Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic endocrine carcinoma

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Abstract

About 40% of nonfunctioning pancreatic endocrine carcinomas (NF-PEC) cannot be cured by surgery due to advanced stage disease. Somatostatin analogues have been proposed as first line therapy in these cases. We performed a prospective phase IV study to assess the efficacy of octreotide in advanced NF-PEC and identify factors predictive of response to therapy. Twenty-one consecutive patients with octreoscan-positive advanced-stage well-differentiated NF-PEC were treated with long-acting release octreotide 20 mg i.m. at diagnosis. The immunohistochemical expression of somatostatin receptor 2 (SSTR2) and the quantitative mRNA analysis of SSTR2 and SSTR5 were assessed in 12 tumours. The tumour proliferative fraction was assessed by immunohistochemistry for Ki-67. Eight patients (38%) had stable disease (SD) after a median follow-up of 49.5 months. Thirteen patients (62%) developed progression after a median of 18 months. Tumour progression correlated with a proliferative index $\geq$5% (P=0.016), weight loss (P=0.006) and absence of abdominal pain (P=0.003) at diagnosis. Other clinical (age, gender and primary tumour resection) or pathological parameters (site, size and liver metastasis) lacked significant correlation with tumour progression. No difference in the amount of SSTR2 mRNA and protein or SSTR5 mRNA was found between tumours that were stable (n=5) and seven tumours that progressed (n=7). Treatment with long-acting release octreotide was associated with stabilization of disease and a good quality of life in 38% of patients. A Ki-67 index $\geq$5% and/or the presence of weight loss may justify more aggressive therapy without waiting for radiologically proven progression of disease.

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Introduction

Pancreatic endocrine tumours (PET) are clinically defined as functioning (F-PET) or nonfunctioning (NF-PET) depending on the presence of symptoms due to hormone hypersecretion. According to the WHO classification, the vast majority of PETs, whether functioning or not, are classified as well-differentiated endocrine tumours that may be either benign or malignant (Kloppel *et al.* 2004). The latter are characterized by the presence of invasion or metastases and are termed pancreatic endocrine carcinoma (PEC) (Kloppel *et al.* 2004). The therapy of choice for these tumours is surgical resection with curative intent. However, almost 40% of the patients suffering from NF-PEC are not candidates for radical surgery due to either locally advanced disease or unresectable liver metastases (Gullo *et al.* 2003).

More than 80% NF-PEC express receptors for somatostatin (SMS) and may be easily identified by somatostatin receptor scintigraphy (octreoscan) (Reubi *et al.* 1990). Several studies, including three phase-II trials (Saltz *et al.* 1993, Arnold *et al.* 1996, Eriksson *et al.* 1997), reported frequent stabilization of

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the disease in progressive gastroenteropancreatic neuroendocrine tumours (Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Angeletti *et al.* 1999, Ricci *et al.* 2000, Aparicio *et al.* 2001, Panzuto *et al.* 2006). It is widely recognized that among the latter, NF-PEC has the worse prognosis and the shortest stabilization rate (Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Angeletti *et al.* 1999, Ricci *et al.* 2000, Aparicio *et al.* 2001, Panzuto *et al.* 2006).

The optimal treatment for advanced well-differentiated NF-PEC that are not suitable for radical surgery remains controversial (Oberg *et al.* 2004). Therapeutic options include SMS analogues (Kraenzlin *et al.* 1983, Saltz *et al.* 1993, Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Tomassetti *et al.* 1998, 2000, Angeletti *et al.* 1999, Ricci *et al.* 2000, Aparicio *et al.* 2001), chemotherapy with doxorubicin and streptozotocin (Murray-Lyon *et al.* 1968, Moertel *et al.* 1980, 1982, 1992, Cheng & Saltz 1999, Ramanathan *et al.* 2001, Delaunoit *et al.* 2004), chemoembolization (Ruszniewski & Malka 2000), and receptor-mediated radiotherapy (Paganelli *et al.* 2001, Waldherr *et al.* 2002).

Several clinical studies have evaluated the efficacy of SMS analogues in treatment of neuroendocrine tumours (Kraenzlin *et al.* 1983, Saltz *et al.* 1993, Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Tomassetti *et al.* 1998, 2000, Angeletti *et al.* 1999, Ricci *et al.* 2000, Aparicio *et al.* 2001, Panzuto *et al.* 2006). However, it is difficult to draw definitive conclusions and compare the results of these studies due to the heterogeneity of the patients enrolled. In fact, studies of therapeutic efficacies with SMS analogues have often included heterogeneous series of patients suffering from endocrine tumours with different anatomical sites of origin, functioning or nonfunctioning nature, and histological subtype. Additional confounding factors include the different timing for enrolment of patients (e.g. at diagnosis or with progressive disease (PD)) (Kraenzlin *et al.* 1983, Saltz *et al.* 1993, Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Tomassetti *et al.* 1998, 2000, Angeletti *et al.* 1999, Ricci *et al.* 2000, Aparicio *et al.* 2001). More importantly, follow-up information for NF-PEC treated with SMS analogues is available only for 18 patients, whose treatment started after documented progression of disease (di Bartolomeo *et al.* 1996, Angeletti *et al.* 1999, Tomassetti *et al.* 2000).

Here, we report a prospective single centre phase IV study restricted to octreoscan-positive well-differentiated nonfunctioning pancreatic endocrine carcinomas. Twenty-one consecutive patients were treated with long-acting release octreotide. All the patients were symptomatic, had either metastatic or bulky disease, and no previous therapy. Treatment with SMS analogues was started at diagnosis and continued until tumour progression was observed.

The aims of our phase IV study of the somatostatin analogue octreotide were (i) to determine the response rate, duration of response and overall survival of patients with advanced nonfunctioning pancreatic endocrine carcinomas expressing somatostatin receptors as demonstrated by octreoscan scintigraphy and (ii) to identify factors predictive of response to therapy.

Materials and methods

Patients and tissue samples

Patients with well-differentiated nonfunctioning PECs not suitable for radical surgery were enrolled after obtaining informed consent. The clinical study was single centre, prospective and not sponsored. All cases were classified according to the criteria established by the World Health Organization (Kloppel *et al.* 2004).

Inclusion criteria were positivity for somatostatin receptors upon octreoscan scintigraphy of all lesions visible by abdominal ultrasonography and CT scan. Exclusion criteria were previous chemotherapy or liver chemoembolization, pregnancy or life expectancy less than 6 months, and histological diagnosis of undifferentiated endocrine carcinoma.

The following parameters were recorded for each patient: age, sex, symptoms at diagnosis, serum neuron-specific enolase (NSE) and chromogranin A (CgA) (evaluated by IRMA SCHERING-CIS), tumour site and size, number and site of metastasis (liver, distant lymph nodes, lung and bone).

Tumour tissues were obtained from all patients either during intervention or by percutaneous needle biopsy under ultrasound guidance. Biopsies were fixed in formalin and paraffin-embedded as for routine diagnostic procedures. In 12 cases, more than one biopsy was obtained and the additional material was snap-frozen in liquid nitrogen and stored at $-80\ ^{\circ}C$ for RNA studies.

Expression of somatostatin receptors 2 and 5

The expression of somatostatin receptors 2 (SSTR2) and 5 (SSTR5) was assessed by quantitative RT-PCR in 12 patients for which frozen tissue was also available (12 primary tumours, three of which were with matched liver metastasis). ß-actin transcript levels were used for normalization and the SSTR2 and SSTR5 transcript levels of normal insulae of Langerhans were used as a control. Human islet preparations were obtained from pancreata of multiorgan donors

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obtained through the North Italian Transplant Organization using pancreas digestion according to the previously described automated procedures (Piemonti *et al.* 2002).

For tissue samples, RNA was prepared from 15 cryostat sections (40 μm thick) and checking the cellularity every five sections. Tissue sections were placed in 4 M guanidine thiocyanate containing 0.1 M 2-mercaptoethanol and centrifuged through a $CsCl_2$ gradient. cDNAs were synthesized from 1 μg total RNA using random primers and the Superscript II reverse transcription kit (Invitrogen). Quantitative RT-PCR mRNA expression analysis was performed using an ABI PRISM 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). PCRs contained 20 ng cDNA, 200 nM primers and 1× SYBR GREEN PCR Master Mix (Applied Biosystems) in a final volume of 25 μl. Sequences of primers used for PCR assays were: SSTR2-F, GTCCTCTGCTTGGTCAAGGTG and SSTR2-R, TGGTCTCATTCAGCCGGGATT; SSTR5-F, GCCTGGGTCCTGTCTCTGTG and SSTR5-R, TACCGCCCTCCTGCACGT; ß-actin-F, GGAGTCCTGTGGCATCCACG and ß-actin-R, CTAGAAGCATTTGCGGTGGA. Calibration curves for each couple of primers were obtained by serial dilution of cDNA. Similar PCR efficiencies (calculated as $10^{-1/\text{slope}}$) were assumed; therefore, expression data were analysed by the comparative threshold cycle (C_t) method accordingly to User Bulletin #2 (Applied Biosystems). The C_t value is defined as the PCR cycle number at which the fluorescence generated from a sample reaches intensity appreciably above the background signal. Results were expressed in terms of the $\Delta\Delta C_t$ value that represents the difference between the ΔC_t of the sample (ΔC_{t_s}) and the islet cells (ΔC_{t_i}). ΔC_{t_s} and ΔC_{t_i} are the difference in threshold cycle value between the target gene and the normalizer gene in the sample and the islet cells respectively. All experiments were performed in triplicate.

QRT-PCR data were expressed as relative to normal human pancreatic islet cells and the differences between the groups were evaluated by the Mann–Whitney test.

The expression of SSTR2 was also assessed by immunohistochemistry on formalin-fixed, paraffin-embedded material using an anti-SSTR2 antibody from Biotrend/Gramsch Laboratories (Schwabhausen, Germany) as described (Papotti *et al.* 2002). The tumour proliferative fraction was assessed by Ki-67 immunostaining as previously detailed, scanning at least 2000 neoplastic cells in randomly selected fields (Pelosi *et al.* 1996).

Somatostatin analogue treatment

Treatment consisted of an s.c. injection of octreotide (Sandostatina, SMS 201–995, Sandoz, Basel, Switzerland), 100 μg thrice daily for 2 weeks, followed by an i.m. injection of octreotide acetate LAR (Novartis) at a dosage of 20 mg on day 14 and then every 28 days until PD was observed. The treatment was in accordance with the official indications of the Italian Ministry of Health (Note 40, Health Ministry CUF deliberation 7.8.1998).

Response and survival evaluation

All patients were monitored every 3 months with contrast enhanced CT scan, clinical evaluation of symptoms and body weight, measurement of blood parameters and tumour markers. According to the criteria of the WHO (Miller *et al.* 1981), PD was defined as an increase of $\geq$25% of the product of tumour's largest perpendicular dimensions; stable disease (SD) as an increase $<$25% or a decrease within 50% of these measurements; and a partial response (PR) was considered as a decrease $>$50%. Biochemical response was defined as a CgA marker level reduction of $\geq$50%. Time to progression (TP) and survival were calculated from the first SMS analogue administration.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR). Quantitative data were assessed using the Mann–Whitney *U*-test. Qualitative data were analysed with the χ^2-test using Yates correction and Fisher's exact test when necessary. Survival and TP were analysed using Kaplan–Meier function and the Log-Rank test was used to verify differences between groups. All *P* values were two sided and considered significant when $<$0.05. All calculations were performed with SPSS 11.5 statistical package (SPSS, Chicago, IL, USA) and R software v. 2.1.1 and Survival package (http://www.R-project.org).

Results

Twenty-one consecutive patients, 8 males and 13 females (median age 59.2 years; IQR 52.5–70.9), were enrolled from January 1999 to March 2004. At the time of inclusion in the study, the predominant symptoms were weight loss in ten patients, abdominal pain in eight, palpable mass in four, anorexia in two, obstructive jaundice in two and upper digestive obstruction in a single case. All patients had advanced disease with either liver metastases (18 cases; 85.7%)

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or involvement of major vessels with a median primary tumour size 60 mm (IQR 45–75). The clinicopathological data are summarized in Table 1.

Eleven patients underwent surgery: two biliary and gastric by-passes were performed due to the presence of mechanical symptoms and five were exploratory-diagnostic procedures; the latter four were debulking procedures consisting in the resection of the primary pancreatic tumour (three left pancreatectomies and one pancreaticoduodenectomy) in metastatic patients. Cholecystectomy was performed in all patients undergoing surgery.

Table 1 Clinicopathological data of patients grouped by response to somatostatin analogue therapy

Disease	Stable ($n=8$)	Progression ($n=13$)	*P* value
Patients features			
M/F (%)	4/4 (50/50)	4/9 (31/69)	n.s.
Age at diagnosis (years)[a]	59 (51–64)	61 (53–71)	n.s.
	Patients (%)	**Patients (%)**	
Symptoms			
Biliary lithiasis	1 (12)	2 (15)	n.s.
Diabetes	1 (12)	7 (54)	n.s.
Peptic disease	4 (50)	1 (8)	0.05
Acute pancreatitis	1 (12)	0 (0)	n.s.
Arterial hypertension	0 (0)	5 (38)	n.s.
Abdominal pain	6 (75)	2 (15)	0.01
Obstructive jaundice	0 (0)	2 (15)	n.s.
Anorexia	1 (12)	1 (8)	n.s.
Vomiting	0 (0)	1 (8)	n.s.
Weight loss	1 (12)	9 (69)	0.02
Bowel habit change	0 (0)	1 (8)	n.s.
Palpable mass	1 (12)	3 (25)	n.s.
Tumour characteristics			
Tumour site			
Head-uncinate process	4 (50)	3 (23)	n.s.
Body–tail	2 (25)	9 (69)	n.s.
Total	2 (25)	1 (8)	n.s.
Liver metastases	6 (75)	12 (92)	n.s.
Size of primary tumour (mm)[a]	67.5 (52.5–100)	55 (37.5–70)	n.s.
Ki-67 (%)[a]	3 (1.7–3.2)	5 (3–9.5)	n.s.
Laboratory data			
CgA at diagnosis[a] (ng/ml) (normal value <98)	100 (29–553)	338 (68–789)	n.s.
CgA at the end follow-up[a]	130 (78–138)	660 (37–1310)	n.s.
NSE at diagnosis (ng/ml)[a] (normal value <12.5)	7 (6–9)	11 (8–15)	n.s.
Surgical treatment			
Resection of primary tumour	2 (25%)	2 (15%)	n.s.
Palliative surgical procedures	0	2 (15%)	n.s.
Explorative procedure	2 (25%)	3 (23%)	n.s.

[a]Median (IQR); CgA, chromogranin A.

Tumour response and progression free survival

Complete follow-up was obtained for all patients (ending October 2005). Two-, three- and five-year overall survival rates were 74.9, 74.9 and 52.4% respectively (Fig. 1). Two-, three- and five-year progression-free survival rates were 57.1, 51.4 and 32.1% respectively (Fig. 2). Median progression-free survival was 41 months (95%, CI 18–64). SD was observed in eight patients (38%) after a median follow-up of 49.5 months (IQR 26–67). After a median of 18 months (IQR 6–38.5), tumour progression was seen in 13 out of the 21 patients (62%). In this group of patients, the median follow-up was 21 months (IQR 12.5–34.5) with seven disease-related deaths, with a median survival of 45 months (95%, CI 21–∞) and median survival after progression events of 9 months (95%, CI 2.6–11.4). Neither the location of the tumour nor the type of surgery affected the response to treatment. In particular, among the four patients having palliative resections, two had SD after 74 and 23 months of follow-up, while the other two had disease progression after 4 and 22 months.

Clinical and biological response

After starting treatment with SMS analogues, complete resolution of abdominal pain was observed in all the eight patients who had complained of this symptom. An increase in body weight was observed in seven out of the ten patients with weight loss; in three patients with rapidly PD, weight loss persisted. Among 13 patients with pathological levels of serum CgA at diagnosis (>98 ng/ml), six had a decrease of more than 50% of the marker during the progression-free survival interval.

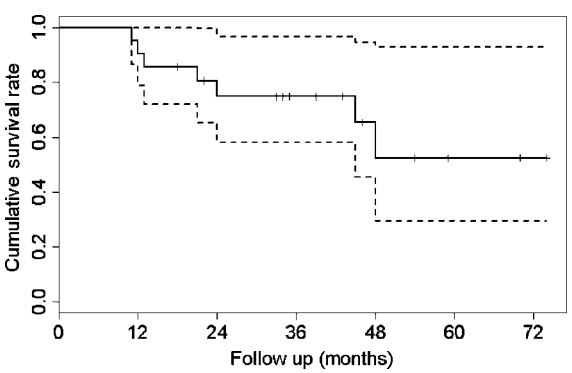

Figure 1 Survival curve of the 21 patients enrolled in the study. Follow-up began when patients began octreotide treatment. All the observed events were related to disease. Dotted lines represent 95% CI.

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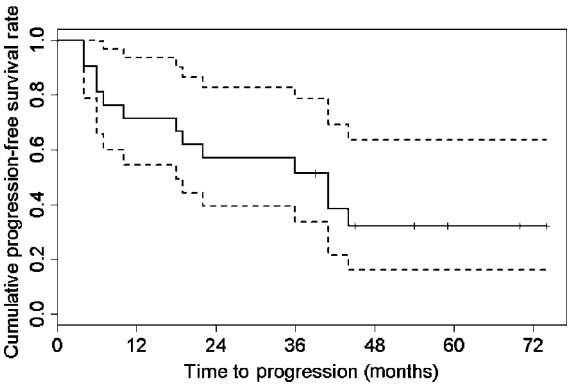

Figure 2 Progression-free survival curve. Dotted lines represent the 95% CI.

Therapeutic side effects

The therapy was well tolerated with no major side effect and no dose modification was required. Among eight patients, whose gallbladder had not been removed, an 84-year old woman experienced a symptomatic lithiasis after 36 months of therapy and was conservatively treated with no need to stop SMS analogue therapy.

Expression of somatostatin receptors 2 and 5

Quantitative RT-PCR demonstrated expression of SSTR2 mRNA in all 12 cases analysed (Table 2). In particular, there was no significant difference between the expression levels in stable (mean $\Delta\Delta C_t \pm$ S.D., 4.7 ± 1.6) and PD (mean $\Delta\Delta C_t \pm$ S.D., 4.9 ± 0.8) compared with normal islets. The expression level of SSTR5 showed a higher variability and no significant difference was seen between patients with SD (mean $\Delta\Delta C_t \pm$ S.D., 5.3 ± 3.3) compared with those whose tumours progressed (mean $\Delta\Delta C_t \pm$ S.D., 6.3 ± 1.6). Definite staining was observed in all samples evaluated for SSTR2 expression by immunohistochemistry, confirming that observed with octreoscan scintigraphy. In all cases, the immunostaining of tumour cells was stronger than that observed in normal insulae of Langerhans (Fig. 3). No significant correlation was observed between the expression of SSTR2 or SSTR5, either at mRNA or protein level, and the response to treatment.

Table 2 Quantitative RT-PCR and immunohistochemistry for SSTR2 and SSTR5

Patient ID	Disease status[a]	SSTR2 mRNA ($\Delta\Delta C_t$)[b]	SSTR2 IHC[c]	SSTR5 mRNA ($\Delta\Delta C_t$)
6	S	2.8	1	0.2
8	S	4.8	1	7.7
11	S	4.3	1	4.6
19	S	7.3	2	8.9
21	S	4.5	2	5.3
13	P	3.6	2	8.2
14	P	5.7	1	5.8
15	P	4.3	1	8.8
17	P	4.3	1	5.4
18	P	5.5	2	6.5
3	P	5.8	2	5.1
4	P	5.3	1	4.3

[a]SD, stable disease; P, progressive disease.
[b]$\Delta\Delta C_t$ were obtained sequentially subtracting median C_t of the beta-actin gene and median ΔC_t of islet cell samples used as a control.
[c]IHC, immunohistochemistry; 1, positive staining; 2, strong positive staining.

Prognostic factors

Tumour progression correlated with a Ki-67 proliferative index $\geq 5\%$ at diagnosis ($P = 0.016$; Fig. 4), absence of abdominal pain ($P = 0.005$) and weight loss ($P = 0.006$). In addition, serum CgA > 200 ng/ml at follow-up (HR 5.0 95% CI 1.46–17.10; $P = 0.005$) was also associated with tumour progression. No other clinicopathological or laboratory parameter, or the type of surgical procedure showed any significant correlation with treatment outcome.

Discussion

The main results of the present prospective trial on SMS treatment of 21 NF-PEC may be summarized as follows: (i) eight patients (38%) had long-term SD at a median follow-up of 49.5 months; (ii) the TP was 18 months for 13 patients (62%), who had a median survival of 9 months after progression occurred; (iii) a Ki-67 proliferation index $\geq 5\%$ appears to be a reliable marker for identifying the latter group; (iv) additional predictive factors were weight loss and absence of abdominal pain; (v) SMS treatment resulted in clinical benefits in virtually all symptomatic patients; (vi) the expression level of SSTR2 and SSTR5 receptors had no correlation with response to therapy.

The common belief that the gastroenteropancreatic neuroendocrine tumours at an advanced stage are still low-grade malignancies, with a long period of stability of disease even without treatment, is not applicable to NF-PEC. In our experience, these patients almost invariably present with symptoms, consisting of abdominal pain, body weight loss or obstruction (jaundice or upper digestive occlusion) (Gullo *et al.* 2003). This is also true in the present series in which

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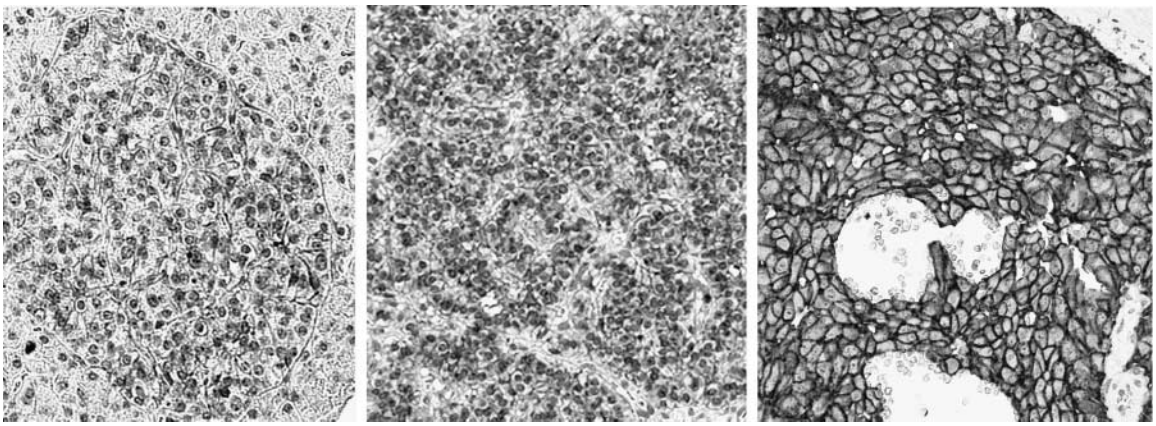
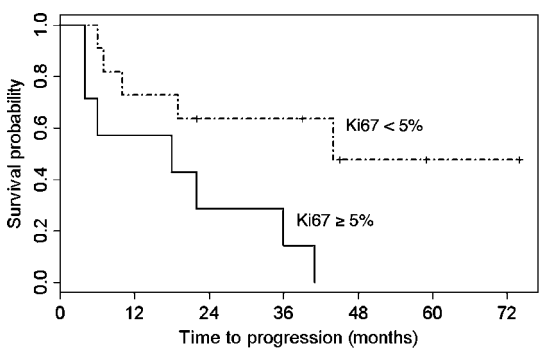


Figure 3 SSTR2 expression by immunohistochemistry. On the left, a normal pancreatic islet showing immunostaining in the majority of cells. Pancreatic endocrine tumours (middle and right panels) may show variable staining intensity, which was however always stronger than that seen in normal islet cells.

the median tumour size was 60 mm and all patients were symptomatic. Thus, the presence of high tumour burden or metastasis associated with invalidating symptoms is sufficient justification to initiate therapy at the time of diagnosis, avoiding any observation period to wait for radiologically proven progression.

Our prospective phase IV study assessed the efficacy of the SMS analogue octreotide in advanced NF-PEC positive at octreoscan scintigraphy. A significant proportion of our patients (38%) showed long-term SD. Although we did not observe any complete or PR, the 3-year overall survival rate of 74.9% and the median progression-free survival of 41 months can be considered as a good result for patients with advanced NF-PEC. Moreover, this was associated with a high quality of life consisting of a clear clinical benefit with regards, relief of symptoms and treatment tolerability. Such benefits were also seen in the 13 patients who experienced progression.

Although several studies have reported that SMS analogues can achieve stabilization of disease in patients with gastroenteropancreatic neuroendocrine carcinomas, only nine reports included NF-PEC (Table 3). A total of 68 NF-PEC have been treated with octreotide or lanreotide, but follow-up data are available only for 18 patients (di Bartolomeo *et al.* 1996, Angeletti *et al.* 1999, Tomassetti *et al.* 2000). Among these latter cases, 17 were enrolled with PD and only two cases (11%) experienced disease stabilization (Tomassetti *et al.* 2000), while the remaining 15 rapidly progressed (Table 3). The median progression-free survival of 41 months observed in the present trial is, by far, the best reported to date, and cannot be simply explained by the natural history of the disease. A recent study confirmed that the treatment of PEC with SMS analogues initiated after documentation of PD may achieve disease stabilization (5 out of 18 cases, 28%) (Panzuto *et al.* 2006), while the majority of patients further progressed within 6 months. The higher response rate observed in our study may be due to the early start of treatment in contrast to other studies, and partly to the inclusion of



Proliferation index Ki67 < 5%

Time	N.risk	N.event	Survival	std.err	95% CI
6	11	1	0.909	0.087	0.754 - 1.000
7	10	1	0.818	0.116	0.619 - 1.000
10	9	1	0.727	0.134	0.506 - 1.000
19	8	1	0.636	0.145	0.407 - 0.995
44	4	1	0.477	0.176	0.232 - 0.981

Proliferation index Ki67 ≥ 5%

Time	N.risk	N.event	Survival	std.err	95% CI
4	7	2	0.714	0.171	0.447 - 1.000
6	5	1	0.571	0.187	0.301 - 1.000
18	4	1	0.429	0.187	0.182 - 1.000
22	3	1	0.286	0.171	0.089 - 0.922
36	2	1	0.143	0.132	0.023 - 0.877
41	1	1	0.000	NA	NA NA

Figure 4 Kaplan–Meier curves for progression-free survival in patients with Ki-67 proliferation indices less than or greater than 5%.

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Table 3 Summary of published data on patients with nonfunctioning pancreatic endocrine carcinomas treated with somatostatin analogues

Authors	Study design	Patients (*n*)	Status of the disease at enrolment (pts)			Treatment	PD (%)	Time to progression (median in months)	Follow-up (median in months)
			PD	SD	nr				
Saltz *et al.* (1993)	P II	6	6			Oct 250 mcg/3 daily	nr	nr	nr
Arnold *et al.* (1996)	PMT	15	8	3	4	Oct 200 mcg/3 daily; 500 mcg/3 daily on clinician decision	nr	nr	nr
di Bartolomeo *et al.* (1996)	PMT	12	12			Oct 500/1000 mcg/3 daily	100	6	12
Eriksson *et al.* (1997)	P II	4			4	Lanreotide 750 mcg/daily up to 12 000 mcg/daily	nr	nr	nr
Tomassetti *et al.* (1998)	CS	4			4	Lanreotide 30 mg/10 days	nr	nr	12
Angeletti *et al.* (1999)	PMT	3	3			Oct 500 mcg/daily	100	3	nr
Tomassetti *et al.* (2000)	CS	3	2		1	Oct LAR 20 mg/4 weeks	33	nr	10.7
Ricci *et al.* (2000)	CS	11			11	Lanreotide 30 mg/2 weeks	nr	nr	nr
Aparicio *et al.* (2001)	RS	10	10			Oct 100 mcg/3 daily + Lanreotide 30 mg/2 weeks	nr	7	nr
Present series	CS	21	[a]	[a]	[a]	Oct 100 mcg/3 daily followed by Oct LAR 20 mg/4 weeks	62	18	21

PD, progressive disease; SD, stable disease; nr, not reported; P II, phase II trial; PMT, prospective multicenter trial; RS, retrospective study; CS, clinical study; Oct, octreotide; LAR, long-acting release.
[a]All 21 patients were enrolled at diagnosis; thus the status of the disease (i.e. stable or progressive) was unknown.

patients with less aggressive diseases as they were enrolled at diagnosis.

The true challenge is to identify markers capable of discerning patients, who would benefit from aggressive therapies. In this respect, our study demonstrated that a Ki-67 index $\geq 5\%$ is useful in identifying patients suffering from an aggressive and quickly PD, thus justifying the indication for more aggressive therapeutic regimens. Further support to our finding has also been provided by Aparicio *et al.* (2001), who reported that a slow tumour growth rate is the only predictive factor for response to therapy with SMS analogues. Additional factors associated with PD were weight loss and lack of abdominal pain at diagnosis. The presence of abdominal pain may be due to the mass effect, thus correlating with a median tumour size in the stable subgroup greater than that in the progressive one (67.5 vs 55 mm, $P = 0.09$).

In conclusion, our study supports the use of SMS analogues as first line therapy at diagnosis in well-differentiated NF-PEC with a low proliferation index, resulting in a substantial rate of SD for up to 5 years associated with a good quality of life. A Ki-67 value $\geq 5\%$ and the presence of weight loss may justify more aggressive therapy without waiting for radiologically proven progression of disease.

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