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Malignant Insulinoma: Permanent Hepatic Artery Embolization of Liver Metastases—Preliminary Results

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Abstract

Purpose: To evaluate permanent hepatic artery embolization of liver metastases of malignant insulinoma as a therapeutic procedure.

Methods: Three female patients had persistent severe hypoglycemia after distal pancreatectomy because of a malignant insulinoma. Computed tomography (CT) and CT-portography (CTAP) were used for tumor assessment and follow-up and demonstrated multiple hypervascular metastases 0.5–3 cm in diameter in both lobes of the liver. Unilobar sequential transcatheter embolization of the hepatic artery was performed with an interval of 1–2 months between the procedures. Permanent occlusion was achieved by using a mixture of n-butyl-2-cyanoacrylate and ethiodized oil as an embolizing agent.

Results: In all patients, embolization of the hepatic artery was technically feasible and complete occlusion could be obtained. In two patients, collaterals originating from the right inferior phrenic artery were embolized superselectively 3 months after bilobar embolization. CTAP at that time revealed marked decrease in tumor size of more than 50%. All patients responded to the treatment as confirmed by normalization of measurable hormone levels, glucose levels, and disappearance of symptoms. Two patients are still alive after 24 and 31 months from the time of the first embolization. Current investigations revealed normal laboratory data and no further tumor progression in the liver. The third patient died 15 months after the first embolization; she also had developed ileus due to local recurrence of the primary tumor and lymph node metastases.

Conclusion: Hepatic arterial embolization appears to be an effective means of palliation for liver metastases of malignant insulinoma. Long-term improvement seems most likely to be the result of extensive ischemia from permanent occlusion.

Key words: Malignant insulinoma—Islet cell tumor—Transcatheter arterial embolization

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Insulinomas are endocrine tumors belonging to the group of gastroenteropancreatic tumors. The majority secrete active hormones and may be associated with distinctive clinical syndromes [1]. They arise from the so-called diffuse neuroendocrine system, a large reservoir of cells that secrete amines and peptides [2]. Although insulinomas are the most common endocrine tumors of the pancreas, they remain rare, affecting 1 person in 100,000 [1, 3]. About 80% are solitary and benign, about 10% are malignant, and the remainder are either multiple benign adenomas or islet cell hyperplasia [1–3]. In malignant insulinomas, metastases are usually evident at the time of diagnosis or may develop during the postoperative course [4]. Those metastasizing active insulinomas constitute a clinical and therapeutic challenge. The uncontrolled production and release of insulin by disseminated metastases, even after successful resection of the primary tumor, cause hyperinsulinism and hypoglycemic episodes [4].

Concepts in the treatment of functioning liver metastases include liver resections for solitary metastases or multiple enucleations to reduce the tumor mass [5, 6]. Surgical ligation of the common hepatic artery or temporary dearterialization are currently replaced by interventional radiologic procedures such as transcatheter arterial (chemo) embolization. Several studies have

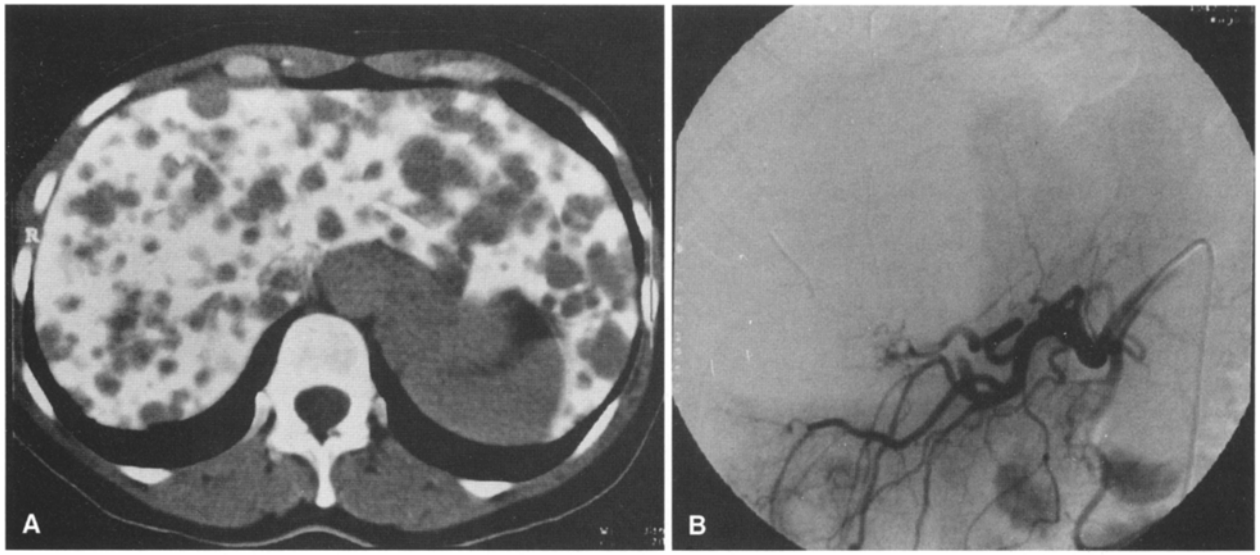

Fig. 1. A 63-year-old female patient with liver metastases after malignant insulinoma. **A** Computed tomography portography (CTAP) before embolization shows multiple small metastases in both lobes of liver. **B** Angiogram of the common hepatic artery after the first embolization shows defect in arterial perfusion of right lobe of liver.

reported the effectiveness of these techniques in the treatment of liver metastases of other endocrine tumors [4, 7–14]. However, only a few reports are available on the management of malignant insulinoma [4, 9, 15–17]. Keeping in mind the individual course of each of these neuroendocrine gastroenteropancreatic tumors and the possibility of life-threatening hypoglycemic episodes that may cause sudden death, we report upon functioning malignant insulinomas as a peculiar entity. The preliminary clinical and biochemical course of three patients with metastasizing insulinoma and percutaneous selective permanent arterial transcatheter embolization is described.

Patients and Methods

Three female patients aged 42, 63, 66 years (mean 57 years), underwent distal pancreatectomy for malignant functioning neuroendocrine tumor of the pancreas, in which the primary lesion in all three patients was removed. In one patient the gall bladder was removed in the same setting. The intervals between surgery for removal of the primary tumor and embolization treatment were 1, 6, and 96 months, respectively. The biochemical profile and the clinical symptoms of two patients were typical of an insulinoma. One patient was initially classified clinically and biochemically as having a glucagonoma. Eight years later she developed a nonresectable local recurrence and bilateral liver metastases and converted clinically and biochemically to an insulinoma. None of the patients had evidence of multiple endocrine neoplasia syndrome. Clinical and biochemical diagnosis was verified histopathologically in all patients at the time of the primary surgery. Adjacent lymph nodes were involved in all three patients but there were no signs of extraabdominal sites of involvement.

Two patients had previous failures of chemotherapy with streptozocin; one developed a local recurrence and liver metastases despite several chemotherapeutic sessions; in the other patient, neither growth of the metastases nor hormonal activity could be influenced by streptozocin. The third patient is still on interferon α2B (Intron A,™ Aesca-Schering, Vienna, Austria), which was started immediately after the second embolization and was considered a prophylaxis to inhibit further proliferation. However, success of the embolization treatment was obvious at the time of the first interferon α2B administration.

Serum levels of fasting blood glucose, insulin, and C-peptide were measured before therapy was started, after the procedure, weekly until termination of the embolization treatment, and monthly thereafter, if available. Glucose and liver function tests were performed daily during the hospital stay.

An objective pre- and postinterventional assessment of tumor status with CT, and CT-portography (CTAP) was required [18]; the latter was performed in the same setting as the scheduled embolizations and 3 months after bilobar hepatic arterial occlusion. CT studies were done thereafter at 3-month intervals for follow-up.

After initial peripheral embolization of the lobe bearing the greater tumor bulk, subsequent embolization of the remaining lobe was spaced 1–2 months apart, depending on the severity of the postembolization syndrome. Any collaterals to the liver were occluded at the 3-month control CTAP in a superselective manner using the same embolic agent. There was no special preembolization preparation done apart from mild i.v. sedation with 2.5 mg midazolam (Dormicum, Sandoz, Basle, Switzerland). Glucose i.v. was administered if intraprocedurally measured blood glucose levels were less than 60 mg/100 ml. Pain was controlled with fentanyl (Fentanyl, Janssen, Beerse, Denmark) as needed; antibiotics were not administered routinely. Standard hemodynamic monitoring was performed during the procedure. Written informed consent was obtained from all patients.

Using femoral access, a 6 Fr sidewinder 1 catheter was introduced via a sheath using the Seldinger technique. Preliminary celiac and superior mesenteric angiography with arterial and venous phase filming was done routinely to define the hepatic arterial anatomy and to establish the patency of the portal vein. After superselective intubation with a coaxially used Tracker 18 catheter system (Target Therapeutics, San Jose, CA, USA), embolization of both the branches and the mainstem of the hepatic artery was performed. To achieve permanent occlusion we used a mixture of n-butyl-2-cyanoacrylate (Histoacryl blue, B. Braun Melsungen AG, Melsungen, Germany) and ethiodized oil (Lipiodol Ultrafluide, Guerbet, Zürich, Switzerland) as embolizing agent (ratio 1:4). To avoid catheter occlusion, the system was flushed with 10% glucose solution prior to the embolization and

immediately thereafter. The mixture was applied without force and under fluoroscopic control until stasis of arterial blood flow was achieved. Major symptomatic response was defined by an asymptomatic patient with normal blood glucose levels. A major biochemical response was defined as a greater than 50% decrease or normalization of the level of marker hormone, and a minor response as a 25%–50% reduction in hormone levels. Morphological tumor responses were defined as follows: a complete regression denoted the absence of any detectable tumor mass, and partial regression denoted a reduction by at least 50% of the product of the longest perpendicular diameters of the most clearly measurable mass lesion with no progression of any other lesion or new sites of metastatic disease.

Patient survival was evaluated from the time of the first embolization. Follow-up health status was obtained either by death certificate or clinical follow-up. The patients' outcomes were determined in January 1995.

Results

Preembolization hepatic arteriography demonstrated multiple hypervascular masses of 0.5–3 cm in diameter involving both lobes of the liver (Fig. 1A). All patients completed the scheduled treatment plan. Embolizations were technically feasible in all patients. Follow-up angiography revealed collateral vessels feeding the capsule of the liver in two patients; both originated from the right inferior phrenic artery and were successfully embolized in a superselective manner 3 months after bilobar embolization. There was confirmation of complete occlusion of the previously treated hepatic artery in all patients (Fig. 1B).

No death attributable to the embolization occurred. One patient, of the two without immediate cholecystectomy, had to undergo cholecystectomy because of ischemic cholecystitis 5 days after the first embolization due to reflux of embolization material into the cystic artery. All patients presented with nausea and pain which was successfully controlled by symptomatic therapy within a mean of 3 days. Postembolization syndrome was found to be more severe after the first embolization, with a mean duration of 4 days compared with 1 day after the second embolization and correlated in time and intensity with the degree of liver enzyme elevation. Liver function studies revealed a transient elevation of lactic dehydrogenase (LDH) with a peak 24–48 hr after embolization and gradual decrease within the next 14 days to preembolization values. There were no other significant changes of laboratory data that could be causally linked to the embolization procedure. Mean duration of hospitalization was 3 days, depending on the severity of postembolization symptoms.

Results of objective tumor responses after the first embolization treatment are summarized in Table 1. Hormone-mediated symptomatic episodes were considerably reduced in all patients after the first embolization. After complete arterial occlusion of the liver, all patients were asymptomatic and could resume a normal life-style.

After a short initial peak of both insulin and C-peptide during the embolization procedure, normalization of the levels of marker hormones was achieved 3 months after completion of treatment, which indicates major biochemical response according to World Health Organization (WHO) criteria.

CTAP showed marked regression of tumor deposits by at least 50% in the specific area of embolization, indicating partial regression according to WHO criteria. In metastases greater than 2 cm in diameter, small amounts of intralesional gas could be detected incidentally. Lesions up to 1 cm in diameter often decreased in density to cystic or nearly cystic values and were sharply marginated. CT scans performed prior to control CTAPs revealed a decrease in tumor density compared to preembolization CT scans (Figs. 2, 3).

Two patients are alive after 24 and 31 months, respectively, from the time of the first embolization. Glucose and hormone levels evaluated during follow-up have remained within normal range up to the present time (Table 2). Recent CT scans revealed little further decrease in tumor size without any complete regression of metastases, however, there were no signs of progressive disease or new sites of metastases. One patient was in recovery for 15 months and thereafter died of ileus subsequent to local recurrence of the primary tumor and growth of intestinal lymph node metastases. The last evaluation of symptoms and biochemical parameters revealed an asymptomatic patient and normal hormone levels. The patient was lost to follow-up 3 months before her death in a hospital abroad. Unfortunately, the autopsy report gave no information about the effects of hepatic arterial embolization on metastases and normal liver parenchyma.

Discussion

Percutaneous superselective transcatheter embolization of the right and left hepatic artery successfully influenced tumor growth and hormone excess in all three patients studied.

It is well known that functioning and nonfunctioning tumors of the pancreas grow slowly [1, 6]. Even after formation of metastases, they may be associated with prolonged survival [8, 16]. Patients, however, not only have to bear the burden of primary and metastatic tumor bulk; those with malignant insulinoma are at risk of sudden death due to hypoglycemia. There is lack of effective medical treatment for the hyperinsulinism caused by hormone secretion directly into the systemic circulation by metastases.

Most tumors in the liver are predominantly supplied by the hepatic artery, whereas healthy liver paren-

Table 1. Patient history

Patient	Tumor	Prior therapy	Number of embolizations	Complications	Symptoms pre/post embolization	Glucose in serum pre/post first embolization (mg/100 ml)	Insulin in serum pre/post first embolization (μU/ml)	C-Peptide in serum pre/post first embolization (ng/ml)	LDH in serum pre/post first embolization (U/l)
1	Malignant insulinoma	Streptozocin	3	Cholecystitis	Hypoglycemic episodes/ asymptomatic	65/108	35.0/14.0	5.0/2.0	170/1079
2	Malignant insulinoma	Interferon α2B	3	None	Hypoglycemic episodes/ asymptomatic	55/95	37.7/28	3.1/2.0	234/644
3	Glucagonoma converted to malignant insulinoma	Streptozocin	2	None	Hypoglycemic episodes/ asymptomatic	33/87	34.4/21.2	7.8/3.4	272/1570

Normal ranges: Glucose in serum: 70–110 mg/100 ml; insulin: 5–25 μU/ml; C-Peptide: 0.4–4.2 ng/ml; LDH: 120–240 U/L.

Table 2. Patient follow-up

Patient	Parameter	Follow-up (months) 3	6	9	12	15	18	21	24	27	30	Outcome	WHO responses
1	Symptoms	None	None	None	None	None	None	None	None			Alive	Major
	Glucose[a]	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal			24 months	Major
	Insulin[b]	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal				Major
	Tumor size[c]	Regression	Regression	Stable	Stable	Stable	Stable	Stable	Stable				Partial
2	Symptoms	None	None	None	None	None	None	None	None	None	None	Alive	Major
	Glucose[a]	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	31 months	Major
	Insulin[b]	Slightly elevated	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal		Major
	Tumor size[c]	Regression	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable		Partial
3	Symptoms	None	None	None	None	Lost to						Died	Major
	Glucose[a]	Normal	Normal	Normal	Normal	follow-up						15 months	Major
	Insulin[b]	Normal	Normal	Normal	Normal								Major
	Tumor size[c]	Regression	Stable	Stable	Stable								Partial

Regression = decrease in size of liver metastases by at least 50%. Stable = no further measurable regression, no progression of any lesion, no new sites of metastases in the liver.
WHO = World Health Organization.
[a] Fasting glucose in serum.
[b] Insulin in serum.
[c] Tumor size evaluation by CTAP at 3 months and by CT thereafter.

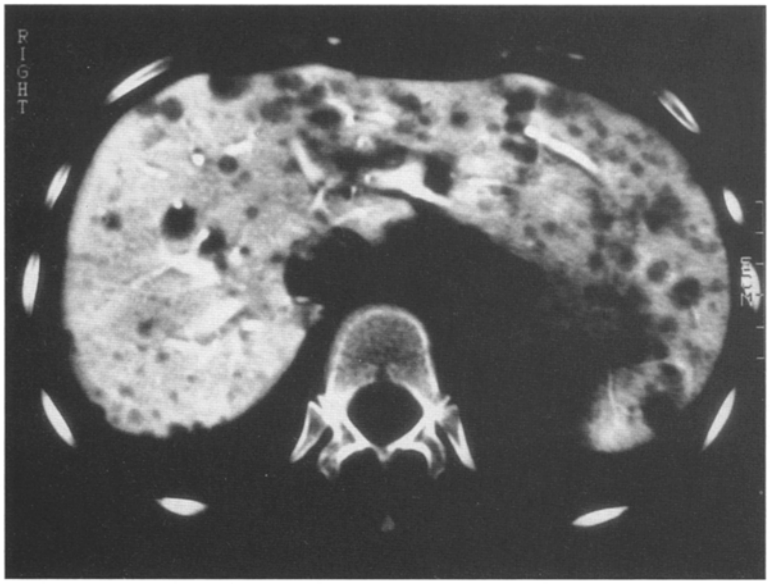

Fig. 2. CTAP after completion of embolization treatment shows multiple hypodense lesions indicating tumor necrosis.

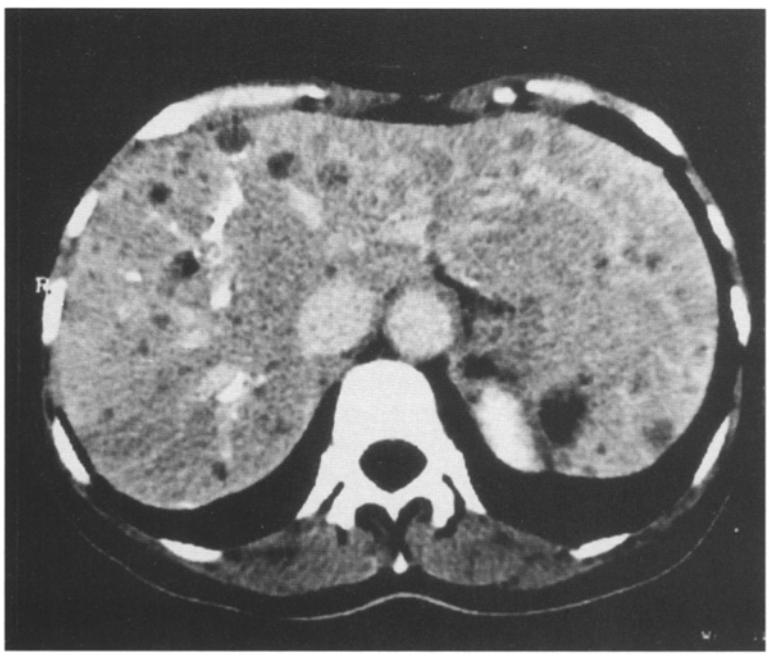

Fig. 3. Contrast-enhanced helical CT after embolization shows multiple hypodense and cystic lesions. Embolization material can be depicted as hyperdense rods in hepatic arteries.

chyma is supplied by the portal vein in 75%–80% of cases, preventing ischemic damage to the liver in case of occlusion of the hepatic artery [4, 7]. Thus, the dual blood supply of the liver and the hypervascularity of endocrine metastases provide a strong rationale for interrupting the arterial supply as a therapeutic maneuver [4, 11]. As little as 10% of the normal functioning liver parenchyma is sufficient for maintaining metabolic activity [7]. Although there are reports on complete hepatic embolization at one time tolerated equally well by patients [7, 9], we decided to perform unilobar sequential embolizations in our series.

There are a great variety of embolic agents available, differing in physical properties, vascular reaction, duration, quality, and level of obstruction [20]. Collaterals developing in any part of the hepatic arterial system after embolization will determine the degree of necrosis [8]. More peripheral and persistent occlusion prevents constitution of effective collateral circulation and thus provides for more effective tumor necrosis [9].

The smaller the particle size, the more distal will be the occlusion, however, damage to the peribiliary arterial plexus and injury to normal liver parenchyma must be avoided. Liquid agents, polyvinyl alcohol foam particles 150–250 μm in size, and gelatin sponge powder may reach the capillary bed, however, there is a risk of necrosis as the human liver tolerates emboli as small as 250 μm [7, 13]. Animal experiments with 175-μm microspheres resulted in liver dysfunction [19, 20]. Ethanol embolization of the hepatic artery resulted in severe damage to intrahepatic bile ducts with subsequent sclerosing cholangitis [20, 21]. Doppman et al. in 1978 [21] used silicone rubber for embolization in an animal study and reported multiple infarcts and bile cysts. Polyvinyl alcohol foam particles 250–590 μm in size have been used in several studies [9, 14]. There is a limitation in that the Tracker 18 catheters which are currently used for superselective vessel intubation, allow only particles smaller than 250 μm to pass. The fine particles of gelatin sponge powder interrupt the microcirculation [16], however gelatin sponge is resorbable and the length of time before recanalization is not known precisely [20, 22]. Taourel et al. [22] recently demonstrated a reversal of postembolization flow changes in the hepatic artery within 2 days after embolization with 1–2-mm gelatin sponge. Thus, quick reestablishment of blood flow to the metastases must be considered.

In recent reports, chemoembolization was favored by many authors [10–12, 17]. Ethiodized oil is used as a carrier for various cytotoxic drugs. Subsequent temporary embolization of the hepatic artery may allow for delayed wash-out and increased levels of the cytotoxic drug in tumor tissues [12]. However, determination of optimal doses and maintenance of stable emulsions of the ethiodized oil and cytotoxic drugs remain problems in this form of treatment [23]. The mechanism for chemoembolization effectiveness is not clear yet; further randomized studies will be required to assess the influence of either local administration of cytotoxic drugs or repetitive occlusive treatment on results in patients with liver metastases [23].

We used n-butyl-2-cyanoacrylate to obtain a peripheral, complete, and permanent arterial occlusion without damage to nontumorous structures. N-butyl-2-cyanoacrylate belongs to the group of liquid embolic agents that almost instantaneously polymerizes on contact with ionized material such as blood or endothelium [24, 25]. With the addition of ethiodized oil to the glue, polymerization time could be prolonged to 10–15 sec in our study, allowing transport of the mixture into peripheral segmental and subsegmental arteries before polymerization occurred. As the oil rendered the glue radiopaque and was captured within polymerizing glue clots, the process of occlusion could be well visualized fluoroscopically. The viscous mixture filled the arterial tree after injection and was directed towards subsegmental arteries before blood stasis occurred. The procedure produced an effect similar to blood sludge. We therefore can conclude that the mixture did not reach the peribiliary arterial plexus, also confirmed by the absence of any clinical or biochemical evidence of damage to bile ducts. Additionally the mixture could not be demonstrated in the portal vein or in the systemic circulation.

Our patients presented with numerous small hypervascular lesions invading both lobes of the liver. After successful embolization, intralesional gas formation occurred in metastases up to 2 cm in diameter, indicating necrosis [4]. In some smaller metastases, a cyst-like decreased attenuation was evaluated. This cyst-like involution of tumors after embolization has been described previously [17]. As these cysts were demonstrable in areas of former metastases, they apparently were not associated with infection nor was there biochemical evidence of bile duct injury. Therefore we assume that they represent necrotic tumor rather than bile cysts. No patient presented with symptoms of a hepatic abscess or needed antibiotics in the postembolization course.

The more complete and permanent an arterial occlusion is, the more severe the postembolization syndrome is. Pain related to increased tension of the capsule due to transient swelling of the liver after embolization could be controlled by symptomatic therapy in all patients. Additionally, after embolization, the pain related to the mass effect of neoplastic liver involvement was well arrested. Liver function test derangement correlated in time and intensity with the postembolization symptoms and was more severe after the first embolization session.

No serious complications occurred in our study except gall bladder infarction in one patient, where it was impractical to avoid embolization of the cystic artery. Although in the literature this complication is reported to be rare, patients in whom embolization may be performed as an additional treatment should undergo cholecystectomy at the time of primary surgery [7].

Although arterial devascularization was very effective, demonstrated by sustained symptomatic improvement and significant reduction of hormone levels, we chose to occlude any collaterals to the liver developing after the embolization procedure to achieve the greatest arterial occlusion. We believe that the complete and long-lasting symptomatical and biochemical response obtained in our patients is secondary to the sustained ischemia of metastases and a higher degree of necrosis.

Interestingly, excellent results were obtained in one patient despite local recurrence. As the recurrent tumor was considered inoperable and chemotherapy had failed to improve her clinical status, we intended to reduce the tumor mass by embolization of the liver metastases and by this reduce the patient's frequent hy-

poglycemic attacks. Normalization of glucose and hormone levels after hepatic devascularization leads to the assumption that either the recurrent tumor converted to a nonfunctioning insulinoma where the liver metastases were responsible for the clinical and biochemical course of an insulinoma, or a conglomerate of lymph node metastases was the substrate for the tumor mass. The kind of tissue responsible for the recurrent tumor mass could not be definitely differentiated by CT.

Due to the rarity of functioning malignant insulinoma, our series is quite small. However, in view of the documented influence on hormone excess and tumor growth, hepatic artery embolization appears to be an effective means of palliation for liver metastases of malignant insulinoma. Long-term improvement seems most likely to be the effect of extensive ischemia obtained from permanent occlusion. Further study will be required to determine the duration of responses and the role of permanent embolizing agents.

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