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Malignant Metastatic Insulinoma—Postoperative Treatment and Follow-up

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Abstract. The rarity of malignant insulinoma limits reports on therapeutic strategies and outcome. The treatment and follow-up of 10 patients, all presenting an insulinoma with metastatic disease of the liver and newly diagnosed between 1992 and 2002, is reported. Pancreatic surgery with successful removal of the primary tumor preferentially located in the tail was performed in 7 women and 3 men, median age 55 years (range 36–82 years). If appropriate, 5 patients underwent additional hepatic surgery and lymph node resections. Liver metastases as the major cause of postoperatively persistent hypoglycemia were subsequently treated by repeated transarterial hepatic chemoembolization and chemoperfusion protocols using high-dose transhepatic streptozocin perfusions (3–4 g per session). The current median survival time for all 10 patients is 2.6 years (range: 1.6–9.7 years). Six patients are currently alive with a median survival of 3.7 years (1.7–9.7 years), five of them with stable disease and free of hypoglycemia. Four patients died after a median survival of 1.8 years (range: 1.6–7.5 years) from complications of unmanageable hypoglycemia. It is concluded that the necessity to treat debiliating and life-threatening hypoglycemia in metastatic malignant insulinoma warrants the option of radical endocrine surgery in combination with extended and repeated postoperative chemoembolization of liver metastases.

The malignant metastatic form of usually benign insulinoma is an extremely rare pancreatic neuroendocrine tumor. Reported incidence rates range from 5% to 15% of all insulinomas [1–5]. Complications related to symptoms or treatment of debiliating hypoglycemia may be life-threatening when hormone active metastases occur predominantly in liver but are found also in lymph nodes, bones, and peritoneal tissue, and are the cause of uncontrolled insulin secretion. Occasional case reports from all over the world [6–12] including one or a few patients and featuring unusual aspects of the disease are published. Controlled studies that address a specific therapeutic approach to the treatment of metastatic insulinoma have not been performed and seem to be unfeasible. Usually affected patients are included with other neuroendocrine tumor patients in study protocols intended to evaluate the effectiveness of chemotherapy or adjuvant treatments such as somatostatin analogues [3–16]. Severe hypoglycemia may persist or recur after successful removal of the primary tumor and often requires urgent treatments, most of which are invasive, because the majority of insulinomas do not respond to somatostatin treatment [17]. Increasing experience with hepatic embolization alone or in combination with chemotherapy [18–22], selective hepatic surgery [23, 24], intraoperative radiofrequency ablation [25, 26], and systemic radiopeptide therapy with labeled somatostatin analogues [27] offer new treatment options for this rare and uniquely anabolic endocrine tumor. We report our experience with 10 patients with metastatic malignant insulinoma, newly diagnosed within the decade 1992–2002. We focus on the primary surgical approach and postoperative attempts to control or prevent hypoglycemia. Postoperative streptozocin (streptozotocin) chemotherapy, introduced into the treatment of neuroendocrine tumors and particularly insulinomas as early as 1968 [28, 29], was used as the drug of choice and was administered as a high-dose treatment via transarterial hepatic chemoperfusion in combination with hepatic embolization.

Patients and Methods

From 1992 to 2002 we treated a total of 77 patients with insulinoma. All tumors were surgically removed. Ten patients presented with a malignant insulinoma (incidence rate 13 %) with predominantly hepatic metastases diagnosed preoperatively in 6 patients and found incidentally during surgery in 4 patients. Liver metastases were proven by subsequent histological examination. Median age of the 7 women and 3 men was 55 years (range: 36–82 years), the body mass index (BMI) was 29.5 kg/m_2 (range: 22.1–35.4 kg/m_2). The 10 patients with malignant meta-

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static insulinoma were slightly older and more obese when compared to our total group of patients with benign insulinoma (N = 107 since 1975; 72 women and 35 men with a median age of 50 years—range: 15–89 years,—median BMI of 25.6 kg/m$_2$ in women and 26.1 kg/m$_2$ in men). All patients underwent pancreatic surgery with successful removal of the primary tumor. An extended left-sided pancreatic resection was performed in 8 patients when the tumor was located in the tail or in the body of the pancreas. Isolated tumor resection from the pancreatic head was performed in 2 patients. Further surgical procedures included simultaneous or sequential hemi-hepatectomy of the right lobe (n = 2), partial segmental hepatectomy (n = 1), and appropriate lymph node dissection (n = 2). Characteristics of the patients are summarized in Table 1.

Therapeutic Procedures

Intravenous streptozocin chemotherapy was administered to the initial two patients according to published protocols [13] calling for 500 mg/m$_2$ streptozocin (Zanosar, Pharmacia & Upjohn Co., Kalamazoo, MI,) on 5 consecutive days and repeated every 6–8 weeks. Both patients refused an additional doxorubicin chemotherapy. The initially clear-cut response of blood glucose and insulin levels waned after 12–18 months of biochemical remission.

Transarterial hepatic chemoperfusion (TACP) consisted of single intra-arterial high-dose administration of streptozocin at a dose of 3000–4000 mg over 60 minutes via the main, left, or right hepatic artery. Effective standard antiemetic and corticosteroid therapy was given before and after treatment as required. Seven patients were treated repeatedly 1–6 times (mean:3 times).

Transarterial hepatic chemoembolization (TACE) was carried out after a high-dose streptozocin perfusion as described. Thereafter, Contour-PVA particles (BostonScientific Co., Natick, MA; mesh 150–250 μm) or polyacrylic microspheres (Embospheres, Biosphere Medical Co., Louvre, France; mesh 100–300 μm and 300-500 μm), were suspended in appropriate amounts of radiocontrast dye. The solution was injected into selected hepatic arterial branches or into the major lobe arteries until complete blockade of hepatic blood flow was visualized. Eight patients were treated repeatedly 2–9 times (mean:4 times). Unlike in any other malignant tumor, postinterventional estimation of blood glucose and serum insulin levels allows immediate evaluation of the effectiveness of embolization therapy. In addition, these markers clearly indicate the necessity for subsequent treatments as shown by the three consecutive sessions within 300 days in our patient No. 1 (Fig. 1)

Results and Follow-up

Table 1 summarizes the initial values of insulin, proinsulin, neuron-specific enolase (NSE), and HbA_{1c} when biochemical hypoglycemia below 40 mg/dl was documented and the diagnosis of endogenous hyperinsulinemia was proven. The majority of patients showed insulin levels well above 200 pmol/l (range:60–500 pmol/l). Conventionally, insulinoma is considered to represent the rare malignant variant when metastatic spread preferentially into the liver and surrounding lymph nodes is proven, irrespective of eventual hormone production. This was the case in all reported patients. Nevertheless, venous invasion of small clusters of typical neuroendocrine tumor cells into venules may be seen regularly

Table 1. Characteristics of 10 patients with malignant insulinoma, ordered by year of diagnosis.

Patient No./date	Gender (M/F)	Age (years)	BMI (kg/m$_2$)	Insulin (pmol/l)	Proinsulin (pmol/l)	HbA_{1c} (%)	NSE (μg/l)	Tumor size (ml vol.)	Tumor size (mm diameter)	Localization	Surgery	Metastases	iv-STZ (n)	TACE (n)	TACP (n)	Survival (years)
#1/1992	F	63	23.1	188	—	3.8	7	2.6	17-17–17	Tail	LR	Liver	12	9	—	7.5 / dead
#2/1993	M	82	29.5	384	—	5.2	9	7.2	25-22-24	Head	TR, hHpx	Liver	7	—	2	1.6 /dead
#3/1994	M	36	36.9	270	156	5.1	13	42	45-40-43	Tail	LR, hHpx	Liver, retroperit.	1	1	6	9.7
#4/1995	F	56	32.4	394	—	3.2	7	160	80-66-58	Head	TR	Liver	—	3	1	8.8
#6/1996	F	54	29.5	281	—	5.2	139	160	68-68-66	Tail	LR	Liver	—	5	—	1.8 /dead
#6/2000	F	64	24.8	98	93	4.5	112	0.7	13-8-12	Tail	LR, ly-nx	Liver, Lymphnodes	—	—	6	4.1
#7/2001	F	59	32.0	505	419	5.1	12	1.4	16-14-12	Body	LR	Liver	—	2	3	3.3
#8/2001	F	39	35.4	450	—	—	—	6.9	25-24-22	Tail	LR	Liver, Bone	—	6	—	1.8 / dead
#9/2002	F	50	22.1	218	145	5.5	62	5.6	22-22-22	Tail	LR, pHpx	Liver	—	3	2	2.0
#10/2002	M	37	25.1	64	36	4.9	—	1.2	15-14-11	Body	LR, ly-nx	Liver, Lymyphnodes	—	2	2	1.7

BMI: body mass index; NSE: neuron-specific enolase; ml vol.: tumor volume in ml; iv-STZ: intravenous streptozotocin; TACE: transarterial chemoembolization; TACP: transarterial chemoperfusion; LR: left resection; TR: tumor resection; hHpx: hemihepatectomy; pHpx: partial hepatectomy; ly-nx: lymph node resection; M/F: male/female; perit.: peritoneal

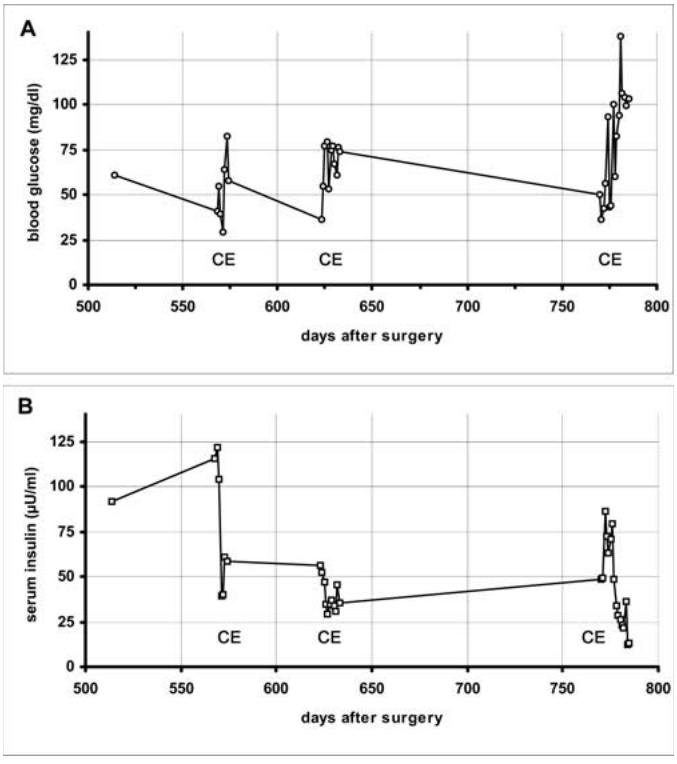

Fig. 1. Fasting blood glucose (*A*) and serum insulin levels (*B*) in patient No. 1 during three consecutive chemoembolization procedures (CE).

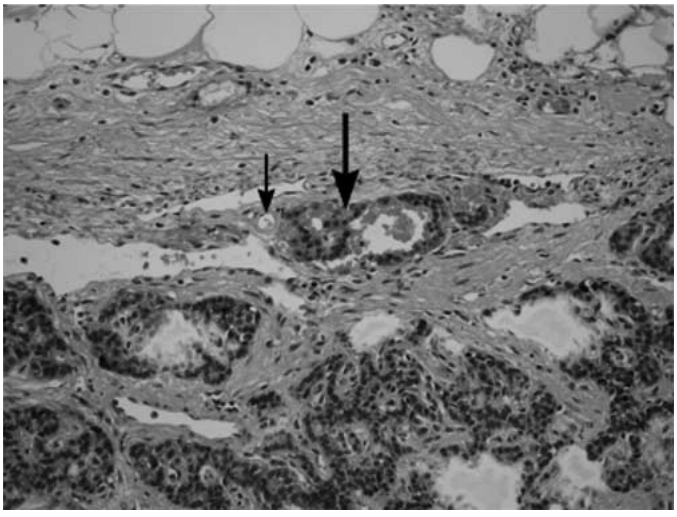

Fig. 2. Venous invasion of neuroendocrine tumor cell clusters (large arrow) into a small venule near the periphery of a malignant metastatic insulinoma seen in the bottom section (patient No. 10), HE stain; magnification factor × 200. The small arrow indicates an adjacent arteriole.

upon careful inspection of stained tumor tissue, as shown in Figure 2.

As mentioned earlier, all patients underwent primary pancreatic surgery with successful removal of the tumor. Up to now, there is no indication of tumor relapse in any of the patients. Only

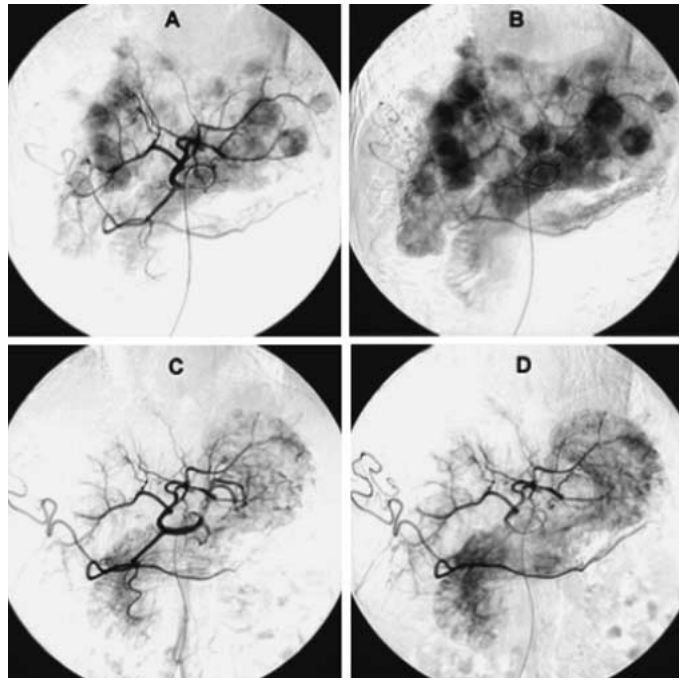

Fig. 3. Angiography of the liver in a patient (No. 9) with metastatic malignant insulinoma. *A*, *B*: arterial and venous phase before hepatic embolization; *C*, *D*: arterial and venous venous phase after hepatic embolization.

3 tumors exceeded an average diameter of 40 mm (maximal 80 mm) with a calculated volume of 40–160 ml. Seven tumors were <30 mm with a volume of 6–7 ml, and 4 of these tumors were even smaller than 20 mm with volumes of 0.7–2.6 ml. The median diameter of all tumors was 24-22-22 mm, the median volume was 6 ml. There was no preferential location for larger or smaller tumors, although most tumors were located in the tail of the pancreas. When compared to data from >100 benign insulinomas with median tumor diameters of 15-12-10 mm (range: 3–35 mm) and a median volume of 1.0 ml (range: 0.01–9.6 ml) evenly distributed over the entire organ, malignant insulinomas are definitely larger. Six patients of the original 10 remain alive with a median survival of 3.7 years, (range: 1.7–9.7 years). Of these, 3 patients were rendered free of hypoglycemia by means of initial TACE treatments, which were subsequently switched to high-dose streptozocin perfusion. Two of these patients are stable and free of symptoms after 3.3 and 8.8 years, respectively. The third patient, with the longest survival time of 9.7 years, recently presented with disease progression marked by retroperitoneal lymph nodes and peritoneal lesions despite hemihepatectomy 3 years ago. The peritoneal lesions are sstr-receptor positive, and the patient is undergoing radiopeptide therapy.

In the remaining three patients without persistent hypoglycemia, liver metastases were occluded by primary TACE treatments and followed by TACP treatments. Of these, one patient presented with massive liver disease which completely disappeared after three treatments with TACE (Fig. 3). In two of the patients pancreatic lymph node metastases were removed during surgery. Thus, five patients with currently stable disease after initial hepatic embolization continue to receive transhepatic streptozocin chemotherapy every 6–12 months.

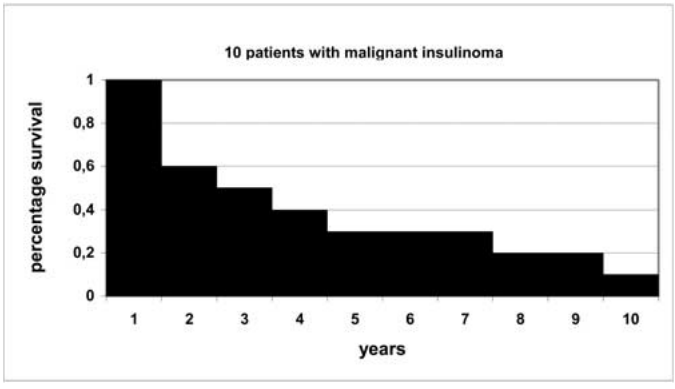

Fig. 4. Survival time (years surviving as of 2004; adapted from Kaplan-Meier plot) for all 10 patients diagnosed with malignant insulinoma since 1992.

Four patients died after a median survival of 1.8 years (range: 1.6–7.5 years). These patients all experienced repetitive hypoglycemic attacks after pancreatic surgery, although none of them died from hypoglycemia. By means of repetitive TACE treatments intervals free of hypoglycemia lasted from several weeks to several months. However, three patients died within two years after surgery. One of them committed suicide at the age of 84 years. The other early causes of death were a fatal pulmonary embolism from a cava thrombosis due to a large liver nodule in one patient and septic complications in another patient receiving continuous intravenous glucose administration. The latter patient showed somatostatin-receptor positive metastases of liver and bone but did not respond to radiopeptide therapy with labeled somatostatin analogs. The fourth patient survived for nearly 8 years receiving annual TACE treatments. The cause of death was obesity-related heart failure at the age of 71 years. The current median survival of all 10 patients is 2.6 years (range: 1.6–9.7 years). A 10-year survival plot as of 2004 for all 10 patients is shown in Figure 4

Discussion

Gastrointestinal neuroendocrine tumors have recently been extensively reclassified [30], and the treatment of these tumors has changed considerably. Management includes a more radical surgical approach of treatable tumor masses [23,24] and treatment of liver metastases by embolization or thermoablation [18,25,26]. In addition, the use of radiopeptide therapy is increasingly advocated [27].

In contrast to the study conducted by the Eastern Cooperative Oncology Group (ECOG, [13]) in all our 10 patients with malignant insulinoma the primary pancreatic tumor was resected. If feasible, hepatic tumor masses were simultaneously or subsequently removed by means of partial hepatectomy, total hemihepatectomy of the right hepatic lobe, and isolated metastasectomy.

To date, the ECOG trial remains the most cited chemotherapy trial in patients with well-differentiated pancreatic neuroendocrine tumors, and applied combinations of streptozocin, doxorubicin, 5-fluorouracil, and chlorozocin. Patients (n = 105) with advanced unresectable or metastatic islet cell carcinoma were enrolled, including six patients with malignant insulinoma. Primary surgical resection of the pancreatic tumor was not required in this study, and more than half of the patients presented with non-functioning tumors.

Insulinoma is a unique tumor that is most commonly benign and cured after surgical removal. However, patients with malignant metastatic insulinoma usually continue to have life-threatening and debiliating hypoglycemia even after resection of the tumor. These patients require additional treatment and therefore are not able to be enrolled in controlled studies. Here we report our own experience with 10 patients newly diagnosed after 1992, the publication year of the ECOG trial. Only the first two patients in the series received a temporarily effective conventional intravenous streptozocin mono-chemotherapy for 12–18 months. Thereafter hepatic chemoembolization was chosen as the first-line procedure in all patients with hepatic disease and it included a high-dose streptozocin bolus for transarterial perfusion of the liver. Thus, an average weekly conventional dose was directly administered into the liver over a period of 1 hour. Side effects were neglegible because of use of modern antiemetic pharmacotherapy. In addition, significant increases of serum creatinine or proteinuria as a consequence of potential nephrotoxicity were never recorded even after cumulative doses of > 30 g.

After chemoperfusion an appropriate occlusive embolization of selected hepatic vessels or major lobe arteries was performed, and the success was documented angiographically. Embolization was repeated to treat recurrence of hypoglycemic attacks, with largely varying intervals in individual patients. In the four patients who died from aggressive tumors, embolization intervals were as short as 6–8 weeks. In patients with stable disease the intervals could be extended as long as 1 year. In patients with evidence of metastases, hormonally inactive or invisible angiographically, liver chemoperfusion was performed at 3- to 6- month intervals for the first 3 years, and annually thereafter.

In summary, patients with malignant insulinoma should undergo surgical removal of the primary pancreatic tumor despite the presence of liver metastases likely to produce insulin. If appropriate, the surgery should be combined with hepatic tumor reduction. This procedure offers the opportunity to evaluate and control the extent of hepatic disease by means of repeated chemoembolization protocols without interference of the primary tumor. In patients with stable disease and occluded liver metastases, high-dose streptozocin chemoperfusion is recommended. Five of our 10 patients survived for more than 3 years, and 6 of them remain alive. A proven effect on survival cannot be concluded from this series because of the small number of patients. The promising effects of this well-tolerated treatment have to be weighed against the overall poor responsiveness of these tumors to conventional systemic chemotherapy with severe side effects.

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