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Novel reflux-control microcatheter: an alternative to maximize the effect of superselective embolization

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ABSTRACT

In the following technical note, after appropriately selecting three patients with intermediate-stage hepatocarcinoma (HCC), who are candidates for transarterial chemoembolization (TACE), we describe and show details of the TACE procedure performed with a novel reflux-control microcatheter (Sequre®, Guerbet). Through a typical endovascular approach and angiographical imaging, lesions were identified and then treated supra-selectively with the microcatheter, whose particularity is to limit the reflux of particles to non-target areas.
Autor para correspondencia:

INTRODUCTION

The field of interventional radiology is progressing rapidly in parallel with technological advances. New materials usually simplify daily work, improving technical performance, expand the indications of use for many devices and often increase the 24 survival rates in patients. However, these rapid technical advances may also lead to new complications or changes in the mechanisms of their development. Complications due to embolization and chemoembolization procedures are usually reported and well described in the medical literature, although the underlying mechanisms are not always well explained[1, 2, 3].

Transarterial chemoembolization (TACE) belongs to the arterially directed embolization procedures and is a widely used locoregional therapy for the treatment of unresectable hepatocellular carcinoma (HCC) from early to advances stages. Drug-eluting beads (DEB)-TACE has been shown to provide slow drug elution, reduced liver and systemic toxicity increased local drug concentration, and tissue necrosis[4, 5].

Aside from TACE, other transarterial options include bland embolization, or hepatic artery embolization (HAE), and transarterial radioembolization (TARE). All have an acceptable safety profile, and each has its associated procedural and peri-procedural complications[6, 7].

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One potential complication that may occur during all embolization procedures is when the embolic material migrates outside the desired treatment area, leading to a non-target embolization (NTE). When collateral vessels are embolized, there is a risk of embolizing branches indicating non-target tissue or organ embolization, which can lead to different consequences, depending on the location.

NTE following TACE, in particular, has two dangerous characteristics for the healthy tissue, one is ischemia, and the other is directly related to the cytotoxicity from the chemotherapeutic agent. For example, cutaneous problems, such as itching, erythema, and necrosis, may arise when the internal mammary, intercostal, or lumbar artery are embolized[6]. Gastrointestinal erosion, ulceration, or perforation can be caused by gastric, omental[4,8], and colic branch artery embolization. Paraplegia may result from the inadvertent embolization of spinal branches arising from intercostal or lumbar collateral vessels, and embolization of the cystic artery may cause cholecystitis or gallbladder infarction. Chemoembolization of the inferior phrenic artery may result in shoulder pain, pleural effusion, or basal atelectasis[7].

NTE is highly recognized and different complications can be caused by it, there may appear to be no evidence of NTE during the intraprocedural imaging. Post-procedural imaging like 57 Computed tomography (CT) can allow the recognition of NTE that otherwise could be clinically unrevealed, which might not be associated with an adverse clinical outcome. Cone-beam CT (CBCT) is also likely to help detect and therefore reduce NTE8. These sophisticated imaging techniques have particular importance during TACE procedures when treating extrahepatic vessels that may supply hepatic tumors. In light of such considerations, meticulous and thorough angiographic examinations, as well as a good understanding of classic and variant hepatic anatomy are vital to reduce the incidence of NTE.

It is important to analyze the incidence of NTE after an embolization procedure, especially to assess the effect on complication rate and length of hospital stay.

To avoid the complications due to NTE, apart from the aforementioned importance of the pre-, intra- and post-procedural imaging, selective catheterization should be achieved by placing the microcatheter tip as close as possible to the specific branch or branches supplying the desired target[7]. Embolic materials should be infused at a slow rate and in a controlled manner, to reduce reflux into a non-target vessel[4, 8, 9].

Coils and gelatin sponge particles may also be used to occlude and protect the territory of the normal distal branches before embolization, although this solution is not always feasible nor convenient.

However, even CBCT or CT-angiography with the microcatheter in the vessel to be embolized will not eliminate the risk of NTE, since NTE may occur as a result of changes in flow dynamics that occur during the embolization procedure, particularly when the endpoint is the flow stasis. These changes could result in reflux into non-target territories, which could be prevented with the use of specific microcatheters intended to reduce reflux. The importance of using a dedicated delivery device which prevents reflux should be taken into consideration, to optimize and save time during embolization procedures.

Microcatheters are commonly used during most arterial embolization procedures. SeQure® (Guerbet, Roissy, France) is an innovative reflux-control microcatheter for peripheral embolization procedures which relies on flow dynamics as the foundation of its mechanism of action. It can optimize the delivery of calibrated microspheres of specific sizes.

The device has a regular microcatheter characteristic with a non-tapered internal lumen for the delivery of embolics, and two radiopaque markers (placed at a distance of 11 mm) at the tip (distal marker being at 0.5-1 mm from the point of exit). Near the distal atraumatic tip, between the two markers, it has a specific characteristic of side slits (approximately 50 µm in width) which allows contrast media to exit radially in addition to the standard fluid flow through the distal tip of the catheter. The contrast 94 media that comes out of the side-holes creates turbulence in the space surrounding the slits, between microcatheter and vessel, which acts as a fluid barrier in that given portion. This fluid-dynamic barrier redirects the beads that tend to create upstream reflux back to their flow-directed trajectory, preventing the beads from refluxing into non-target areas, and thus eliminating, or strongly reducing, undesired NTE. Moreover, Sequre® allows for the hemodynamic arrangement to be preserved, by favoring and maintaining unaltered the natural blood flow. The side slit patterns are specifically configured per catheter size. These patterns were designed to enable the contrast media to exit radially with the same effect in the different microcatheters, despite the dimensional differences, allowing the diverse models to be compatible with variable embolic beads sizes. Under fluoroscopy, the radial flow of contrast media exiting through the side holes in the SEQURE®

microcatheter can be seen, giving the physician indication of the vessel flow dynamics. This design not only attempts to reduce the risks of NTE, with less potential damage to surrounding tissue but may deliver more amount of treatment embolic, as the beads are redirected towards the target.

The purpose of this study is to demonstrate early results and the expert opinion after initial experience in two patients using specific antireflux microcatheter (SEQURE®) in the treatment of unresectable HCC with TACE.

MATERIALS AND METHODS

PATIENTS

1. A 61-year-old man with a medical history of alcoholic liver cirrhosis under routine surveillance in the hepatology outpatient clinic underwent percutaneous microwave ablation of focal HCC of 3.1 cm under US guidance.

   Four months later, pre-procedural abdominal CT and Magnetic resonance imaging (MRI) imaging demonstrated multiple liver lesions, with a dominant lesion in the IV hepatic segment of 55 mm of diameter that showed significant growth. Further workup revealed an aspartate aminotransferase level of 65 U/L (normal range, 124 0-39 U/L), an alanine aminotransferase level of 60 U/L (normal range, 7-41 U/L), alkaline phosphatase level of 85 U/L, total bilirubin level of 1.2 mg/dl, negative hepatitis serology, normal renal function, alpha-fetoprotein level of 11 UI/ml (normal range, 0-5 UI/ml). The multidisciplinary liver tumor board consensus was a recommendation for chemoembolization, (intermediate stage patient, according to BCLC), to limit disease progression, downstaging it, and potentially select the patient for a future liver transplant.
2. 75-year-old woman with a medical history of C virus cirrhosis diagnosed in the past 21 years under routine surveillance in the hepatology clinic. During the last liver CT imaging control, two HCC lesions greater than 3 cm were demonstrated at right lobe liver segments. The HCC dominant lesion was located in segment VIII with a major diameter of 42 mm. Further workup revealed an aspartate aminotransferase level of 82 U/L (normal range, 0-39 U/L), an alanine aminotransferase level of 65 U/L (normal range, 7-41 U/L), alkaline phosphatase level of 92 U/L (normal range, 47-111 U/L), total bilirubin level of 1.5 mg/dl, normal renal function, alpha-fetoprotein level of 13 µg/L. The multidisciplinary liver tumor board consensus was a recommendation for chemoembolization, (intermediate stage patient, according to BCLC), to limit disease progression.

PROCEDURE

The procedure was carried out by two interventional radiologists with an experience of 11 and 17 years, respectively, performing TACE in unresectable HCC.

CASE 1:

After local anesthesia (mepivacaine 2%), a 5-FR sheath (Terumo®, Tokyo, Japan) was inserted into the femoral artery. Using a combination of a C2 – 5FR catheter and hydrophilic guidewire of 0.035 inches, the celiac trunk and the proper hepatic artery were catheterized. Angiography was then performed to study and identify the pathological vessels leading to the lesion and segment VI, collateral arteries, and the potential presence of arteriovenous fistulae or malformations.

Once the angiographic images were carefully assessed, the 2.8Fr SeQure® microcatheter (Guerbet, Roissy, France) was advanced on a 0.014" guidewire, 165 cm (Transend®, Boston Scientific, Marlborough, MA, US) right hepatic artery branch feeding the target lesion, in segment VI (Figure 1). Another selective angiography was then performed from the microcatheter to better study the peripheral branches of the catheterized vessel. Once the microcatheter was placed in the desired position, embolization was performed using 300-500 µm DC-beads®, BTG (Boston Scientific Corporation) mixed with saline solution and iodinated contrast (ratio 1:1). The injection was carried out slowly until the reflux of the embolizing material became evident at the proximal radiopaque mark of the microcatheter (Figure 2). By avoiding, or

CATHETER	CATHETER OD	Length (cm)	Inner diameter (in/cm)	Max GW (in)	Embolic Compatibily	Max injection pressure
SEQURE®	2.4 Fr (0.8mm)	105, 130 150	0.022'' (0.57 mm)	0.018''	Medium Embolics (70-500 µm)	1200 PSI
SEQURE®	2.7 Fr (0.9mm)	105, 130, 150	0.025'' (0.65 mm)	0.021''	Medium Embolics (70-500 µm)	1200 PSI
SEQURE®	2.8 Fr (0.93mm)	105, 130 150	0.027'' (0.70 mm)	0.021''	Medium-Large Embolics (70-700 µm)	1200 PSI

strongly reducing, the reflux of particles, non-target embolization was also highly controlled during the procedure. The injection was stopped when the blood flow was slowed, and the typical endpoint was reached once stasis was achieved. The complete occlusion of the branches feeding the tumor was achieved (Figure 3). Final control angiography was performed, which demonstrated a successful embolization.

Figure 1. Hepatic artery angiogram demonstrated a dominant hepatocarcinoma lesion located in segment VI.

The total amount of doxorubicin administered was 150 mg, 47 minutes of procedure duration, and fluoroscopy time 13 minutes. No immediate complications were observed. The patient was discharged after 48 hours without postembolization syndrome.

CASE 2:

After local anesthesia (mepivacaine 2%), a 5-Fr sheath was inserted into the common femoral artery. Using a combination of a C2 of a 5-Fr catheter and hydrophilic guidewire of 0.035 inches, the celiac trunk and the proper hepatic artery was catheterized. Angiography was then performed to study and identify the pathological vessels leading to the lesion and segment VIII, collateral arteries, and the potential presence of arteriovenous fistula or malformations.

Once the angiographic images were carefully assessed, the 2.8Fr SeQure® microcatheter (Guerbet, Roissy, France) was advanced on a 0.014" guidewire, 165 cm (Transend®, Boston Scientific, Marlborough, MA, US) 181 into the right hepatic artery branch feeding the target lesion, in segment VIII (Figure 4).

Another selective angiography was then performed from the microcatheter to better study the peripheral branches of the catheterized vessel. Once the microcatheter was placed in the desired position, embolization was performed using 100 µm Embozene TANDEM®

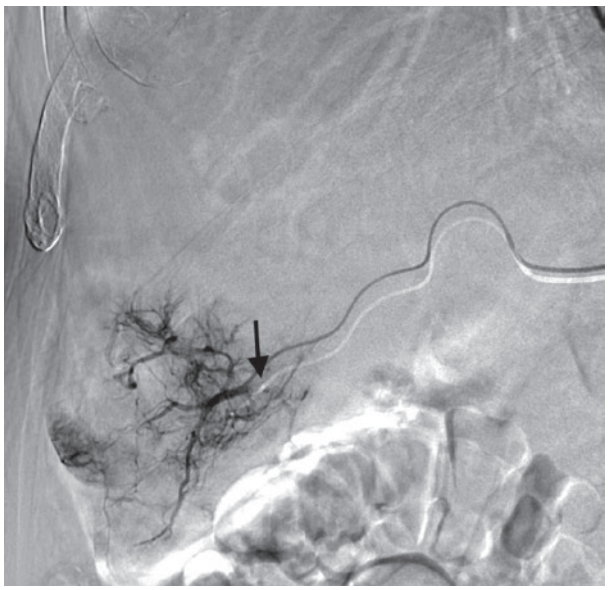

Figure 2. A 2.8 French Sequre® Guerbet microcatheter (Roissy, France) was advanced to the feeding tumoral artery and embolization was performed without undesired occlusion of other right segmental arteries. Microcatheter proximal radiopaque mark (black arrow).

Figure 3. After embolization, there was no further flow into the tumoral branch vessel. Arterial flow into other segmental nontarget branches.

microspheres, (Varian Medical Devices, Palo Alto, CA, US) 3 cc of microspheres solution mixed with 5 cc saline solution and 7 cc of iodinated contrast.

The injection was carried out slowly until the reflux of the embolizing material became evident at the proximal radiopaque mark of the microcatheter (Figure 5). Is important to consider flushing with saline solution after each microspheres doses injection to prevent microcatheter clogging. By avoiding, or strongly reducing, the reflux of particles, non-target embolization was also highly controlled during the procedure.

The injection was stopped when the blood flow was slowed, and the endpoint was reached once stasis was achieved. The complete occlusion of the branches feeding the tumor was achieved (Figure 6). Final control angiography was performed, which demonstrated a successful embolization.

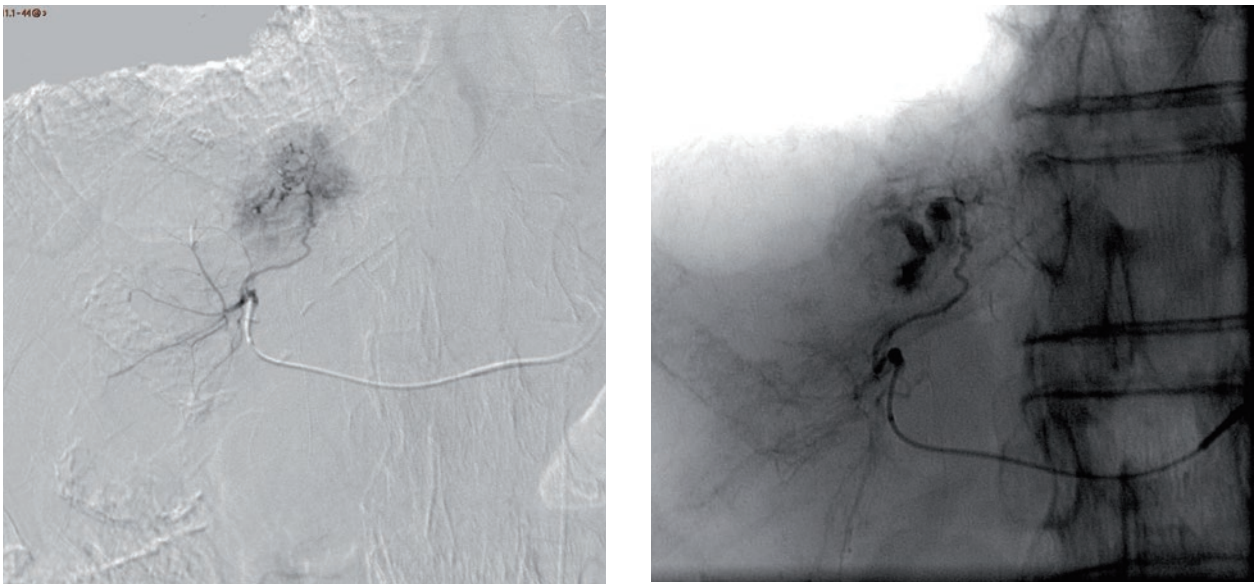

Figure 4. Hepatic artery super selective angiogram demonstrated a hepatocarcinoma lesion located in the segment VIII.

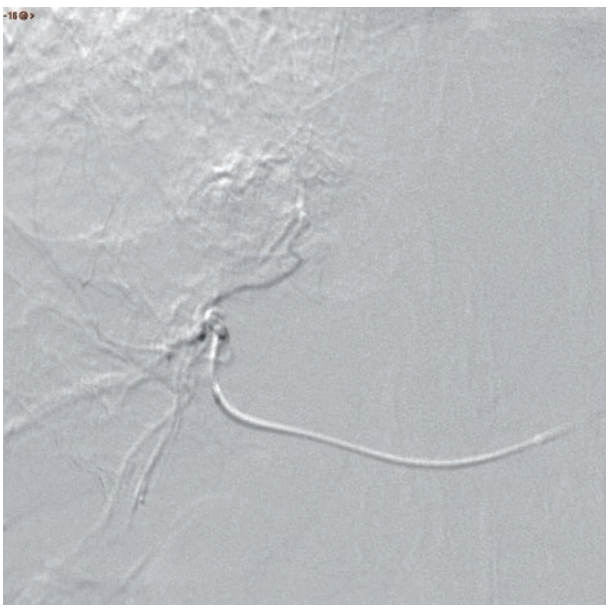

Figure 5. A 2.8 French Sequre® Guerbet microcatheter (Roissy, France) was advanced to the feeding tumoral artery and embolization was performed without undesired occlusion of other right segmental arteries. Microcatheter proximal radiopaque mark (black arrow).

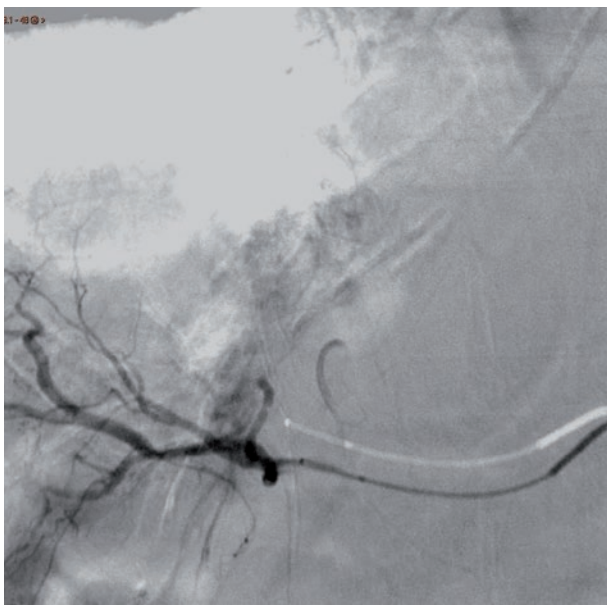

Figure 6. The final hepatic angiogram showed occlusion of the desire arterial branch. No evidence of nontarget embolization.

The total amount of doxorubicin administered was 75 mg. No immediate complications were observed. The patient was discharged after 48 hours with the mild postembolization syndrome.

THE EXPERT OPINION

SeQure® microcatheter (Guerbet, Roissy, France) provides similar visibility and trackability than other very known microcatheters in our practice. Additionally, this device is compatible with 5Fr catheters, and microwires ranging from 0.014''to 0.018''. Possibly, this device allows the same or a higher load of embolization material (particles loaded with doxorubicin in this technical note) to be inserted more safely than other microcatheters by allowing more clear control of reflux and nontarget embolization. Future studies will be aimed at demonstrating this possibility. It is very important to remember that during particle administration, we must perform it at a steady pace and flushing with saline solution to avoid clogging of the microcatheter.

DISCUSSION

In recent years, with the increasing amount of embolization procedures for different therapeutic indications, many new materials have become available for clinical use, alongside potential complications that must be constantly monitored, to guarantee safe and effective procedures[7, 8].

Besides complications like drug toxicity, allergic reactions, and bleeding of the puncture site, the potential consequences of inadvertent involuntary of NTE, mainly due to nonvisible reflux of embolic material, remains one of the main challenges to be addressed in interventional radiology[4]. Particle reflux during tumor embolization or chemoembolization procedures, particularly in the liver, has always been considered one of the most important mechanisms leading to the development of potential negative clinical consequences, such as an increase in mortality and morbidity with consequential lengthening of hospitalization stay.

Factors influencing the severity of complications related to NTE include the amount of reflux material, size and type of embolic material used, the organ involved in reflux, the functional status of the affected organ, collateral perfusion, and the patient's general condition.

A large number of complications have been described in association with embolization techniques; however, their rate varies widely in the different series because not all institutions use the same embolization techniques, and because the inclusion criteria and patient selection are not always identical. The most frequently reported complications in the different series, independent of the embolization technique used, include liver infarction/abscess, acute cholecystitis, pulmonary embolism, splenic infarction, ischemic hepatitis, acute pancreatitis, gastrointestinal mucosal lesions, and spinal cord injury[5]. Overall, the most frequent causes of death associated with embolic complications are fulminant pancreatitis, spinal shock, liver necrosis, and ischemic hepatitis. When referred to the liver TACE procedures, particle reflux has normally been attributed to an increase in the injection rate during the embolization phase. However, there are many other factors which may influence it, like the pressure variations of the different vessels during embolization, and alterations of flow dynamics[1, 4, 5].

A significant factor that can influence the severity of complications is the amount of embolic material used[1, 5]. The total amount of particles injected can also lead to reflux if the target area is filled with particles and also an excessive embolization is performed. Also, the particle size plays an important role regarding that small particles can reach more distally (more peripheral) vascular areas, whereas large particles can occlude more proximal vessels more quickly, increasing the risk of embolization into other areas.

Particles, particularly small ones, can reach other areas via intra-arterial communications or collateral vessels. Both mechanisms may lead to NTE. In the case of intrahepatic NTE, liver function is another important factor influencing the severity of complications: it mostly occurs undetected and is usually not clinically relevant in patients with sufficient functional hepatic reserves (Child A-Class patients). For example, the best candidates for liver embolization are those with preserved liver function and asymptomatic multinodular tumors but without vascular invasion or extrahepatic spread, while patients with liver decompensation or hepatic failure (Child-Pugh B and C Classes) should be excluded since ischemic insult of the liver can lead to severe adverse events. Although the incidence of liver abscess following TACE is generally low (0.26–3.12%), mortality can reach as high as 20%[10]. In patients with reduced liver function, even a low degree of intrahepatic NTE may represent a serious problem[1, 3].

The elasticity of the particles used to embolize and the material of which they are made from is also an important characteristic to address for the penetration rate and therefore in the pathophysiology of NTE and

reflux. Microspheres with a high degree of elasticity are more likely to reach deep areas within the vessels. Clinical studies and the results of studies on animal models have shown that certain gelatin particles, considered to have a transient and temporary embolic effect can initially produce occlusion of a vessel on angiography. However, after some time, in the order of weeks, it is possible to detect reperfusion within the same vessel[8]. Other materials, which are permanent embolizing agents, can instead produce wide ischemic effects because of the reduced likelihood of revascularization within the same vessel. These particles may seem attractive if a permanent or long-term vascular occlusion is desired; however, the use of these particles can also result in a severe ischemic event if NTE occurs[2]. Moreover, the ability of target-specific microspheres to carry therapeutic agents (such as drugs, genes, or proteins) is essential for the treatment of liver tumors in particular.

The importance of combining therapeutics with a target-specific microsphere is the resulting capacity for concentrating high doses of therapeutic agents in the target region while minimizing systemic toxicity[4, 5]. The proposed mechanisms for drug release from particles to target cells can also affect healthy tissue if particles migrate with NTE.

Variants in vascular anatomy as well as collateral circulation are also factors that should be sufficiently known to every interventional operator to prevent NTE. A blood vessel whose origin contacts another embolized vessel increases the likelihood of NTE in this vessel, even if only low particle reflux is present. In the same way, collateral vessels that normally present reduced flow can increase their flow after embolization of other main arteries and, therefore, facilitate particle flow to other organs.

One point that has not been completely understood is the reflux of particles during angiographic control. In general, the operators performing an embolization procedure easily state that injection should be slow, with continuous fluoroscopic monitoring to ensure that there is no reflux of chemoembolization material. Angiographic control is a very important aspect during embolization, to evaluate whether more material is needed as well as to exclude particle reflux; paradoxically, this is one of the phases of particle embolization in which there is more likelihood of reflux.

Two strategies are recommended to avoid reflux and NTE induced by angiographic controls. The first is, of course, to try to reduce the velocity of the injection. The second is to recommend waiting 3–5 min before performing the last control; this gives the particles time to accumulate and compact deep in the vessels with every blood pulse. The same occurs if a microcatheter is used, which is why this component plays such an important role in embolization procedures[1, 3, 4].

CONCLUSION

The most serious complications after chemoembolization are mostly derived from inadvertent embolization and non-super selective embolizations, as well as an excessive dose of chemotherapy, which is why it is essential to choose the appropriate materials to use, to avoid complications such as liver failure, bilomas, ischemic cholecystitis, etc. Since the Precision V study, many authors have found themselves searching for the optimal treatment of TACE. Different studies have reported high percentages of toxicity concerning DEB-TACE, although most of these are incidental findings, without symptomatic repercussions.

NTE is a dynamic process that should be well understood to allow a better understanding of its effects and to prevent its development. Complications related to embolization and chemoembolization remain a problem, even with the development of low-profile catheters and the introduction of new embolization agents. Techniques described for preventing NTE include protection against reflux by use of occlusion balloons and coils or the use of dedicated delivery microcatheters.

The use of a reflux-control type of microcatheter (Sequre® Guerbet), as tested in the 2 cases presented in this technical note, is a valid alternative to reduce inadvertent NTE during embolization with microspheres. With its radiopaque markers at the tip, and a particular mechanism allowing to clear the portion of reflux from the beads, the Sequre microcatheter has slits that are smaller than the smallest particles used, creates a fluid barrier that prevents the embolic material from migrating to undesired vascular territories.

CONFLICTS OF INTEREST

All of the authors declares they have no conflict of interest.

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