

Ablative therapies for liver metastases of digestive endocrine tumours

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Abstract

Hepatic metastases are frequently encountered in patients with digestive endocrine tumors and their presence plays an important role in quality of life and overall prognosis. Surgery is the treatment method of choice for hepatic metastases but this is frequently impossible due to the extent of disease. Systemic chemotherapy is offered to patients with diffuse and/or progressive liver metastases but results are disappointing especially in patients with metastases of midgut origin. In the latter patients with carcinoid syndrome, somatostatin analogs are frequently initially effective but their efficacy wanes due to disease progression and development of tachyphylaxis. Other therapeutic options in the treatment of hepatic metastases are locoregional strategies where vascular occlusion induces ischemia in these highly vascular tumors using either surgical or radiological techniques. Available methods include surgical ligation of the hepatic artery, transient hepatic ischemia or sequential hepatic arterialization. Trans-catheter arterial chemoembolization has proven effective in terms of long palliation and objective tumor responses. Other treatments aimed at regional destruction either alone or in combination with surgery include radiofrequency ablation and cryotherapy. The latter are usually important adjuncts to surgery and are usually reserved for limited disease.

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Introduction and rationale for local treatment strategies

Hepatic metastases in patients with digestive endocrine tumors are frequent (25–90%) and their presence has obvious implications in terms of patients' quality of life and overall prognosis. The 5-year survival rates for patients with hepatic metastases of midgut origin (midgut carcinoids) are 0–40% compared with 75–99% in those free of liver metastases (Godwin 1975, Zeitels *et al.* 1982, McDermot *et al.* 1994). The presence and extent of liver metastases has also been shown to be of prognostic significance in patients with gastrinomas (Jensen 1999). The National Institutes of Health (NIH) group found the 10-year survival figures went from 96% in patients without liver metastases to 85% in those who developed hepatic metastases during follow-up compared with 26% for patients with synchronous liver involvement at diagnosis (Jensen 1999). Similar results have been observed for other types of endocrine tumors of pancreatic origin with 5-year survival rates of 40 and 100% in patients with and without liver metastases respectively (Madeira *et al.* 1998). In addition, the rate of progression of liver metastases has also been shown to be of prognostic significance and should be taken into consideration prior to choosing management

strategies (Sutliff *et al.* 1997, Madeira *et al.* 1998). Apart from the prognostic implications of liver metastases, these tumors may also result in endocrine hyperfunction resulting in symptoms which are frequently difficult to control. Lack of response to somatostatin analogs due to tachyphylaxis is well described in the carcinoid syndrome (O'Toole *et al.* 2002) and measures to decrease peptide secretion have included cytoreductive surgery (Ahlman *et al.* 1996).

Liver metastases of endocrine origin are frequently diffuse at the time of diagnosis and this often precludes curative surgical options (McEntee *et al.* 1990). The fact that metastatic disease in digestive endocrine tumors is often isolated to the liver without other metastases means that local treatment strategies such as embolization or chemoembolization are favored. Systemic chemotherapy in patients with diffuse and/or progressive liver metastases using mainly streptozotocin (STZ) in combination with 5-fluorouracil and/or anthracyclines have yielded disappointing results in terms of objective responses, and a clear impact on patient survival is lacking (Broder & Carter 1973, Kessinger *et al.* 1983, Moertel *et al.* 1994). This is especially true for patients with liver metastases of midgut origin where systemic chemotherapy has very poor efficacy (Engstrom *et al.* 1984).

Vascular occlusive therapies with induction of ischemia to treat hepatic metastases have been adopted for some time using surgical ligation of the hepatic artery, transient hepatic ischemia or sequential hepatic de-arterialization. Abrogation of the blood supply to hypervascular tumors, such as liver metastases of digestive endocrine tumors which derive their blood from the hepatic artery, can be achieved using surgery or under radiological control. Arguments in favor of a combination of intra-arterial chemotherapy with embolization or surgical ligation of the hepatic artery include the fact that certain drugs such as doxorubicin, mitomycin C and STZ are more efficacious in anoxic cells (Roche 1989), and anoxia and reduced vascularization can increase intra-tumoral drug concentrations and dwelling times in cancer cells (Taourel *et al.* 1994, DeBaère *et al.* 1995).

Here, we outline the historical aspects and currently available regional therapeutic options for treating patients with liver metastases of endocrine origin with emphasis on chemoembolization.

Surgical ligation of the hepatic artery and transient hepatic ischemia

The treatment of liver metastases to the liver by dearterialization was first proposed by Bengmark and colleagues in 1974. While the beneficial effects of ischemia on hepatic tumor deposits were obtained in patients with metastatic endocrine tumors as witnessed by improvement in symptoms and decreases in tumor markers, namely urinary 5-hydroxy-indoleacetic acid (5-HIAA) levels (Jugdutt *et al.* 1975, Sivula & Sipponen 1976), clinical response was short-lived (~ 4 months) largely due to revascularization from collaterals. The technique was abandoned following recognition of its high peri-operative morbidity rates with frequent complications (abscess formation and gall bladder perforations) and unacceptably high mortality (up to 20%) (Arcenas *et al.* 1995).

A second technique was also developed by Bengmark's group in 1982 where following isolation of the hepatic artery, a silastic ring was passed around it and exteriorized through the abdominal wall (Bengmark *et al.* 1982). In the days following surgery, the hepatic artery was occluded by traction for a few minutes daily. Reasonable results were obtained in 19 patients with metastatic disease from mid-gut carcinoids with improvement in symptoms in 63% of patients at 1 year and objective tumor responses in 37% of patients (Bengmark *et al.* 1982). The same group went on to modify this method developing a system with an implantable vascular occluder placed around the hepatic artery (an inflatable balloon connected to an implantable subcutaneous port) permitting intermittent occlusion of the hepatic artery (Persson *et al.* 1989). Of 7 patients with carcinoid syndrome, 5 were symptom-free at 4.7 years from treatment and all had initial biochemical responses (Persson *et al.* 1989).

Sequential hepatic artery embolization

Hepatic arterial embolization using a percutaneous Seldinger technique under radiological control was developed for metastatic endocrine tumors in the early 1970s (Allison *et al.* 1977). Following catheterization of the hepatic artery, an hepatic arteriogram was obtained demonstrating anatomic hepatic arterialization, tumor vascularization followed by careful appraisal for portal vein patency. Selective catheterization of hepatic artery branches in the vascular distribution of the tumor, as proximal as possible to avoid rapid collateral development, was followed by contrast injection and embolization of fragments of absorbable gelatin sponge. The technique for hepatic artery embolization remains much the same in current practice; however advances in materials have made selective catheterization feasible. Another modification stems from the use of different embolizing agents. In carefully selected patients, hepatic arterial embolization has been shown to offer a significant survival benefit in patients with unresectable hepatocellular carcinoma (HCC) and its use in the management of both HCC and other metastatic disease (e.g. colorectal cancer) has led to important advances in techniques and the materials employed (Ahrar & Gupta 2003).

Ajani *et al.* (1988) examined the value of sequential percutaneous hepatic artery embolization with polyvinyl alcohol particles in 22 patients with duodenopancreatic endocrine cancers metastatic to the liver (9 gastrinomas; 2 glucagonomas; 11 non functioning tumors). Ninety-seven embolizations were performed with a median number of 4 (range 1 to 12) per patient. Twelve of twenty evaluable patients had a partial response (subjective improvement and decrease in hormone levels) with a median survival of 33.7 months (range 1 to 72) (Ajani *et al.* 1988). These results were confirmed by Marlink *et al.* (1990) showing symptomatic improvement as well as biochemical and morphological responses in 10 similarly treated patients with liver metastases from midgut or duodenopancreatic endocrine tumors.

Trans-catheter arterial chemoembolization (TACE)

Technique

The same basic technique for hepatic arterial embolization applies to TACE where a diagnostic superior mesenteric and celiac trunk arteriography is first obtained to evaluate distribution of hepatic arteries, portal blood flow, and the number and location of hepatic metastases. An emulsion is then made of cytotoxic drug (adriamycin 50 mg/m² or STZ 1.5 g/m²) dissolved in 10 ml normal saline (0.9%) combined with 10 ml iodized oil (Lipiodol) which is injected into the branches of the hepatic artery distal to the origin of the gastroduodenal artery. This is followed by embolization with gelatin sponge 2–3 mm particles or microspheres (Embosphere), which are

placed distally in the hepatic artery until a marked decrease in blood flow is observed (Therasse *et al.* 1993). Patients should be pre-medicated with i.v. hydration and antibiotics (for up to 72 h post procedure) and somatostatin analogs (in cases of carcinoid syndrome to avoid a crisis); provision for anti-emetics and adequate analgesia should be made following the procedure. In the case of STZ use, general anesthesia is warranted due to the intense pain associated with its highly acidic nature (pH 3.5–4.5). The interval of time between sessions varies from 1 to 3 months and the need for repeated sessions should be guided by the individual patient's response. As in all cases of hepatic arterial embolization, contraindications include complete portal vein occlusion, hepatic failure and previous biliary anastomoses (Roche 1989). Diffuse liver involvement without hepatic failure is not a contraindication and the procedure can be alternately performed in both liver lobes.

Indications for chemoembolization

It should be stressed that chemoembolization and other ablative therapies should be largely reserved for patients with advanced tumors which are not amenable to surgical cure (2-stage hepatectomies are currently feasible in the presence of bi-lobar non-diffuse liver metastases (Ahlman 1996, O'Toole *et al.* 2002)). In patients with either progressive or symptomatic tumors of midgut origin and if metastases are confined to the liver, chemoembolization can be proposed as a first-line treatment. Extensive hepatic metastases from tumors of duodenopancreatic origin are normally treated with systemic chemotherapy but as the overall prognosis pertains to hepatic metastases, alternating chemoembolization with chemotherapy may be an alternative approach even in the presence of systemic disease (authors' personal experience); additionally chemoembolization may also be proposed after failure of systemic chemotherapy or to control symptoms of hormone excess in such patients.

Results of TACE

Symptom control and tumor marker response

As summarized in Table 1, TACE has proven effective in symptom relief of between 60 and 100% of patients treated. Long-term palliation (>4 years) can be achieved with repeated TACE sessions (Roche *et al.* 2003). Most studies have been primarily devoted to patients' metastases from midgut carcinoids (which is logical given the poor response to systemic chemotherapy in these patients) and thus the clinical benefit has been correctly assessed by using carcinoid syndrome symptoms as an accurate marker of response. Nonetheless, clinical responses have also been observed following TACE for metastases from foregut and indeed hindgut tumors. Sustained improvement in hypoglycemic episodes have been reported in some cases of patients with metastatic insulinomas (Nesovic *et al.* 1992, Dominguez *et al.* 2000) but some small series and case reports have documented symptomatic improvement in other types of functional tumors of duodenopancreatic origin (Lee *et al.* 1988, Casadei *et al.* 1999). Sustained decreases in urinary 5-HIAA (>50% reduction) have been demonstrated following TACE in between 50 and 91% of patients with carcinoid syndrome (Ruszniewski *et al.* 1993, Therasse *et al.* 1993, Clouse *et al.* 1994, Diaco *et al.* 1995, Ruszniewski & Malka 2000, Roche *et al.* 2003).

Tumor responses

Tumor response rates according to the World Health Organization (WHO) criteria following TACE are given in Table 2 (Mavligit *et al.* 1993, Ruszniewski *et al.* 1993, Therasse *et al.* 1993, Clouse *et al.* 1994, Diaco *et al.* 1995, Ruszniewski & Malka 2000, Roche *et al.* 2003). Overall, objective response rates of between 33 and 86% have been observed and differences do not appear to be related to tumor type.

Table 1 Symptoms and hormonal secretion

Reference	No./Type	Chemotherapy	Sustained relief (%) (in symptomatic pts)	5-HIAA decrease > 50% (results only for CT)
Therasse <i>et al.</i> (1993)	23/CT	ADR	100	91
Ruszniewski <i>et al.</i> (1993)	18/CT 5/ICC	ADR	73	57
Clouse <i>et al.</i> (1994)	14/CT*	ADR	90	69
Diaco <i>et al.</i> (1995)	10/CT	CDDP, MMC, ADR**	100	—
Ruszniewski & Malka (2000)	8/CT 7/ICC	STZ (1.5 g/m ²)	67	50
Roche <i>et al.</i> (2003)	10/CT 4/other	ADR	70	75

ICC, islet cell tumor; CT, patients with carcinoid syndrome mostly from midgut origin; ADR, adriamycin; MMC, mitomycin; CDDP, cisplatin.

*Mostly CT; all 14 tumors were functionally active; ** sequential intra-arterial 5-fluorouracil also administered.

Table 2 Variations in tumor size (according to WHO criteria)

Reference	No./Type	Objective response (%)	Mean duration (months)	Progression rate (%)
Therasse <i>et al.</i> (1993)	23/CT	35	—	12
Ruszniewski <i>et al.</i> (1993)	18/CT 5/ICC	33	21	17
Mavligit <i>et al.</i> (1993)	5/ICC	80	18.5	—
Clouse <i>et al.</i> (1994)	20/CTor ICC	78	6–8.5	—
Diaco <i>et al.</i> (1995)	10/CT	60	42.5	—
Ruzniewski & Malka (2000)	8/CT 7/ICC	53	10.5	26
Roche <i>et al.</i> (2003)	10/CT 4/other	86	—	14

ICC, islet cell tumor; CT, patients with carcinoid syndrome mostly of midgut origin.

In addition, the choice of cytotoxic compound employed has also varied as well as the intervals between TACE sessions thus making comparative analysis difficult. Other confounding variables may include the use of concomitant somatostatin analogs, which are almost universally given to patients with active carcinoid syndrome. However, these patients have usually had chronic treatment with such agents and therefore both symptomatic and objective changes should be attributable to TACE. Indeed, a recent series confirmed previous results in 14 patients treated with TACE as a first-line option (Roche *et al.* 2003) with an objective morphological diminution in size of liver metastases in 12 of 14 (86%) patients (10 with midgut carcinoids) treated. In addition, the 5- and 10-year survival rates from diagnosis were 83 and 56% respectively (Roche *et al.* 2003).

Tolerance and complications

Overall, minor side effects due to the post-embolization syndrome are common with mild and transient nausea and vomiting (50–70%), abdominal pain (50–60%), fever up to 38.5 °C (30–60%) and raised liver transaminases (100%). Such symptoms are easily controlled and patients should be made aware that such symptoms may persist for several days. Major complications are rarely seen in TACE but renal and liver failure and bleeding peptic ulcers have been observed. A final point concerns the development of local complications such as stenosis to the hepatic artery or its side branches as observed with repeated TACE sessions. While to date this has not resulted in complications which are clinically apparent, it may make further treatment sessions difficult or pose vascular problems in candidates for potential hepatic transplantation.

Radiofrequency ablation, cryoablation and percutaneous alcohol injection

Tumor destruction with alcohol injection

Ultrasound-guided percutaneous alcohol injection, used frequently in the treatment of hepatocellular carcinoma, has also

been employed to treat unresectable liver metastases from colorectal and endocrine tumors (Livraghi *et al.* 1991, Giovannini & Seitz 1994). Alcohol acts by causing coagulative necrosis, followed by the formation of fibrotic and granulomatous tissue and thrombosis of small vessels, and can be used to treat small lesions of 3 to 5 cm. Much of the experience in percutaneous alcohol therapy of metastases comes from treatment of patients with metastases of colorectal origin, and necrosis is achieved in approximately 50% of cases (Giovannini 2002). While worries as to the inhomogeneous distribution of ethanol within metastatic liver tumors has been raised (Vogl *et al.* 1999) its distribution in highly vascularized endocrine tumors seems greater and allows for perhaps better response rates (Livraghi 1993). Lack of controlled studies and series with large numbers of patients makes interpretation of results pertaining to endocrine metastases difficult. The variable response to percutaneously administered alcohol in the treatment of various types of liver metastases led to the development of other interventional treatments such as radiofrequency and cryotherapy.

Radiofrequency ablation

In situ ablation has potential for the treatment of patients with liver tumors (either primary or secondary lesions) either as a single-modality treatment or in combination with liver resection. Usually, such treatment modalities are reserved for patients with localized and limited or residual disease. Radiofrequency (RF) thermal ablation works by converting RF waves into heat. A high-frequency alternating current, approximately 460 kHz, passes from an uninsulated electrode tip into the surrounding tissues and causes ionic vibration as ions follow the change in the direction of the rapidly alternating current. Friction heating between tumoral particles surrounding the electrodes results in cellular destruction at temperatures above 60 °C (Liu *et al.* 2003). RF ablation has been reported to be an important adjunct in the treatment of hepatic metastases of colorectal origin (Liu *et al.* 2003). Hellman and colleagues (2002) recently used RF alone ($n = 14$)

or in combination with surgery to treat 43 liver metastases in 21 patients with endocrine tumors (12 midgut carcinoids; 4 non functional endocrine pancreatic tumors; 1 VIPoma; 1 glucagonoma; 1 gastrinoma; 2 adrenal carcinomas). Of the 15 patients treated with curative intent, cure (i.e. no residual macroscopic tumor) was observed in 4 patients. Two complications occurred: one patient had a conservatively treated bile leakage, and another patient had a pleural effusion and fever for 7 days post RF. Two lesions developed signs of incomplete necrosis after 6 months, giving a local recurrence rate of 4.6%.

Cryotherapy

Hepatic cryotherapy involves the freezing and thawing of liver tumors by means of a cryoprobe inserted into the tumors (Liu *et al.* 2003). During freeze/thaw cycles, intracellular and extracellular ice formation occurs in an area termed ‘the ice-ball’ leading to tumor destruction. Use of hepatic cryotherapy at laparotomy or laparoscopy surgery for patients with endocrine metastases has been used for a number of years (Cozzi *et al.* 1995, Shafir *et al.* 1996, Shapiro *et al.* 1998, Seifert *et al.* 1998, Duperier *et al.* 2001, Sheen *et al.* 2002, Tait *et al.* 2002) and has demonstrated successful results in terms of symptom control and objective tumor responses (Cozzi *et al.* 1995, Shapiro *et al.* 1998, Seifert *et al.* 1998). Cryotherapy is an important supplement to surgical resection and allows regional destruction to lesions not amenable to resection.

Conclusion

In summary, TACE is an excellent method of treatment of non-resectable metastases from endocrine tumors of digestive origin and gives acceptable results in terms of control of symptoms and tumor response. TACE can also be combined with systemic treatments in selected patients with hepatic metastases and other extra-hepatic disease so as to halt hepatic disease progression and thus have an impact on overall survival. Successful strategies aimed at regional destruction either alone or in combination with surgery include RF ablation and cryotherapy. The latter are usually important adjuncts to surgery and are reserved for limited disease.

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