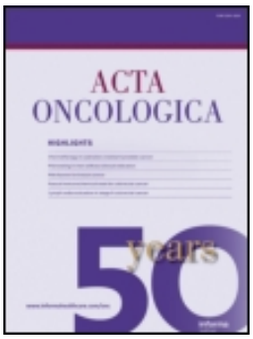

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**REVIEW ARTICLE**

# Treatment of endocrine pancreatic tumors

MARIE-LOUISE FJÄLLSKOG[1] & EVA TIENSUU JANSON[2]

[1]*Departments of Oncology, Radiology and Clinical Immunology, University Hospital, SE-751 85 Uppsala, Sweden,*
[2]*Department of Medical Sciences, University Hospital, SE-751 85 Uppsala, Sweden*

**Abstract**
Endocrine pancreatic tumors are rare with an incidence of 4 per million inhabitants. Most tumors are malignant except for insulinomas that usually are benign. They are slowly growing in the majority of cases but there are exceptions with rapidly progressing malignant carcinomas. Because of the rarity of these tumors large randomized trials are difficult to accomplish. However, most physicians treating these patients agree that surgery should be considered in all cases and that medical treatment with chemotherapy and biotherapy is well established for this group of patients.

Treating patients with endocrine pancreatic tumors (EPTs) is challenging in several different aspects. Both tumor proliferation and hormone production, which can be potentially life threatening, have to be considered. EPTs are classified as functioning if they are associated with clinical syndromes due to hormone release and as non-functioning if they are not. The most common syndromes are insulinomas, which are characterized by hypoglycemias, gastrinomas by repeating ulcers, glucagonomas by necrolytic migrating erythemas and VIPomas by excessive diarrhea [1–4]. Tumors producing somatostatin, ACTH (adrenocorticotropic hormone), GH (growth hormone), calcitonin and recently ghrelin have also been described [5–9]. EPTs have a tendency to switch hormone production thereby causing a change from one syndrome to another. Relevant biomarkers and medical history should be screened on a regular basis to avoid unexpected symptom-generating hormone production.

Another challenge regarding treatment of EPTs is that while most endocrine pancreatic tumors are slowly growing there are quite a few patients with rapidly growing tumors requiring a different type of approach [10]. In the last clinicopathological classification regarding neuroendocrine tumors clinical syndromes, tumor morphology and behavior-predicting parameters are considered. EPTs are divided into well-differentiated endocrine tumors, well-differentiated endocrine carcinomas and poorly differentiated carcinomas where also proliferation, measured as Ki-67, is accounted for [11]. See Table I.

Chromogranin A is a protein which is co-stored and co-released with peptides and amines from granules in endocrine cells. Almost all patients with EPTs have elevated plasma levels of Chromogranin A making it an important tool both in the diagnostic work-up and evaluation of treatment efficacy [12,13].

There is some controversy regarding treatment of EPTs, partly due to the limited numbers of patients making prospective randomized trials difficult to accomplish [10]. Hence, treatment decisions based on high evidence levels are infrequent; instead decisions are based on small non-randomized studies and vast clinical experience. Therefore, these uncommon patients should be treated in large and well-experienced centers where a multidisciplinary approach can be applied and studies performed.

The data and treatment suggestions presented in this paper are in accordance with the recently published guidelines for management of gastroenteropancreatic neuroendocrine tumors issued by the Nordic Neuroendocrine Tumour Group [14,15]. In this paper we have focused on the clinical treatment of patients with endocrine pancreatic tumors.

Correspondence: Marie-Louise Fjällskog, Department of Oncology, University Hospital, SE-751 85 Uppsala, Sweden. Tel: (46 18) 6110000. Fax: (46 18) 6115528. E-mail: marie-louise.fjallskog@ medsci.uu.se

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Table I. Clinicopathological classification of endocrine tumors of the pancreas [11].

| |
|---|
| Well-differentiated endocrine pancreatic tumor |
| Benign behavior: confined to the pancreas, nonangioinvasive, <2cm in size, Ki67 ≤2% |
| *Functioning* |
| -Insulinoma |
| *Nonfunctioning* |
| Uncertain behavior: confined to the pancreas, >2cm in size or angioinvasive, Ki67 ≥2% |
| *Functioning* |
| -Gastrinoma, insulinoma, VIPoma, glucagonoma, somatostatinoma, or inappropriate syndromes[a] |
| *Non-functioning* |
| Well-differentiated endocrine carcinoma |
| Low grade malignant with gross local invasion and/or metastases, Ki67 2–10% |
| *Functioning* |
| -Gastrinoma, insulinoma, VIPoma, glucagonoma, somatostatinoma, or inappropriate syndromes[a] |
| *Non-functioning* |
| Poorly differentiated endocrine carcinoma |
| High grade malignant (small to intermediate cell) carcinoma, Ki 67 >10% |
| [a]Inappropriate hormone syndromes: Cushing (ACTH), acromegaly or gigantism, hypercalcemia, etc |

## Invasive treatment

### *Surgery*

Complete surgical removal of an endocrine pancreatic tumor can be potentially curative but is rarely possible because of metastatic spread [16]. The proportion of patients with resectable liver metastases is only 10% [17]. However, several studies have shown that surgery should be considered despite advanced disease. Partial hepatectomy combined with removal of the primary tumor can result in prolongation of life and possibly cure for patients with metastatic disease [17,18]. Surgical debulking has also proven effective in providing palliation by decreasing hormonal overproduction and local mechanical pressure [19,20]. Despite these promising data, aggressive surgery in metastatic EPTs is controversial and not always performed because of its possible morbidity and mortality. In 1996, Berlin Consensus Conference on neuroendocrine gastroenteropancreatic tumors stated that in spite of the absence of controlled data available to support an aggressive surgery management policy, "primary tumors, liver metastases and extra hepatic metastases should be extirpated if possible" [21]. Since then morbidity and mortality along with survival benefit have been further elucidated in several recently published papers where aggressive surgery of the primary tumor was combined with partial hepatectomy [22–24]. In these studies mortality and morbidity rates were acceptable (0–5% and 18–45%, respectively). Median survival was 6.3–7.5 years which is superior to previously reported 1.7–3.1 years for unresected patients with hepatic metastases [25,26].

Considering these data all patients with endocrine pancreatic tumors should be discussed with a surgeon who has a special interest in these patients.

### *Radiofrequency ablation*

Tumor debulking in the liver can be achieved by local ablation. Today, radiofrequency ablation (RF) has been increasingly used to induce tumor necrosis. Recently, a paper was published on treatment with RF using a cooled-tip needle in 21 patients with mixed endocrine tumors [27]. Forty-three liver metastases were locally ablated using this technique with a success rate, defined as complete radiological necrosis, of 96%. The procedure was safe and efficient. In another study 42 liver metastases were ablated using laparoscopic RF achieving symptom relief in 95% of the patients with significant or complete symptom control in 80% of the patients for a mean of 10 months. Sixty-five percent of the patients showed a partial or significant decrease in their tumor markers during follow-up [28]. There was no mortality and morbidity was 5%. Although RF treatment may seem promising its role in neuroendocrine tumors needs further clarification.

### *Liver transplantation*

During the last few years, liver transplantation has evolved as a potentially curative therapeutic option for patients suffering from neuroendocrine tumors without tumor spread outside the liver. In 1997, Lang et al. published a paper on liver transplantation for metastatic neuroendocrine tumors in 12 patients of which 5 suffered from EPTs [29]. Nine of 12 patients are still alive after a median survival of 55 months and four have no evidence of tumor with a median follow-up of 2–104 months after transplantation. The same group has later performed liver transplantation on 10 patients with EPTs where 9 of 10 patients are alive after a median follow-up of 33 months and 2 are without evidence of disease [30]. The longest disease-free survival is more than 7 years.

In a more recent publication a Spanish group has reported on four patients with neuroendocrine tumors originating from the pancreas and one from the small bowel undergoing liver transplantation [31]. Two patients are alive and free of tumor 3 and 6 years after transplantation whereas 3 died early.

Table II. Chemotherapy regimens in EPTs.

| Regimen | No | OR | Duration | References |
|---|---|---|---|---|
| STZ | 52 | 42% | 13 months | Broder and Carter[36] |
| Adriamycin | 20 | 20% | 4 months | Moertel et al. [37] |
| DTIC | 10 | 50% | 48 months | Altimari et al. [38] |
| STZ versus | 42 | 36% | 17 months for | Moertel et al. [39] |
| STZ+5-FU | 42 | 63% | both arms | |
| STZ +5-FU versus | 33 | 45% | 14 months | Moertel et al. [40] |
| STZ+adriamycin vs | 36 | 69% | 18 months | |
| Chlorozotocin | 33 | 30% | 17 months | |
| STZ+5-FU | 19 | 58% | 36 months | Eriksson et al. [41] |
| STZ+adriamycin | 25 | 36% | 22 months | |

No = number of patients, OR = objective response (>50% reduction in tumor markers or size),
Duration = duration of response.

To sum up, it seems like most patients develop tumor recurrences within the first years after liver transplantation while there are some long-term survivors and occasional patients that seem to be cured. The success rate of liver transplantation is probably correlated to the accuracy of the pretransplantation investigation, and every effort should be made to detect extra hepatic disease before liver transplantation is considered.

*Liver embolization*

The majority of patients with malignant EPTs have most of their tumor burden in the liver. The hepatic metastases derive almost all of their blood supply from the hepatic artery whereas normal liver parenchyma receives about 20–25% of its blood supply from the hepatic artery and the rest from the portal vein [32]. Because of its dual blood supply, the normal liver is protected against infarction caused by occlusion of hepatic arterial branches, while hepatic metastases undergo varying degrees of necrosis. Several reports have demonstrated that selective embolization of a hepatic artery branch can provide reduction of hormonal symptoms and tumor burden in patients with neuroendocrine gastrointestinal tumors [32–34]. Peripheral arterial embolization allows repeated embolizations since the vessels undergo recanalization.

Overall response rates from liver embolization vary between 50–90% and median duration of response is 10–15 months. Symptomatic and biochemical responses are more frequent than radiological responses (40–90% versus 15–40%). Complications such as postembolic syndrome with pain, fever, nausea, leucocytosis and liver enzyme derangements occur in 50–90% of the patients. Severe complications such as renal failure, liver necrosis, intestinal ischemia or cholecystitis, are noted in 10% of the patients and the mortality rate is 3–7% [32–34].

Liver embolization is considered standard treatment in patients with metastatic EPTs offering good palliation. The proceeding is safe provided that it is performed in well experienced centers with multidisciplinary back-up.

## Medical treatment

*Chemotherapy*

Streptozotocin is a nitrosurea compound which inhibits DNA synthesis by alkylation in all stages of the cell cycle [35]. It was chosen for treatment against islet cell carcinomas because of its previous shown activity in mouse leukemia and its cytotoxic effect on beta cells causing diabetes.

In 1973, Broder and Carter treated 52 patients with metastatic islet cell carcinomas with streptozotocin on a weekly schedule and achieved a response rate of 42% where responders showed a significantly higher 1-year survival rate and a doubling of median survival compared to non-responders [36]. See Table II. One decade later, doxorubicin administered every 3–4 weeks induced objective responses in 4 of 20 (20%) patients with heavily pretreated islet cell carcinomas [37]. Another attempt with a monotherapy regimen using monthly cycles of dacarbazine (DTIC) showed radiological responses in 5 of 10 patients with a median duration of response of 48 months [38].

Polychemotherapy has produced better results. In a randomized study 84 patients with advanced EPTs received either streptozotocin alone or streptozotocin combined with fluorouracil [39]. The combination treatment had significantly higher response rate (63 versus 36%) and rate of complete responses (33 versus 12%) than streptozotocin alone, but duration of response was equal in both arms (17 months). The combination treatment yielded a non-significant survival advantage of 26 versus 16.5 months over single treatment. Because of promising results with adriamycin as single treatment, Moertel et al. randomized 104 patients with advanced EPTs to treatment with streptozotocin combined with fluorouracil or adriamycin, or single treatment with chlorozotocin [40]. Streptozotocin plus adriamycin had a significantly higher response rate (69 versus 45 and 30%) and survival (2.2 versus 1.4 and 1.4 years) than the two other treatment arms. Durations of responses were 14–18 months. However, a previous study comparing streptozotocin combined with fluorouracil or adriamycin in 44 patients showed

higher response rate (58% versus 36%) and also significantly longer duration of response (36 versus. 22 months) for the fluorouracil-containing combination [41]. Median survival was 4.9 years which was more than double as high as reported in previous studies. Because of well-known cardiotoxicity for adriamycin and contradictory study results the combination with streptozotocin plus fluorouracil is most commonly preferred today. During the last years a liposomal adriamycin has been registered showing equal efficacy but much less cardiotoxicity than adriamycin. Moertels promising results in the beginning of the 90's with 69% response rate combining streptozotocin with adriamycin has led to a study combining liposomal adriamycin with streptozotocin. Study results with response rates and incidence of cardiotoxicity are currently being processed and will be published shortly.

Streptozotocin is known to be a nauseating drug and despite adequate premedication with 5-hydroxytryptamine (5-$HT_3$)-blockers approximately 10% vomit [42]. Dose-related renal dysfunction including proteinurea and decrease in creatinine clearance is the dose-limiting factor which occurs in 20–70% of the patients. However, blood counts are rarely affected [35].

There is a subset of patients with EPTs that are poorly differentiated and behave aggressively from initial diagnosis and others that start out as indolent tumors suddenly changing their behavior into rapidly progressing tumors. For these aggressive tumors previous treatments are not enough. The most common malignancy derived from neuroendocrine cells, small cell lung cancer, is a rapidly growing malignancy which responds well to treatment with cisplatin combined with etoposide. The same regimen was tried in 45 patients with neuroendocrine gastroenteropancreatic carcinomas [43]. Among patients with anaplastic tumors 67% achieved partial or complete response whereas only 7% of patients with well-differentiated tumors responded partially. Duration of response was 8 months for anaplastic tumors and median survival 19 months which seemed favorable compared to results from previous studies on this aggressive tumor type. Two years ago data was published from a study using a similar regimen when treating heavily pretreated patients with poorly differentiated and/or rapidly progressing neuroendocrine carcinomas [44]. The results confirm previous good results achieving almost 60% response rate among foregut carcinoids and 50% response rate among EPTs. Duration of response was 9 months which was similar to that achieved by Moertel. However, median survival in the study was 38 months which was higher than expected in this category of aggressive and poorly differentiated carcinomas.

Nephrotoxicity is the dose-limiting factor in treatment with cisplatin and etoposide occurring in two-thirds of the patients. Hematological toxicity is universal, even though septic fevers and/or hospitalizations due to this are uncommon [43,44].

Chemotherapy is efficacious in producing responses, both biochemically and radiologically, and in prolonging lifes in patients with EPTs. Streptozotocin combined with fluorouracil is the first choice of chemotherapy. However, if the tumor is poorly differentiated and/or rapidly growing cisplatin combined with etoposide should be chosen instead.

### *Biotherapy*

α-interferon was initially discovered in 1957 [45] and it has later been shown to induce cell blocking in G0 and G1, reduce mRNA for hormones and growth factors and to generally stimulate the immune system [46,47]. In 1983, Öberg et al. published data showing that α-interferon could control hormone secretion, clinical symptoms and tumor growth in carcinoid tumors [48]. Since EPTs are closely related to carcinoids, a study was conducted on 18 patients with advanced EPTs receiving 3–6 MU human leucocyte α-interferon daily [49]. Objective responses (more than 50% reduction in tumor markers or size) were achieved in 77% of the patients with radiological responses in 35% of the patients with a median duration of 8.5 months. A few years later the same authors reported an objective response rate of 51% with a median duration of 20 months when treating 57 patients with α-interferon at a dose of 15–18 MU weekly. In this study only 12% of the patients achieved a radiological response, which is well in line with later published studies.

Previously reported side-effects from treatment with α-interferon are influenza-like symptoms (77%), weight loss (59%), chronic fatigue syndrome (50%), bone-marrow depression (anemia, leucopenia, thrombocytopenia) (38–66%) and transient liver dysfunction (13%) [49]. Autoimmune phenomena, such as systemic lupus erythematosus, vasculitis, polymyositis or thyroiditis, are experienced by about 10–15% of the patients [50]. About 5% of the patients develop neutralizing antibodies with loss of therapeutic effect, which can be restored after switching to natural interferon [51]. Another side effect is mental depression [52], which can be successfully treated with antidepressant therapy.

Somatostatin is a naturally occurring peptide, which was discovered by Brazeau in 1973 [53]. It has been shown to inhibit hormone release, impair

gall bladder and gastrointestinal motility and to inhibit tumor growth in vitro [54]. Somatostatin acts through five different somatostatin receptors and induce different second messenger systems depending on which receptor is stimulated. Inhibition of hormone secretion is mediated through somatostatin receptors 2 and 5 [55], growth inhibition through receptors 1,2 and 5 [56,57] and apoptosis through receptors 2 and 3 [58,59].

It is well known that neuroendocrine tumors express somatostatin receptors to a high extent and this is the rationale for treatment with somatostatin analogs in EPTs [60]. Somatostatin analogs are mainly used for symptomatic treatment because of their ability to decrease the level of circulating hormones [61]. The antiproliferative effect seen in vitro is rarely seen in patients [57]. In 1993, Eriksson et al. reported data from treatment of 19 patients with advanced EPTs with octreotide at a dose of 100 μg twice daily [42]. Significant biochemical responses were achieved in 31% of the patients with a median duration of 16 months. No radiological responses were seen. Arnold et al. claims that octreotide can inhibit tumor growth in metastatic gastroenteropancreatic tumors. They treated 52 patients with progressing disease (about one third EPTs) with 200 μg octreotide thrice daily and managed to achieve stable disease in 36.5% of them lasting for a median of 18 months [62].

Treatment with high-dose (up to 12 000 μg/day) lanreotide has shown biochemical response in 58% and tumor response rate in 11% of patients with neuroendocrine gastrointestinal tumors failing on treatment with standard doses of octreotide [63]. Induction of apoptosis could be demonstrated in the tumors.

Adverse effects from treatment with somatostatin analogs are mild compared to those seen with chemotherapy or treatment with interferon. Most side-effects such as nausea, transient abdominal pains, flatulence, diarrhea and local reaction at the injection site dissolve with time [42,62]. In 20–50% of the patients, gall-stones are formed, but these virtually always remain asymptomatic [64].

Combined treatment with α-interferon and somatostatin analogs has been shown to produce higher biochemical response rates than either drug alone in midgut carcinoids [65]. Recently, data was published from a study examining the effects of combination treatment in 16 patients with metastatic EPTs [66]. Biochemical response was achieved in more than 60% of the patients and objective radiological response in almost 20% of them, median duration of response 23 and 22 months, respectively. The results are encouraging with higher response rates for combination treatment both biochemically and radiologically, but the study did not manage to prove that combination treatment is better than either drug alone in EPTs. The combination treatment was not accompanied with additional adverse effects, apart from those previously described for each drug.

Recently, Faiss et al. published data from a prospective and randomized study comparing the antiproliferative effect of lanreotide, interferon-alfa and their combination in 80 patients with metastatic neuroendocrine gastroenteropancreatic tumors [67]. All treatment arms achieved similar rates of biochemical and objective responses. Symptomatic responses were achieved in all treatment arms but significant differences could only be shown in the combination arm compared to base-line. The antiproliferative effect was lower than that previously reported, only 5%.

Biotherapy is a well-established treatment in metastatic EPTs which mainly induces biochemical responses but also tumor reduction in some patients. Combination treatment with α-interferon and somatostatin analogs can induce responses that are comparable to those achieved by chemotherapy and it can be used as a good alternative treatment in patients that no longer responds to chemotherapy or in those who cannot or do not want to receive chemotherapy.

### *Treatment with radiolabelled somatostatin analogs*

Since neuroendocrine tumors contain high numbers of somatostatin receptors scintigraphy using the radiolabelled somatostatin analog octreotide (Octreoscan) has enabled in vivo visualization of the primary tumor and metastases. The first attempts to treat patients using high dose radiolabelled somatostatin analogs were reported about 10 years ago. In a phase I study, Krenning et al. treated 6 end-stage patients suffering from neuroendocrine tumors with [$^{111}$In-DTPA-*D*-Phe$^{1}$]-octreotide (OCT) up to a cumulative dose of 53 GBq per patient and achieved impressive effects on hormone production and a likely anti-proliferative effect without any major side effects [68]. These promising results have been repeated by a Swedish group treating five patients with neuroendocrine tumors with OCT at high doses (6 MBq every third week) and an American group treating 27 patients with neuroendocrine tumors with at least 2 monthly injections of 180-mCi OCT [69,70]. In the latter study biochemical response was achieved in 81% of the patients and objective tumor response in 8% of the patients. Patients included in the study had a life expectancy of 6 months and survival achieved in the study was threefold longer, 18 months. The treatments were

well tolerated with transient side-effects including nephrotoxicity and bone-marrow depression.

In recent years researchers have developed new somatostatin analogs with higher affinity for somatostatin receptors and they have also tried linking different radioisotopes to the analogs. If isotopes emitting β-particles, for example yttrium, are used neighboring cells might also be killed since β-particles can extend over several cell diameters. In a prospective phase II study, thirteen patients with endocrine pancreatic tumors were treated with four equal intravenous injections of a total of 7.4 GBq yttrium labeled octreotide ($^{90}$Y-DOTATOC) and achieved an objective response rate of 38% with one complete response [71]. Renal insufficiency was the dose limiting toxicity and one patient experienced non-transient renal insufficiency grade 2 despite infusion with amino acid for renal protection. The most common side-effect was nausea which could be successfully treated with domperidone or odansetron.

In a more recent study octreotate, which is a somatostatin analog with nine fold higher affinity for somatostatin receptor subtype 2 than octreotide, was used in conjunction with lutetium ($^{177}$Lu) which is a beta- and gamma-emitting radioisotope. Previous comparisons between patients receiving $^{111}$In-octreotide and patients receiving $^{177}$Lu-octreotate had shown comparable uptake in kidneys, liver and spleen but three to fourfold higher uptake in the tumors favoring $^{177}$Lu-octreotate [72]. Thirty-five patients with gastroenteropancreatic tumors were treated with a final cumulative dose of 600–800 mCi $^{177}$Lu-octreotate and of these one patient (3%) achieved a complete response and 12 (35%) achieved partial response [73]. Nausea was common, but no renal toxicity was reported. In this study even patients with grade 2–3 tumor uptake on Octreoscan were included and tumor response was significantly higher in patients with grade 4 uptake compared to grade 2–3 uptake.

Despite these promising results the place for radioactive targeting therapy is still not clear. The selection of patients and the timing for the procedure have to be further established.

### *Symptom relieving treatments*

All previously described treatments aim to reduce tumor burden and hence decrease hormone production, which will result in symptomatic improvement for the patients. However, sometimes these treatments are not enough to control the patients' symptoms. In these cases there are symptom relieving treatments that do not effect tumor burden or hormone production, but only alleviate the symptoms. Patients with insulinomas suffering from severe hypoglycemias might benefit from treatment with corticosteroids, which causes glucose intolerance with insulin resistance [74] or diazoxid, which reduces insulin secretion from beta cells resulting in increased blood glucose [75]. If the symptoms still are uncontrolled the patients need continuous intravenous infusion with glucose. Patients with glucagonomas may have the opposite problem suffering from hyperglycemias requiring injections of insulin lowering the blood glucose values. Glucagon production may result in skin lesions called necrolytic migratory erythema which often are successfully treated by injections of somatostatin analogs [76] but in severe cases treatment with amino acid and fatty acid infusions may be successful [77]. The introduction of proton pump inhibitors has been a break through for patients with gastrinomas suffering from repeating ulcers [78]. Severe diarrheas that often torment patients with VIPomas can be reduced by loperamid, opium drops and bulk-forming laxatives [79,80]. Tumors producing ACTH may be very aggressive with rapidly progressing Cushing's syndrome requiring substitution with potassium or medication with ketoconazol or metyrapone which both interfere in the synthesis of corticosteroids [81,82]. In severe cases with life-threatening Cushing's syndrome adrenalectomy has to be considered [83].

## Future aspects

New high-affinity and subtype selective somatostatin analogs for each of the five somatostatin receptors have been identified, but are not yet commercially available [84]. A somatostatin analog which binds selectively to somatostatin receptor 3 might induce apoptosis and thereby tumor regression to a greater degree than those available today. It has been suggested that somatostatin analogs act not only directly on tumor cells, but also on peritumoral vessels [85]. In a recent paper 23 tumor specimens from EPTs were examined regarding the expression of somatostatin receptors in intratumoral vessels and the authors found that somatostatin receptors 2 and 4 were highly expressed whereas the other three receptors were more rare [86]. There have been reports claiming that somatostatin potently inhibits angiogenesis [87]. Combination treatment with other known angiogenesis inhibitors might achieve stronger angiogenetic inhibition than single drug treatment.

Molecular targeting with tyrosin kinase inhibitors and monoclonal antibodies is a new and exciting approach to cancer treatment. Today there are tyrosine kinase inhibitors on the market inhibiting

signaling through c-kit, EGFR and PDGFRs which have proven effective in the treatment of gastrointestinal stromal tumors, chronic myeloic leukemia and lung cancer [88–93]. In a recently published study, 38 tumor specimens from EPTs were examined immunohistochemically showing that most tumor cells expressed c-kit and PDGFRb whereas about half expressed EGFR [94]. Furthermore, recently ZD 1839, which is an EGFR tyrosine kinase inhibitor, was found to induce growth inhibition, apoptosis and cell cycle arrest in human neuroendocrine gastrointestinal tumor cells [95]. These results are very interesting and it appears as though EGFR tyrosine kinase inhibition may be a promising novel approach for the treatment of neuroendocrine tumors. Clinical studies have been initiated and we await their results.

## Conclusion

Despite controversy regarding treatment of EPTs most physicians agree that surgery should be considered for all patients-as first-line treatment offering a chance for cure in a small number of patients [16] or as palliative treatment in patients with advanced stage disease where it may offer symptom relief and a delay for medical treatment [19,96]. Ablation of liver metastases using RF has shown promising results, but needs further clarification before used as standard treatment [27,28]. Liver transplantation is exciting, but additional studies are required to state which patients are suitable for this approach and the shortage of donor organs also needs to be considered [29–31]. Combination treatment with streptozotocin and 5-fluorouracil/doxorubicin have shown high response rates lasting for up to 3 years making it a standard medical treatment in many centers around the world [10]. An alternative to chemotherapy is treatment with somatostatin analogs and/or α-interferon which have shown good results with biochemical responses and symptom relief in most patients, however only few objective tumor responses [42,66,67]. Liver embolization can produce good biochemical symptomatic responses in patients with most tumor burden in the liver [32–34]. Promising results from treatment with radio labeled somatostatin analogs have been published during the last years showing positive effects both on symptoms, hormone levels and tumor size [68–73].

Consequently, there are several treatment options to consider when treating patients suffering from EPTs. The most difficult task is to decide which therapeutic intervention should be initiated and when. There is no obvious order in which different treatments should be begun. For example, in one patient surgery might be the first choice of therapeutic intervention whereas in another patient medical treatment with chemotherapy might be necessary to make the tumor operable. In a third patient, biotherapy and symptom releasing therapy might be first choice of treatments because of uncontrolled hormone production and/or poor general health etc. A multidisciplinary approach is obliged to provide for different needs in different patients. We strongly recommend that these patients be taken care of in centers where this is possible.

The present work with new somatostatin analogs and radioisotopes in the treatment of EPTs with radiolabelled somatostatin analogs is very exciting and we look forward to more studies establishing its role in the standard treatment arsenal. Molecular targeting is becoming increasingly important in oncology and we await clinical studies elucidating the role of tyrosine kinase inhibitors in EPTs.

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