemic complications, such as hepatic infarction, gallbladder infarction, bile duct necrosis, pancreatitis, gastrointestinal infarction, and splenic embolization, may also develop. Pelvic abscess and uterine and bladder necrosis after pelvic embolization, splenic abscess after PSE, and gastric and intestinal infarction after embolization for GI bleeding have been reported. The incidences and grades of ischemic complications generally depend on the size of the embolized areas, particle size, and magnitude of embolization.

Ischemic complications are often related to nontargeted embolization [73, 77]. This might happen when nontargeted branches are inadvertently embolized by refluxed GS particles; therefore, GS should be carefully injected to avoid reflux during intra-arterial injection.

CQ5: How can we use GS particles safely?

Recommendations

We should carefully use GS particles <500 μm for TACE of HCC (recommended grade C1). In addition, we should use 1-mm Gelpart particles for UAE (recommended grade C1).

Specific comments

In an experimental study by Sonomura et al. [78], hepatic arterial embolization using GS particles >500 μm did not cause necrosis of the bile duct, gall bladder, or pancreas; however, GS particles <200 and 200–500 μm induced bile duct necrosis. In addition, GS particles <200 μm also induced pancreatic necrosis. In the clinical cases, bile duct necrosis and pancreatic injury caused by GS powder have also been reported [74, 77]. However, these procedures were undertaken without a microcatheter, and so the situation might be different in the present clinical setting. Since the introduction of a microcatheter into TAE and TACE procedures, GS particles of 200–500 μm in diameter can be used at the more peripheral hepatic arterial branches without severe complications [11] and microspheres <100 μm in diameter are also used in Western countries [79]. Ischemic complications after GS embolization may be related to the embolization point and magnitude of embolization rather than the particle size.

In an experimental study of UAE reported by Sone et al. [80], 1- and 2-mm Gelpart particles occluded almost the same-sized arteries (478 and 465 μm, respectively). As for the extent of microscopic necrosis, no statistically significant differences were observed between 1- and 2-mm particles. However, the qualitative inflammatory reaction around embolized arteries was significantly greater with 2-mm particles compared to 1-mm particles ($p < 0.001$). Therefore, 1-mm Gelpart particles should be selected when UAE is performed using Gelpart.

CQ6: What are the technical tips for using GS effectively and safely?

Recommendations

Manually prepared GS particles have jagged edges and the particle size is not uniform; however, the manual preparation of GS particles has the advantage of being able to control the particle size according to the disease condition or targeted vessel diameter. A catheter should be advanced into the target vessel as selectively as possible to keep embolized areas to a minimum when GS embolization is performed.

Specific comments

The sizes of GS particles cut with scissors into small cubes are relatively uniform compared to those crushed by the pumping method using two syringes and three-way stopcock valve [81]; however, the cutting method requires time and skill. On the other hand, the pumping method makes GS particle production speedy and easy [82]. Pumping back and forth 30 times mainly produces particles of 800 μm–1.6 mm in diameter; however, it involves a significantly higher rate of including small particles ≤500 μm, as well as larger particles >2,000 μm, compared with the cutting method [81]. In addition, the pumping method involves a significantly higher rate of producing smaller particles ≤500 μm in Spongel compared with Gelfoam [81]. Pumping back and forth 50 times mainly produces particles of 200–400 μm in diameter [11]. Gelpart particles can also be crushed with the pumping method [83]. There are no data about Serescue particle production; however, the similar-sized particles to Spongel particles could be produced with use of the above-mentioned techniques.

In previous reports, the optimal size of GS particles for TACE of HCC was ≥500 μm; however, smaller particles of 200–400 μm in diameter can be used safely at the distal hepatic arterial branches [11]. In BAE and UAE, GS particles of 500–1,000 μm in diameter are mainly used [12–14, 36, 37], as well as 1-mm Gelpart particles [15, 79]. In PSE, larger-sized GS particles of 1–5 mm in diameter that

are soaked in antibiotics are generally used to avoid splenic abscess [55–60]. However, it is usually difficult to estimate the embolized vessel diameter with GS particles, because various sized particles are included in the handmade GS particles, even in ready-made Gelpart particles [84], and the fragmentation and aggregation of handmade GS particles also frequently occurs [85].

For performing embolization, a superselective approach should be used whenever possible with a microcatheter. The injection of GS particles should be slow and must be stopped when the stasis of target vessel flow is observed. At that point, no additional GS particles should be injected and those in the catheter lumen should be retrieved by aspiration to avoid reflux of GS particles.

CQ7: How should we manage the pain associated with GS embolization?

Recommendations

Opioid analgesics are widely used for pain control associated with GS embolization without sufficient scientific evidence (recommended grade C1). For pain control associated with TACE for HCC, the administration of controlled-release oxycodone (CRO) 1 h before TACE and 12 and 24 h after the procedure is recommended (recommended grade A). In addition, the injection of 2 % lidocaine through a catheter immediately before TACE can reduce the pain (recommended grade A).

Specific comments

Opioid analgesics are widely used for the control of TAE or TACE-related pain, although there is no evidence regarding when and how these should be administered. One randomized clinical trial showed that 10–20 mg of CRO administered 1 h before TACE and 12 and 24 h after the procedure could significantly reduce the pain within 48 h compared to placebo administration ($p < 0.001$) [86]. In addition, another randomized clinical trial showed that the injection of 5 ml of 2 % lidocaine through a catheter immediately before embolization could significantly reduce the pain during and after TACE for HCC compared to lidocaine injection immediately after TACE or without lidocaine injection [87]. In Japan, lidocaine injection immediately before TACE is performed in most TACE procedures; however, a small amount of lidocaine (0.5–1 ml/embolization procedure) is only injected because it is mainly used for the prevention of vasospasm [6, 11]. The grades of pain differ in individuals and there is no gold standard for pain control during GS embolization; therefore, adequate treatment should be performed according to individual symptoms.

Conclusion

GS is an effective embolic agent for controlling tumors and stopping bleeding. Radiologists should be familiar with not only the preparation and handling of GS particles, but also their disadvantages and potential risks, in order to perform GS embolization safely and effectively.

Conflict of interest The authors declare that they have no conflict of interest.

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CIRSE

TECHNICAL NOTE

Repeated Bland-TAE Using Small Microspheres Injected via an Implantable Port–Catheter System for Liver Metastases: An Initial Experience

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Abstract
Purpose The purpose of this pilot study was to assess the effectiveness of repeated bland-TAE using small-size microspheres for liver metastases. To date, there have been no publications as to whether bland-TAE could be effective for nonhypervascular liver tumors.
Methods Bland-TAE with 100-μm, calibrated microspheres was performed in two chemoresistant patients: one with colorectal metastases and the other with gastric metastases. Both patients had multiple tumors in the entire liver. An implantable port–catheter system was placed in the hepatic artery to conduct repeated embolizations, thereby achieving enough efficacies. Microspheres were injected via the port until the disappearance of the tumor stains. Angiographies via the port were conducted 1, 3, 7, and 14 days after bland-TAE to evaluate the patency of the hepatic artery.
Results The hepatic artery started to recanalize 1 day after TAE and tumor stains appeared again during the 14 days. In both patients, bland-TAE was repeated four times in intervals of 14–21 days. The enhanced CTs showed necrotic changes and the decrease in size of the tumors. The serum CEA level decreased from 2,989 to 70 ng/ml and from 174 to 48 ng/ml, respectively. Bilomas and a liver abscess developed as complications.
Conclusions Repeated bland-TAE using 100-μm microspheres injected via an implantable port–catheter system could be effective for liver metastases, although the caution of biliary injury is needed.

Keywords Interventional oncology · Embolisation · Embolotherapy · Liver · Tumor · Neoplasm

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Introduction

Transarterial chemoembolization (TACE) and intra-arterial chemoinfusion are common interventional techniques used for secondary hepatic malignancies. However, the efficacy of these treatments for patients heavily pretreated by systemic chemotherapy is limited due to acquired drug resistance and lingering chemo-related toxicities.

Several previous reports have shown the effectiveness of bland transarterial embolization (bland-TAE), which does not use chemo agents, for hypervascular liver malignancies, including hepatocellular carcinoma (HCC) and metastases from neuroendocrine tumors (NET) [1–3]. The theory regarding bland-TAE for hypervascular tumors is to create tumor regression by the occlusion of the feeding arteries. Recently, precisely calibrated small-size microspheres,

which could occlude the finer tumor feeding arteries, have been developed [4, 5]. The question is whether bland-TAE could be effective for nonhypervascular liver tumors, including secondary liver cancer.

We conducted bland-TAE using small-size microspheres for two chemoresistant patients with multiple liver metastases. To achieve complete occlusion of fine tumor feeding artery, repeated embolization could be necessary. Therefore, we adopted an implantable port–catheter system that allows repeated injections of microspheres without having to insert a catheter for each additional treatment. An implantation of a port–catheter system also is useful to investigate the optimal treatment timing by referring to the repeated angiographies. To the best of our knowledge, this is the first report regarding the injection of microspheres using an implantable port–catheter system.

Materials and Methods

Two patients with multiple liver metastases, who had received several systemic and intra-arterial chemotherapies, were treated by bland-TAE in our hospital. Under local anesthesia, a 5-F polyurethane catheter with 2.7-F tapered tip, which was coated with a hydrophilic polymer (Anthron PU catheter; Toray Medical Tokyo) was placed in the hepatic artery via the femoral artery. The catheter tip was inserted into the gastroduodenal artery (Case 1) and the hepatic artery (Case 2), with the side hole positioned at the common hepatic artery. The gastroduodenal and right gastric arteries were embolized with metallic coils. The proximal ends of the catheters were connected to an implantable port (Selsite Port; Toray Medical) and embedded in the lower abdominal wall.

Under fluoroscopic guidance, calibrated, 100-μm microspheres (Embozene; CeloNova BioSciences, Newnan, GA), diluted 60 times with contrast material (iopamidol 150 mgI/ml), were injected slowly by hand via the port with a 2.5-ml syringe until the disappearance of the tumor stains. The injection speed was approximately 1 ml per minute. Angiographies via the port were conducted 1, 3, 7, and 14 days after bland-TAE to evaluate the patency of the hepatic artery, with the injection of 5 ml of iopamidol (300 mgI/ml) at an injection rate of 1 ml/s. Bland-TAE was repeated four times in intervals of 14–21 days. The tumor response was evaluated by contrast-enhanced CT and the tumor marker of carcinoembryonic antigen (CEA).

Case 1

A 63-year-old male with rectal liver metastases was treated. Previously, three systemic chemotherapy regimens, FOLFOX (5-fluorouracil plus leucovorin with oxaliplatin) combined with bevacizumab, FOLFIRI (5-fluorouracil plus leucovorin with irinotecan), and FOLFIRI combined with bevacizumab, and one intra-arterial therapy, cisplatin mixed with degradable starch microspheres, had been conducted. The treatment period from the initiation of the first-line therapy was 57 months. The liver metastases were rapidly growing and obstructive jaundice was observed (Fig. 1A, B). We conducted percutaneous biliary drainage before bland-TAE. The right and left hepatic bile ducts were obstructed due to the tumor invasion. The first bland-TAE was performed using 100-μm microspheres via a microcatheter that was inserted at the proximal site of the right and left hepatic arteries (Fig. 1C, D). The angiography obtained 13 days after the first TAE showed the recanalization of the hepatic arties and the tumor stains appeared again (Fig. 1E). From these results, we considered that repeated TAE was necessary to suppress the tumors. We then adopted an implantable port–catheter system as a novel technique in performing repeated bland-TAE. To investigate when the hepatic arteries would be recanalized, the angiographies were repeatedly obtained as mentioned above. Consequently, the following results were identified; the hepatic artery started to recanalize 1 day after TAE and tumor stains appeared again during 14 days after TAE. A similar finding was found after the third bland-TAE (Fig. 1F, G). A total of four bland-TAE were performed for 42 days. Two weeks after the fourth TAE, two biliary stents were placed from the hepatic segment III bile duct to the right anterior duct and the common bile duct using the partial stent–in stent technique, and then the drainage tubes were clamped. However, after 1 week, a liver abscess developed in the hepatic segment II, and percutaneous drainage was performed. The contrast-enhanced CT showed necrotic changes and the decrease in size of the tumors, although a liver abscess and a biloma were presented (Fig. 1H, I). The serum CEA level decreased from 2,989 to 70 ng/ml. Since the first bland-TAE, this patient survived for 5.8 months without receiving any additional treatments.

Case 2

A 63-year-old male with gastric liver metastases was treated. Previously, the standard systemic chemotherapy using S1 and cisplatin for 13 months and intra-arterial infusion of 5-FU, epirubicin, and mitomycin (FEM regimen) had been conducted for 2 months. The liver metastases were rapidly growing when the patient came to our hospital (Fig. 2A, B). An implantable port–catheter system had been already placed for the previous intra-arterial chemoinfusion. The repeated bland-TAE was performed with the same methods as discussed in case 1. The recanalization times of the hepatic arteries were similar to those of case 1, and a total of four

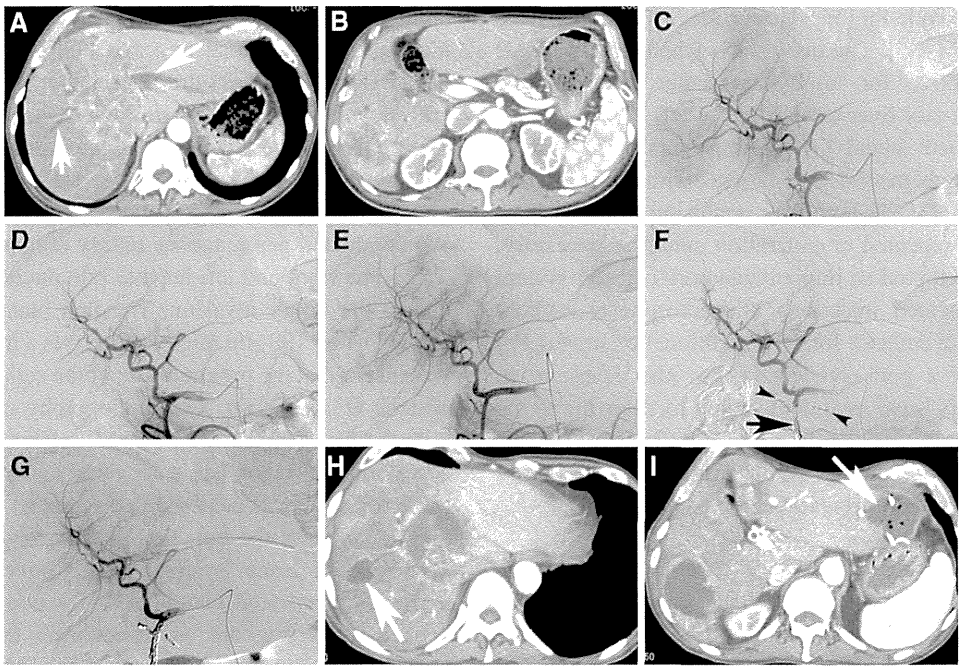

Fig. 1 A 63-year-old male with rectal liver metastases. **A**, **B** CT before treatment showed large tumors located in the hepatic hilum and the right hepatic lobe. The intrahepatic bile ducts were dilated by the tumor invasion. **C** Hepatic arteriography before the first bland-TAE showed large and fine tumor stains in the liver. **D** Hepatic arteriography immediately after the first bland-TAE showed that tumor stains disappeared. **E** Hepatic arteriography conducted 13 days after the first bland-TAE showed the tumor stains obviously appeared again. **F** Hepatic arteriography via the implantable port–catheter system, which was obtained immediately after the third bland-TAE, showed that tumor stains disappeared. The catheter tip was inserted into the gastroduodenal artery, which was fixed with metallic coils (*arrow*). The right gastric artery and the posterior superior pancreaticoduodenal artery also were embolized with coils (*arrowheads*). **G** Hepatic arteriography via the port conducted 14 days after the third bland-TAE showed the tumor stains had still remained, although the reduction of the stain was seen. **H**, **I** CT obtained 2 months after the initiation of repeated bland-TAE successfully showed necrotic changes in the large part of the tumors. Biloma in the segment V and liver abscess in the segment III developed

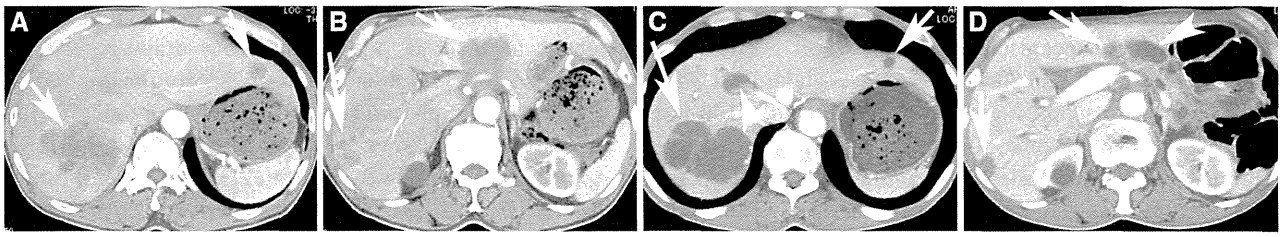

Fig. 2 A 63-year-old male with gastric liver metastases. **A**, **B** CT obtained before the first bland-TAE showed multiple liver metastases in the bilateral hepatic lobes (*arrows*). **C**, **D** CT obtained 2 months after the initiation of repeated bland-TAE showed necrotic changes of the tumors (*arrows*), although bilomas developed (*arrowheads*)

bland-TAE were conducted for 49 days. After the fourth TAE via the port, a microcatheter was inserted and the extrahepatic collateral blood supplies, the dorsal, and the inferior phrenic arteries were embolized using 100-μm microspheres. In this patient, systemic chemotherapy of irinotecan (150 mg/m^2 every 2 weeks) was combined with bland-TAE concurrently. Full doses of irinotecan were administered four times without severe adverse effects during the treatment period of the repeated bland-TAE. The contrast-enhanced CT obtained after treatments showed the necrotic changes and decrease in the size of the tumors, although a biloma was presented (Fig. 2C, D). The serum CEA level decreased from 174 to 48 ng/ml. After that, systemic chemotherapy of irinotecan alone was continued for a maintenance therapy, but eventually the tumors could not be controlled. Since the first bland-TAE, this patient has survived for 10 months, and to date he is receiving additional systemic chemotherapy.

Discussion

Currently, the following interventional therapeutic strategies are being used for treatments of liver metastases: intra-

arterial chemoinfusion, irinotecan-eluting beads (DEBIRI) TACE, and yttrium-90 (^{90}Y) radioembolization [6]. At present, DEBIRI and ^{90}Y-radioembolization are not available in Japan. Previously, there have been no reports regarding bland-TAE for liver metastases, except for hypervascular NET metastases. We conducted bland-TAE for two cases because of the following reasons: in case 1, the patient had received various standard chemotherapies for a long period and was considered to be chemoresistant, and in case 2, two chemotherapies had failed and the prediction of the next-line chemotherapy was low.

In both cases, bland-TAE using calibrated 100-μm microspheres successfully achieved tumor regression for liver metastases that did not have hypervascularity. These results could be caused by peripheral occlusion of the tumor feeding arteries due to the microspheres' characteristics with uniform, small, and spherical shapes. Recently, Bonomo et al. [7] reported that the combination of bland-TAE using 100-μm microspheres and radiofrequency ablation obtained large coagulation volume for liver metastases. This result indicated that 100-μm microspheres could occlude peripheral site of the tumor feeding arteries to prevent heat-sink effect.

In the combination with systemic chemotherapy, bland-TAE could have an advantage of not requiring dose reduction of systemic chemo-drugs, whereas in TACE and intra-arterial chemoinfusion the total chemo dose needs to be considered due to chemotoxicity. In case 2, systemic chemotherapy using irinotecan was successfully combined with bland-TAE without any severe toxicity.

Superselective TAE is the widely used technique for isolated live tumors, which could avoid causing severe damages to the normal part of the liver. On the other hand, for multiple liver tumors located in the entire liver, TAE via the proximal site of the hepatic artery is inevitable. The technique of injecting microspheres via the indwelling catheters placed in the common hepatic artery should be used for multiple liver tumors.

An implantable port–catheter system was developed for intra-arterial chemoinfusion for the injection of solution only [8, 9]. Microspheres of 100 μm in size could be injected via the port–catheter system without system obstruction. Currently, we are conducting a research study to investigate the feasibility of injecting various sizes of microspheres using an implantable port–catheter system.

Spherically shaped microspheres could precisely occlude the targeted vessels compared with nonspherical materials. However, previous animal and clinical studies demonstrated that recanalization were evident after embolization with spherical particles [10–12]. In our cases, the repeated angiographies via the ports demonstrated early recanalization of the tumor feeding vessels during the first 14 days after TAE.

The reasons for the recanalization are considered as follows: (i) Redistribution of the embolic agent due to pulsatile blood flow. The microspheres are pushed more distally into the hepatic artery, which allows reperfusion of the proximally located tumor feeding arteries. (ii) Thrombus resorption: Resorption of the thrombus formation, which is located in the interspace between the microspheres, could cause recanalization [10, 11]. To achieve a good response in one treatment session could be difficult particularly in the tumors with fine vascularity. Therefore, repeated TAE is necessary.

An implantable port–catheter system was clearly beneficial in case 2, in which the system had been already implanted before TAE. However, in case 1, the repeated catheter insertion every 14 days without the system implantation could be another option, because the repeatability of TACE would be limited and the developments of the collateral blood supply would occur due to hepatic arterial occlusion.

Bilomas were found in both cases and a liver abscess developed in case 1, although the liver abscess may not have been related to bland-TAE, because this patient had the bile duct obstructions before TACE and the abscess was found in the nondrainage area. Biloma is a result from necrosis of the bile duct due to ischemic damage of the peribiliary plexus which is the main feeder to the bile duct wall [13]. In our two cases, peribiliary plexus could be tightly occluded with 100-μm microspheres. The size selection of microspheres is the key to achieve tumor necrosis without severe complications. In general, it is considered that small microspheres lead to biliary damages [14, 15], although Guiu et al. [16] reported that 500–700-μm drug-eluting beads frequently caused biliary injury and discussed that small size beads might reduce complications. Another important factor in bland-TAE for nonhypervascular tumors is to determine the endpoint of injecting the microspheres. Injecting over doses of microspheres in order to obtain complete necrosis of the tumor could cause severe damages of the biliary tract.

In conclusion, our pilot study involving two cases demonstrated that repeated bland-TAE using 100-μm microspheres injected via an implantable port–catheter system could be effective for liver metastases, although caution is needed for biliary injury. Further studies to investigate the optimal TAE endpoint and size selection of microspheres are necessary to establish safer bland-TAE for liver metastases.

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