Acute Pancreatitis after Embolization of Liver Tumors: Frequency and Associated Risk Factors

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Key Words
Embolization, bland · Radiology, interventional · Pancreatitis, acute · Chemoembolization, transarterial · Carcinoma, hepatocellular · Hemangioma, liver

Abstract
Introduction: Acute pancreatitis (AP) is a rare complication after liver embolization (LE) of primary and secondary liver tumors (approximately 1.7%), but it has a significant morbidity and mortality potential if associated with other complications. It usually develops early within 24 h after the LE procedure. Study Purpose: To calculate the frequency of AP after LE in our institution and to analyze the factors involved in this procedure (anatomical features, embolization materials, cytostatic drugs, technical factors). Materials and Methods: 118 LE (bland embolization and transarterial chemoembolization) were performed in our institution. The study group included 59 patients who met the following inclusion criteria: one or more LE events, with complete pre- and post-interventional laboratory studies including: serum Ca²⁺, creatinine, blood urea nitrogen, glucose, lactate dehydrogenase, aminotransferases, alkaline phosphatase, amylase, lipase, C-reactive protein, hematocrit and leukocytes. The diagnosis of AP was established according to the criteria of the Atlanta system of classification. For the statistical analysis the association between two response variables (e.g. AP after embolization and risk factor during the embolization, AP after embolization and volume of embolic material) was evaluated using Pearson’s χ² test and Fisher’s exact test. Results: The calculated frequency of AP after LE in our series was 15.2%. Amylase and lipase were elevated up to 8.7 and 20.1 times, respectively, 24 h after LE. We observed a statistically significantly lower incidence of AP in those patients who received 2 ml or less of embospheres compared with those with an embolization volume of >2 ml (Pearson’s χ² = 4.5000, Pr = 0.034, Fisher’s exact test = 0.040). Although carboplatin was administered to 7 of 9 of the patients who developed AP after the embolization procedure, there was no statistical significance (Fisher’s exact test = 0.197) for carboplatin as an AP risk factor when compared with all the patients who received this drug (n = 107). Conclusion: Although AP after LE seems to have a multifactorial etiology, both the toxicity of the antineoplastic drugs (carboplatin-related toxicity) as well as direct ischemic mechanisms (non-target embolization, reflux mechanisms) may be the most important causes of the inflammatory pancreatic reaction after LE. We suggest that systematic measurement of serum
pancreatic enzymes should be performed in cases of abdominal pain following selective LE and transarterial chemoembolization in order to confirm acute pancreatitis after embolization, which can clinically mimic a postembolization syndrome.

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Introduction

Liver embolization (LE) of malignant and non-malignant lesions is a frequently performed interventional procedure. Defined as transarterial chemoembolization (TACE) when combined with chemotherapy, it is currently used as a therapeutic option for patients with unresectable malignant liver tumors or those with tumor recurrence after surgical resection [1]. TACE is also used as an adjuvant treatment before or after surgical resection and before liver transplantation. Hence, TACE is one of the most important treatment modalities for hepatocellular carcinoma worldwide.

In selected cases of benign but clinically symptomatic liver tumors (e.g. liver hemangiomas), bland embolization (when only embolic material is used) has also been advocated as a treatment option [2].

However, occasionally both bland LE and TACE cause several minor and major complications. For example, one large meta-analysis described acute cholecystitis and ischemic hepatitis as the most frequent complications after bland LE; in patients who underwent TACE, cholecystitis and leukopenia where the most frequent complications [3]. Multiple other complications after LE have been described, such as pulmonary thromboembolism, hepatic infarct, liver abscess, liver failure, ischemic biliary strictures and less frequently pancreatic damage [4].

Acute pancreatitis (AP) is a rare complication after embolization and TACE of primary and secondary liver tumors, and usually develops within 24 h of the procedure. As reported in the literature, AP occurs in nearly 1.7–2% of all patients after selective and superselective LE [5]. However, it might bear a significant potential for morbidity and mortality. Since we have identified this complication in many of our patients after LE, we analyzed the frequency of subclinical and clinical symptomatic AP resulting both from TACE and bland embolization of liver tumors in our institution. The anatomic features of the embolized tumors, material used, and other potentially associated risk factors for the development of AP were evaluated.

Material and Methods

Between March 2003 and October 2005, a total of 205 LE were performed in 81 patients. These patients underwent one or more LE episodes with (TACE) or without (bland LE) concomitant intra-arterial chemotherapy. Seventy consecutive patients underwent one or more TACE episodes whereas in 9 patients one or more bland embolization episodes were performed. In all malignant tumors histological confirmation was obtained prior to the LE procedure.

Inclusion and Exclusion Criteria

In this retrospective study we included those patients who underwent one or more LE interventions and met the following inclusion criteria: complete pre- and post-interventional laboratory studies including serum calcium (Ca2+), creatinine (Cr), blood urea nitrogen (BUN), glucose, lactate dehydrogenase (LDH), glutamine transferase (GOT/AST), alkaline phosphatase, amylase, lipase, C-reactive protein (CRP), hematocrit (Hct) and leukocytes.

Exclusion criteria were incomplete laboratory tests before or after LE, transarterial liver chemotherapy without embolization (chemoperfusion) and history of previous chronic pancreatitis.

Definition of Acute Pancreatitis

For the study purposes, the diagnosis of AP was established according to the criteria of the Atlanta classification system [6–8]. Generally, AP was defined as an acute pancreatic inflammatory process with variable involvement of other regional tissues or remote organ systems. Mild AP was defined as a pancreatic inflammatory process with minimal organ dysfunction with an eventful recovery.

A definite diagnosis of AP was established when serum amylase and/or lipase levels were twice the upper limits of normal and when epigastric abdominal pain, nausea and vomiting and fever (38.4–39°C) were present.

Laboratory findings included leukocytosis (10,000–30,000/μl) and clinically relevant biochemical parameters (blood glucose, calcium, CRP, bilirubin, BUN, serum alkaline phosphatase, serum ALT and AST). All the laboratory findings were assayed again 24 h after the intervention. When AP abnormalities had been confirmed, then ultrasound (US) and computer tomography (CT) examinations were performed to rule out or confirm any other complication.

Pre-Interventional Workup

Prior to every LE intervention, CT or MR imaging were performed in all patients to determine the location and size of the lesion(s), patency of the celiac trunk, hepatic artery and portal vein, as well as the presence of other pathological conditions suggesting deteriorated liver function (ascites, esophageal varices, cholestasis and multinodular liver cirrhosis).

Bland LE was indicated in cases with nonmalignant but clinically symptomatic liver tumors (e.g. liver hemangiomas) in those patients with documented allergy to the cytostatic drug and in those patients with arterioportal fistulae in which tumor-selective delivery of the cytostatic was not possible. TACE was indicated in cases of nonresectable primary or secondary liver tumors (multiple liver tumors involving one or more lobules, metastatic disease) in which direct delivery of the cytostatic was possible.
without risk of systemic chemotoxicity. Relative contraindications for surgery included the presence of irreversible or progressive chronic liver disease (cirrhosis), poor clinical condition of the patient, advanced age (>70 years in the presence of associated comorbidities such as liver cirrhosis or vascular invasion) and lack of patient collaboration. Absolute contraindications to perform bland LE and TACE were: uncorrectable coagulopathy, acute liver failure, hepatic encephalopathy, acute infection at the time of the embolization, HIV infection, and severe malnutrition. Relative contraindications to perform LE and TACE were: history of contrast medium allergy, deteriorated renal function, portal and mesenteric vein thrombosis and lack of patient collaboration. Informed consent was obtained from all patients before every LE session.

Angiographic Definition of Vascular Variations
On the pre-interventional celiac trunk angiogram, the vascular anatomy was categorized as normal or variant. A normal vascular anatomy of the celiac trunk was always considered when a common trunk arising from the abdominal aorta was present, subdivided into the following three arteries: left gastric artery (LGA), splenic artery and common hepatic artery (CHA), and furthermore, the CHA had to show a bifurcation between the gastroduodenal artery (GDA) and the proper hepatic artery (AHIP). The latter should have a distinct main trunk before subdividing into left and right hepatic arteries. A vascular anatomical variant of the celiac trunk was considered if the distribution of the vessels mentioned above was different, for example a common hepatic artery arising from the superior mesenteric artery (SMA), a right hepatic artery arising from the SMA, a left hepatic artery arising from the left gastric artery, or an early bifurcation of the celiac trunk.

Angiographic Technique
All the procedures were performed using a conventional coaxial technique by an experienced interventional radiologist from our department. The preferred access was the right femoral artery (less frequently the left femoral artery or left brachial artery access). Catheterization of the celiac trunk was performed using an appropriately shaped 4-french selective catheter (e.g. cobra, Simons sidewinder, hook type). First, diagnostic angiography of the celiac trunk and SMA was performed. Once the vascular anatomy of the tumor was fully understood, a microcatheter (Progreat, Terumo®, Tokyo, Japan) was coaxially deployed directly into the main arterial branch feeding the tumor. In every case, a superselective position was attempted with the catheter tip as close to the tumor as possible. In those patients with vessel displacement because of the large volume of the tumor or with an extremely tortuous vascular anatomy preventing a tumor selective position, the most distal catheter position was tried to avoid vascular structures susceptible to non-target embolization. This was particularly considered when the catheter tip was in potential proximity to the gastroduodenal artery, where several branches to the pancreas and stomach (right gastric artery) arise.

Every LE was performed with the sandwich technique using lipiodol (Guerbet®, Aulnay-sous-Bois, France), Embospheres (Biosphere medical, Roissy, France) and if indicated, chemotherapeutic drugs suitable for the baseline tumor (Carboplatin®, Bristol-Myers Squibb, Latina Italy; Fotemustine®, Blackwell Synergy, Stuttgart, and Doxorubicin®, Aventis Pharma, Berlin, Germany). Lipiodol was administered first to mark the tumor area and fill the distal vasculature of the tumor, and it was administered until visible reduction in flow was observed. In the whole group, the volume of lipiodol ranged from 0.5 to 20 ml depending particularly on the tumor volume. The cytostatic dose was adjusted according to the body surface of each patient, corresponding to the maximum intravenous dose. Embolic particles (Embospheres, Biosphere medical) were administered in a mixture with a volume relation of 2 ml particles to 8 ml contrast medium. If needed, an increase in the particle size was performed (e.g. 120–300 μm). Particle administration was ended when no evidence of flow to the tumoral vessels was seen or when reflux was present. Therefore, the endpoint of every LE was considered as the complete occlusion of the tumor-feeding vessels (stasis of arterial flow). A final celiac trunk arteriography was performed over the 4-french catheter to evaluate the status after embolization of the lesion, as well as to rule out any visible non-targeting embolization into other territories.

In every LE episode, the type, size and amount of the embolization material used were evaluated. Complications that developed during the intervention, such as iatrogenic dissection of the arterial vessel supplying the liver or angiographic evidence of non-target embolization, were also investigated.

Statistical Analysis
Statistical data analysis was carried out by an statistical consultant with the use of SAS version 8.2 (SAS Institute, Cary, N.C., USA) and StatXact and LogXact (Cytel Software, Cambridge, Mass., USA).

The association between two response variables (AP after embolization and risk factor during the embolization or AP after embolization and volume of embolic material) was evaluated using Pearson’s χ² test and Fisher’s exact test.

Results
Of the 81 patients with LE, only 59 patients met the inclusion criteria for the study, with a total of 118 embolization procedures. The number of patients who underwent one LE or TACE procedures was 25, 18 patients underwent two, 11 patients underwent three, 3 patients underwent four, and 2 patients underwent six procedures. The average age of the patients at the time of the embolization was 64.7 (SD ± 9.7) years; there were 14 women (23.7%) in the study.

The histology of the liver tumors was as follows: 51 hepatocellular carcinomas, 1 cholangiocarcinoma, 1 liver hemangioma, 1 liver hemangioendothelioma, and 5 metastatic tumors in liver which were distributed as follows: carcinoid metastasis, endocrine pancreatic metastasis, gastric carcinoma metastasis, breast carcinoma metastasis, and renal carcinoma metastasis.
Frequency and Clinical Course of AP

Nine of our patients developed AP. The calculated frequency of AP after LE was 15.2% (9 of 59 patients), whereas the frequency calculated by procedure was 7.6% (9 of 118 LE). In these patients, amylase and lipase were elevated up to 8.7 and 20.1 times, respectively, 24 h after a LE. Seven patients from the AP group reported severe abdominal pain (epigastric and less frequent right flank tenderness) which was successfully treated with intravenous perfusion of synthetic opioids such as piritramide (Dipidolor, Janssen-Cilag) and metamizol (Novalgin, Aventis). In 3 patients mild fever (<38.5°C) was registered.

In all patients with AP after LE, symptomatic therapy was installed with intravenous fluids, oxygen as needed, nasogastric tube suction and central monitoring. Antibiotics were included in all cases in whom pancreatic necrosis was evident on the CT scans to avoid bacterial translocation from the gut, which usually occurs in the first hours of disease. Octreotide was administered only in patients who developed a severe AP.

In 1 patient partial necrosis of the pancreatic head was encountered (50% of the pancreatic head parenchyma) without involvement of the pancreatic body. No complications were detected and no further procedures were required (fig. 1). None of the patients required surgery because of complications. In all cases of AP after LE and TACE, 2–15 days of hospital stay were required after the initial diagnosis of this complication; in all patients follow-up examinations 5 weeks after the AP episode were performed, and in all patients the laboratory results were normal.

Relevant Factors for AP

Intrahepatic arterio-portal fistulas were angiographically evident in 29 embolizations (24.57%). Anatomic variations of the hepatic artery (solitary right and left hepatic arteries, hepatic artery from the SMA, common celiac-mesenteric trunk, immediate bifurcation of the main hepatic artery) were evident in 26 angiographies (22.03%). There was no statistically significant correlation between post-interventional AP and anatomic variations, or arterio-portal fistulas (anatomic variants: Pearson's $\chi^2$ (1) = 0.6767, $Pr = 0.411$, Fisher's exact test = 0.682; arterio-portal fistulas: Pearson's $\chi^2$ (1) = 0.9530, $Pr = 0.329$, Fisher's exact test = 0.450). Despite the lack of statistical significance of arterial anatomical variations, one of our patients in whom the GDA was very close to the catheter tip developed the most severe (necrotic) AP episode (fig. 1).

Lipiodol and carboplatin were administered to 7 of 9 of the patients who developed AP after the embolization procedure. There was no statistically significant association of carboplatin (Fisher's exact test = 0.197) or lipiodol...
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We observed that in 45% of the procedures (n = 52), a volume of <2 ml of Embospheres™ (Biosphere medical, Roissy, France) was administered (range 0–2 ml). We observed a statistically significantly lower incidence of AP in those patients who received 2 ml or less of embospheres compared with those with an embolization volume of >2 ml. In our series, patients who received an Embosphere™ volume of >2 ml also had a higher incidence of AP after transarterial embolization and TACE with a cutoff of 2 ml (Pearson’s $\chi^2$ (1) = 4.5000, Pr = 0.034, Fisher’s exact test = 0.040). Comparing the patients who received a total volume of <2 ml embospheres with those who received >2 ml, the relation was 1:8 times.

In most procedures the preferred size of the particles was 40–120 μm (94 of the 118 procedures); however, no statistically significant correlation between particle size was encountered (table 1).

Arterial dissections in the hepatic artery were made in 2 patients, but no statistically significant correlation of peri-interventional hepatic artery dissection and pancreatitis was present (Pearson’s $\chi^2$ test (1) = 6.0133, Pr = 0.014, Fisher’s exact test = 0.132).

### Table 1. Relationship between particle size and liver embolization (LE): procedures complicated by acute pancreatitis (AP)

<table>
<thead>
<tr>
<th>Particle size, μm</th>
<th>LE procedures complicated by AP</th>
<th>LE procedures not complicated by AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–120</td>
<td>7 (7.4%)</td>
<td>87 (92.6%)</td>
<td>94 (100%)</td>
</tr>
<tr>
<td>100–300</td>
<td>4 (16.7%)</td>
<td>20 (83.3%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>300–500</td>
<td>2 (14.3%)</td>
<td>12 (85.7%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>0 (0%)</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

(Fisher’s exact test = 0.140) as a risk factor for AP, when compared with all the patients who received these drugs (n = 107).

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### Discussion

**Acute Pancreatitis after Embolization**

The exact incidence of AP in any particular country or region cannot be clearly determined because of the large regional differences in the incidence and etiology of AP. The incidence of AP as well as mortality are influenced by the prevalence of alcoholism and gallstone disease, the two major causes of AP. As an example of this difficulty, in one series in Nottingham, England, an incidence of 4.8 per 100,000 was reported; however, in the northeast of England and just 1 year later the AP incidence was 24.2 per 100,000 [9]. In United States, it was one of the first 15 leading gastrointestinal causes of death at the end of the year 2000 [10].

As reported in the literature, AP occurs in nearly 1.7–2% of all patients after selective and superselective LE; up to 40% of all patients show typical laboratory findings consistent with pancreatitis after embolization. Typically, AP develops within 24 h after embolization. However, neither anatomical arterial variations nor risk factors for AP could be identified so far [5].

In large meta-analyses and trials of bland LE and TACE for the treatment of hepatocellular carcinoma [3, 11–13], the endovascular LE technique demonstrates a statistically significant positive influence on the survival rate when compared with conservative treatment. However, in these series, complications after LE affected 16% of the patients, including some cases of cholecystitis and ischemic hepatitis after LE. However, no cases of AP after LE have been reported [3, 11–13].

Independent of the presumed causative factor, AP is associated with significant morbidity and the potential for mortality. Severe AP with local and systemic complications is associated with a 25% mortality rate. Fortunately for most patients, AP follows an uncomplicated or mild course with a less than 5% mortality rate [9, 14]. These patients are appropriately treated with intravenous fluids, electrolyte replacement, and narcotic analgesics, with monitoring on a hospital ward. Complications of AP are classified as local or systemic. The early identification and admission to the intensive care unit of patients at increased risk of local and systemic complications will enhance the chances for a favorable outcome and minimize the length of hospital stay [15].

Because many cases of mild pancreatitis after embolization are undiagnosed due to a lack of clinical symp-
toms, the results of Khan et al. [4] are very illustrative. The serial changes in serum pancreatic enzyme activity were analyzed in 20 hepatoma patients with liver cirrhosis in an attempt to evaluate the incidence of pancreatic tissue damage by TACE. Serum amylase activities increased in 2 cases (10%), the elastase-1 level in 6 cases (30%), and trypsin and pancreatic secretory trypsin inhibitor levels in 5 cases each (25%). These results indicated for the first time that TACE for the treatment of hepatoma might cause pancreatic tissue damage [4]. Abdominal pain was one of the main features which lead to the suspicion of AP in our patients. In our experience, patients with abdominal pain after an uncomplicated LE have a gradual onset of the symptom, which usually slowly abates during the first 8 h. It is usually projected on the right upper flank or epigastrium (corresponding to the embolized liver segment) and responds well to the conventional analgesic therapy used after LE (metamizol).

On the other hand, abdominal pain in patients with AP after LE usually has an acute onset and increases during the following hours. It is located on the epigastric area, frequently associated with nausea, vomiting and mild fever, and with poor or no response to the conventional LE analgesia.

In a large study on TACE with 164 patients, Stefanini et al. [16] reported fever (46.2%), abdominal pain (36.6%), chemical cholecystitis (8%) and pancreatitis (1.7%) as the most important side effects after the intra-arterial procedure.

The most common complication following embolization in the liver is the post-embolization syndrome consisting of fever, abdominal pain, nausea, and vomiting. According to a study by Leung et al. [17] it occurs in up to 90% of patients after the procedure. The etiology of post-embolization syndrome is not fully understood but it is thought to result from a combination of tissue ischemia and an inflammatory response to chemoembolization [17, 18]. Although abdominal pain can be a worrisome symptom, laboratory analysis of data is crucial to differentiate both etiologies (post-embolization syndrome of pancreatitis). This allows the installation of proper medical treatment.

**Mechanisms Responsible for Acute Pancreatitis**

There is less information concerning the ischemic mechanisms leading to pancreatitis. In a study by Takeda et al. [19] on 102 patients, ischemic changes with vasoconstriction at angiography of the intrapancreatic and extrapancreatic arteries were found in up to 82.4%, corresponding with poorly perfused areas of the pancreas as detected by contrast-enhanced CT done on admission and on follow-up CT. In our study CT examinations, performed after confirmation of AP following LE and TACE, documented that the pancreatic parenchymal changes occur most frequently in the pancreatic head and uncinate process, areas perfused by small branches of the GDA (fig. 2).

**Impact of Cytotoxic Agents in AP**

In an attempt to correlate the clinical parameters with the embolic materials used, Kishimoto et al. [20] investigated the possible effects of TACE on the pancreas by monitoring the activity of serum pancreatic enzyme activities. Serum amylase activity was slightly raised in patients treated with chemotherapy alone versus chemotherapy plus TACE with lipiodol. Amylase activity slightly increased in many of the patients treated with chemotherapy plus TACE with a gelatin sponge and increased in all of the patients treated with chemotherapy plus TACE with gelfoam powder [20]. Many cytostatic agents have been described in the medical literature as causative agents responsible for AP (e.g. irinotecan, carboplatin, estramustine phosphate, paclitaxel), with this complication occurring at a low incidence rate of <5%
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[21–24]. In most of our patients, we directly injected a dose of 100–200 mg carboplatin (Bristol-Myers Squibb®, Latina, Italy) into the feeding tumor vessels. Although the most common toxicity of carboplatin is neutropenia, there are also documented reports about AP after systemic infusion of this cytostatic [21, 25].

Hepatic artery infusion chemotherapy is also a recognized treatment of unresectable hepatic neoplasms. However, many series report gastrointestinal complications because the arterial supply to the stomach and duodenum originates from the celiac and hepatic arteries [26]. In at least three different series there are many reports of acute pyloroduodenitis and also necrotizing pancreatitis. All these complications are secondary to the drug reflux from the hepatic artery or due to a malposition of the infusion catheter [26–28].

Impact of Lipiodol in AP

There are no medical series reporting embolization of liver malignancies with only the use of lipiodol. Most series report the use of the ‘sandwich technique’ (lipiodol-cytostatic drug particles) for liver malignancies. For example, in the series of Civalleri et al. [29], TACE was performed with mitoxantrone and up to 20 ml lipiodol, followed by gelfoam embolization. In this study a 3% frequency of pancreatitis was registered after TACE, however, the side effects were attributed to the mitoxantrone rather than the other embolization materials [29].

Impact of Embolization Particles in AP

The pancreas has a rich vascular net supplied from branches of the celiac trunk and the SMA. It is well known that some of these branches act as collateral pathways to the liver and spleen. The pancreas body also has a rich collateral net derived from branches of the splenic artery (pancreatic magna and dorsal pancreatic arteries) and the celiac trunk (transverse pancreatic artery). However, areas like the pancreatic head are particularly vulnerable to ischemic changes because the supplier arteries (pancreaticoduodenal arcades anterior and posterior) are terminal arteries.

In our experience, when selective embolization of hepatic artery is performed, reflux in the SMA is uncommon, minimizing the risk of ischemic changes in certain regions such as the pancreatic body and tail, while the pancreatic head and uncinate process are more exposed to reflux embolization and, hence, to the development of ischemic changes (fig. 2).

In a study of 46 patients by Brown et al. [30], bland LE was performed. They reported the postembolization syndrome in 81% as the most frequent complication. In this series, non-target embolization was also described (3.5%, including a splenic infarct and two episodes of transient hepatic failure). However, there were no reported cases of AP after LE [30, 31]. In a porcine model Stampfl et al. [32, 33] showed that even with superselective particle embolization, substantial reflux might occur.

No reports on toxicity in humans resulting from the particular use of Embospheres™ (Biosphere medical®) were found in the medical literature. However, in an experimental rat model, Redha et al. [34] found that embolization and complete occlusion of the splenic artery using polystyrene microspheres caused acute hemorrhagic pancreatitis in 100% of the cases. They concluded that AP is the result of an impairment in the arterial blood supply within the organ [34]. More recently, intra-arterial injection of yttrium 90 microspheres was used in the treatment of hepatocellular carcinoma, with a reported incidence of liver toxicity of 42% [35, 36]. However, the use of this drug as embolization spheres makes it not only potentially toxic, but it also has embolic potential in other organs.

In our series we show that 100% of the patients who developed AP after LE received Embospheres™ (table 2). Our study represents just two thirds of the total number of patients who benefited from an embolization or chemoembolization procedure, with an AP frequency after LE of 15.2%. We demonstrated a statistically significant

<table>
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<th>Table 2. Relationship between embolization materials and liver embolization (LE): procedures complicated by acute pancreatitis (AP)</th>
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<tr>
<td>Carboblatin</td>
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<tr>
<td>LE Procedures complicated by AP</td>
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<td>LE Procedures not complicated by AP</td>
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<td>Total</td>
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association between those patients who developed AP after an embolization procedure and the administration of more than 2 ml of particles. Although many patients received more than this amount of embolization material, it seems that many other factors play a critical role in the development of this complication. In one of our patients, the resulting AP was probably also related to an ischemic mechanism due to the iatrogenic dissection of the gastroduodenal artery. Although this vessel usually anastomoses with the mesenteric superior artery via the superior pancreaticoduodenal artery (a. pancreaticoduodenalis superior), an advanced atherosclerotic disease of the patient rendered this anastomosis ineffective (fig. 3). The reflux of particles in other vessels (non-target embolization) might be one of the most common sources of complications during an embolization procedure. This is particularly frequent if many vessels arise from a common trunk or when early bifurcations are present (fig. 1). In patients with visible reflux the velocity of injection of the embolization material was decreased.

It is important to note that in every catheterization maneuver, embolic material from the aortic wall and the celiac trunk ostium can be dislodged, especially in elderly patients as well as in patients with severe atherosclerotic disease and aortic abdominal aneurysms.

**Mortality**

Although the overall mortality rate of acute edematous interstitial pancreatitis is below 1%, up to 10–24% of patients with severe AP die [37]. There are only very few data on mortality due to pancreatitis after LE. Marchiori et al. [38] performed TACE with gelfoam or with an Ivalon sponge in 98 patients with unresectable hepatocellular carcinoma. Seven patients died within 1 month after treatment: 2 from myocardial infarction, 2 from liver failure, 2 from digestive hemorrhage, and 1 from necrotizing pancreatitis. These data suggest a mortality rate in this series of 1.02% [38].

A good quality digital subtraction angiography of the SMA should detect possible accessory arteries feeding the tumor, recognize portal vein patency, as well as confirm
the presence of an anastomosis in the superior pancreaticoduodenal artery.

Large-volume tumors also make superselective embolization more difficult, adding another risk factor for non-target embolization [39]. Thus choosing the correct particle size will be crucial to prevent non-target embolization into the pancreas and secondary development of AP.

Despite a normal vascular anatomy, early bifurcation in every vessel should alert the physician to a non-target embolization.

Although intrahepatic arteriovenous fistulas are not directly related to pancreatic embolization (potentially pulmonary), it is important to remember that this phenomenon is present in the majority of the large hepatic tumors. Secondary embolization of other organs is always a risk because these lesions require larger amounts of embolization material and sometimes the altered anatomy makes it difficult to appreciate the small accessory vessels.

The study by Khan et al. [4] from 1993 is perhaps one of the first and most representative studies to relate pancreatic tissue damage to transcatheter arterial embolization (TAE). They established a clear relationship between catheter tip position and pancreatic tissue damage. A lower frequency of pancreatic tissue damage was clearly shown by performing superselective TAE in comparison with non-superselective TAE [4].

**Conclusion**

The pathophysiological mechanisms of AP after selective and superselective LE and chemoembolization remain unclear. Although it seems to have a multifactorial etiology, both the toxicity of the antineoplastic drugs (carboplatin-related toxicity) as well as ischemic mechanisms (non-target embolization) might be the most important causes of pancreatic inflammatory reactions after these procedures. These suggest that, even with a superselective position in the liver vessels, many crucial factors should be borne in mind before performing embolization. Following selective embolization as well as chemoembolization, we also suggest that measurement of serum pancreatic enzymes should be routinely performed in cases of abdominal pain in order to confirm AP, which can clinically mimic the known postembolization syndrome.

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**References**


