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ORIGINAL REPORT

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival

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A B S T R A C T

Purpose
Despite the fact that most gastroenteropancreatic neuroendocrine tumors (GEPNETs) are slow-growing, median overall survival (OS) in patients with liver metastases is 2 to 4 years. In metastatic disease, cytoreductive therapeutic options are limited. A relatively new therapy is peptide receptor radionuclide therapy with the radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. Here we report on the toxicity and efficacy of this treatment, performed in over 500 patients.

Patients and Methods
Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8-29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients, and efficacy analysis in 310 patients.

Results
Any hematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients, and temporary, nonfatal, liver toxicity in two patients. Complete and partial tumor remissions occurred in 2% and 28% of 310 GEPNET patients, respectively. Minor tumor response (decrease in size $>$ 25% and $<$ 50%) occurred in 16%. Median time to progression was 40 months. Median OS from start of treatment was 46 months, median OS from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis.

Conclusion
Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate has few adverse effects. Tumor response rates and progression-free survival compare favorably to the limited number of alternative treatment modalities. Compared with historical controls, there is a benefit in OS from time of diagnosis of several years.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are relatively rare. The two most common types of GEPNETs, carcinoids and pancreatic neuroendocrine tumors, have incidence rates of one to 2.5 in 100,000 population per year and approximately one in 100,000 population per year, respectively.[1-8] However, since 5-year survival rates in patients with GEPNETs, irrespective of stage of disease, are over 60%,[5,8-11] their prevalence is much higher. Despite the fact that most GEPNETs are slow-growing tumors, and the popular notion that these are relatively benign tumors, median overall survival (OS) in patients with metastatic liver disease is 2 to 4 years.[9,11-14] In this respect, data from an analysis in over 10,000 carcinoid patients, reporting nonlocalized disease at diagnosis in 32% to 47% of cases, is of great impact.[8] This finding is in line with another epidemiological study that reports liver metastases at diagnosis in 22% to 33% of cases.[5] Also, metastases may become apparent only years after the initial presentation of a carcinoid.

In case of metastatic disease, cytoreductive therapeutic options are limited. A relatively new therapy is peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs. Here we report on the toxicity and efficacy of treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate), performed in over 500 patients with somatostatin receptor–expressing tumors. The radionuclide ^{177}Lu has a half-life of 6.7 days and emits both beta-radiation and gamma-radiation, allowing imaging and dosimetry after therapy. Here we present long-term follow-up and survival data in

over 300 patients with GEPNETs and compare these to historical controls and published results for other treatment modalities in comparable patient groups.

PATIENTS AND METHODS

Patients

From January 2000 to August 2006, 1,772 treatments were given in 504 patients who were treated according to protocol. Tumor types were divided into carcinoids, pancreatic neuroendocrine, and neuroendocrine of unknown origin. Gastrinoma, insulinoma, and vasoactive intestinal peptide-secreting tumor (VIPoma) were only used in case of syndromes caused by hormonal hypersecretion. Inclusion criteria were tumor uptake during [^{111}In-DTPA^0]octreotide scintigraphy (OctreoScan, Mallinckrodt, Petten, the Netherlands) preceding the therapy that was at least as high as that in normal liver tissue, no prior treatment with other radiolabeled somatostatin analogs, serum hemoglobin $\geq$ 6 mmol/L, WBC count $\geq 2{\cdot}10^9$/L, platelet count $\geq 75{\cdot}10^9$/L,serum creatinine concentration $\leq$ 150 umol/L or creatinine clearance $\geq$ 40 mL/min, and Karnofsky performance status (KPS) $\geq$ 50.

Preliminary results in 131 patients with GEPNETs were also reported previously.[15] All patients gave written informed consent to participate in the study, which was approved by the hospital's medical ethical committee.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from Mallinckrodt, St Louis, MO. $^{177}LuCl_3$ was obtained from NRG, Petten, the Netherlands and Missouri University Research Reactor (MURR) and was distributed by IDB-Holland, Baarle-Nassau, the Netherlands. ^{177}Lu-octreotate was locally prepared as described before.[16]

Granisetron 3 mg or ondansetron 8 mg was injected intravenously and an infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 L 0.9% NaCl; 250 mL/h) was started 30 minutes before the administration of the radiopharmaceutical and lasted 4 hours. The radiopharmaceutical was coadministered via a second pump system. Cycle dosages were 100 mCi (3.7 GBq) in seven patients, 150 mCi (5.6 GBq) in 16, and 200 mCi (7.4 GBq) in the remaining patients, injected in 30 minutes. The interval between treatments was 6 to 10 weeks. Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8 to 29.6 GBq; corresponding with a radiation dose to the bone marrow of 2 Gy),[16] unless dosimetric calculations indicated that the radiation dose to the kidneys would then exceed 23 Gy; in these cases the cumulative dose was reduced to 500 to 700 mCi.

Routine hematology, liver, and kidney function tests were performed before each therapy, as well as at follow-up visits. Computer tomography (CT) or magnetic resonance imaging (MRI) was done within 3 months before the first therapy, and 6 to 8 weeks, 3 months, and 6 months after the last treatment, and thereafter every 6 months.

In Vivo Measurements

The tumors on CT or MRI were measured and scored according to the Southwest Oncology Group solid tumor response criteria[17] with the addition of the tumor response class minimal response (MR), pertaining to a decrease in summed squares of tumor diameters more than 25%, but less than 50%. The uptake during pretreatment [^{111} In-DTPA^0]octreotide scintigraphy was scored visually on planar images on a 3-point scale; grade 2: equal to normal liver tissue; grade 3: greater than normal liver tissue; grade 4: higher than normal spleen or kidney uptake.

Statistics

Analysis of variance (ANOVA), paired *t* tests, χ^2 tests (or, if applicable, Fisher's exact tests), Pearson's correlation tests, and logistic regression were used. For survival analysis, log-rank tests and Cox regression models were used.

RESULTS

Toxicity

In the 504 patients, acute adverse effects occurring within 24 hours after the administration of the radiopharmaceutical were nausea after 25% of administrations, vomiting after 10%, and abdominal discomfort or pain after 10%. Six patients were hospitalized within 2 days of the administration because of hormone-related crises. All recovered after adequate care.

Subacute, hematological toxicity, WHO grade 3 or 4, occurred 4 to 8 weeks after 3.6% of administrations, or, expressed patient-based, after at least one of several treatments in 9.5% of patients. Temporary hair loss (WHO grade 1; no baldness) occurred in 62% of patients.

Serious delayed toxicities were observed in nine patients. There were two cases of renal insufficiency, both of which were probably unrelated to ^{177}Lu-octreotate treatment. One patient had pre-existent kidney function deterioriation and the other had increasing tricuspid valve insufficiency. There were three patients with serious liver toxicity. In one patient with diffuse liver metastases, liver functions deterioriated in the weeks following the first administration. The patient died of hepatic failure after 5 weeks. Because this patient experienced a similar deterioriation due to rapid tumor growth after his previous course of chemotherapy, the liver failure after ^{177}Lu-octreotate treatment was considered more likely tumor growth–related than radiation induced. Two other patients, who both had multiple liver metastases, had temporary rises in serum ALT, AST, and bilirubin concentrations. In both patients, this condition resolved without causative treatment and both resumed treatment at half doses uneventfully. Lastly, myelodysplastic syndrome (MDS) occurred in four patients. In one patient, previous chemotherapy with alkylating agents was the more likely cause of MDS. In the other three patients, MDS was diagnosed 2 to 3 years after the last treatment with ^{177}Lu-octreotate, and was probably treatment related.

Efficacy

Of the 504 patients, 458 had GEPNETs. Of these, 19 were withdrawn from the study at their own request, because of treatment-unrelated morbidity, or treatment and tumor unrelated death. In two patients, treatment was stopped because of persisting thrombocytopenia. At the time of the analysis, another 79 patients were still being treated or waiting for their first or confirmatory imaging study results. Thirty-seven foreign patients were lost to follow-up after completing their therapy. Lastly, 11 patients did not have tumors that could be measured reliably.

Patient characteristics of the remaining 310 patients are listed in Table 1. There were 164 men and 146 women; mean age at treatment start was 59 years (range, 21 to 85 years).

Forty-seven patients did not receive their intended total cumulative dose of ^{177}Lu-octreotate. In 37 this was because of evident clinical disease progression or death. Treatment responses according to tumor type at 3 months after the last therapy cycle are listed in Table 2. Overall objective tumor response rate, comprising complete response (CR), partial response (PR), and MR, was 46%. Response rates in patients with gastrinomas, insulinomas, VIPomas and nonfunctioning pancreatic NETs were higher than in carcinoid tumor patients. CRs were only called if both conventional imaging (CT scanning or MRI) and the OctreoScan had normalized.

Table 1. Patient, Treatment, and Tumor Characteristics in Patients With GEP Tumor (n= 310)

Characteristic	Yes		No		Unknown	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Male	164	53	146	47		
Somatostatin analog use at referrral	174	56	136	44		
Age ≥ 70*	45	15	265	85		
KPS ≤ 70*	39	13	271	87		
Previous surgery	153	49	157	51		
Previous radiotherapy	16	5	294	95		
Previous chemotherapy	52	17	258	83		
Previous somatostatin analog use	168	54	142	46		
Tumor type gastrinoma/insulinoma/VIPoma*	19	6	291	94		
Baseline tumor progression*	133	43	80	26	97	31
Baseline weight loss*	75	24	235	76		
Liver metastases	276	89	34	11		
Bone metastases*	68	22	242	78		
Ascites*	10	3	300	97		
Tumor uptake on baseline OctreoScan, grade*						
4	72	23				
3	232	75				
2	6	2				
Tumor mass on baseline OctreoScan*						
Extensive	69	22				
Moderate	204	66				
Limited	37	12				
Liver involvement on baseline CT/MRI*						
Extensive	85	27				
Moderate	191	62				
Absent	34	11				

Abbreviations: GEP, gastroenteropancreatic; KPS, Karnofsky performance status; CT, computed tomography; VIPoma, vasoactive intestinal peptide-secreting tumor; MRI, magnetic resonance imaging.
*Refers to inclusion in multivariate analyses mentioned in the text.

Potential prognostic factors for predicting tumor remission (CR, PR, or MR) as treatment outcome, that were analyzed using (multivariate) logistic regression are marked with an asterisk in Table 1. Two significant factors resulted: uptake on the OctreoScan ($P < .01$), and KPS greater than 70 ($P < .05$).

A small percentage of patients who had either SD or MR at their first two evaluations after therapy, had a further improvement in categorized tumor response at 6 months and 12 months follow-up, occurring in 4% of patients and 5% of patients, respectively.

Three of four patients with clinically nonfunctioning neuroendocrine pancreatic tumors that were judged inoperable before treatment with ^{177}Lu-octreotate, and who had PR, were succesfully operated 6 to 12 months after their last treatment, whereas one died of postoperative complications.

Table 2. Tumor Responses in Patients With GEPNETs, 3 Months After the Last Administration of ^{177}Lu-Octreotate (n = 310)

Tumor Type	Response										
	CR		PR		MR		SD		PD		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Patients
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

Abbreviations: GEPNETs, gastroenteropancreatic neuroendocrine tumors; CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; VIPoma, vasoactive intestinal peptide-secreting tumor.

Time to Progression and Survival

In the 249 patients who did not have progressive disease (PD) as treatment outcome, median time to progression was 40 months from start of treatment. Time to progression was analyzed using Cox multivariate regression model, including the variables that are marked with an asterisk in Table 1, with an additional dichomotous variable indicating whether stable disease (SD) or remission (CR, PR, or MR) was the primary treatment outcome. Significant factors were the presence of bone metastases ($P < .001$), extent of liver involvement ($P = .001$), and gastrinoma, insulinoma, or VIPoma tumor type ($P < .01$).

Median OS in our 310 GEPNET patients was 46 months (median follow-up 19 months; 101 deaths). Median disease related survival was more than 48 months (median follow-up 18 months; 81 deaths). Median progression-free survival was 33 months. Survival analysis using Cox regression and using the factors from Table 1 marked with an asterisk, with in addition a variable indicating whether initial tumor response was PD, SD, or remission (CR, PR, or MR), resulted in the same six significant factors both for OS and for disease-specific survival (Table 3). The most important factor predicting survival was treatment outcome (Fig 1). Median time from diagnosis to referral was 21 months, median follow-up from diagnosis 48 months. Median OS from diagnosis was 128 months, median disease-specific survival was more than 180 months.

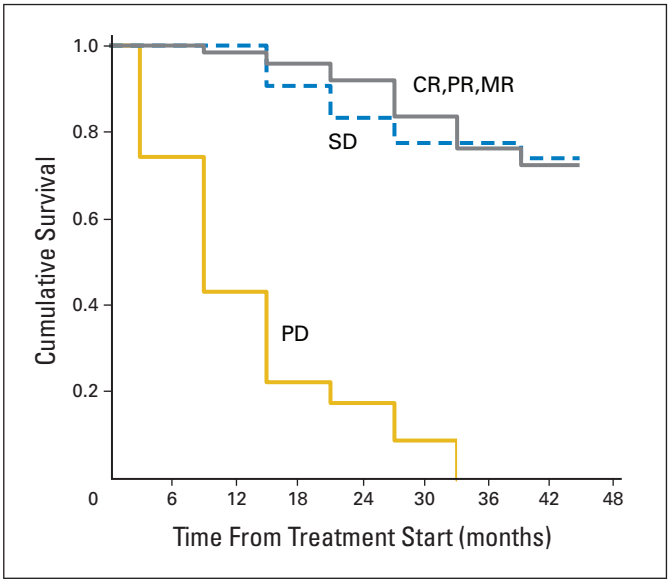

Fig 1. Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly. CR, complete response; PR, partial response; MR, minimal response; SD, stable disease.

DISCUSSION

From our data, we conclude that the treatment with ^{177}Lu-octreotate has few adverse effects and is relatively safe. With adequate clinical scrutiny, patients who have an increased risk to develop hormone-related crises can be identified and adequate measures to contain such events can be taken. Less dramatic acute adverse effects, like nausea and vomiting, occur in a minority of patients and can usually be successfully countered by administering additional antiemetics. Also, serious hematologic toxicity is rare. Other, delayed, serious adverse events that were likely caused by the therapy with ^{177}Lu-octreotate, comprising MDS and liver toxicity, were rare and occurred in approximately 1% of patients. The MDS cases require further attention and indicate that either the radiation absorbed dose to the bone marrow or the susceptibility of the stem cells to radiation varies between patients. Models, based on the biodistribution of radioactivity in the individual patient, will therefore have to be developed for future optimization of this therapy. Using such individualized dosimetry for kidney radiation–absorbed doses, in combination with kidney-protective amino acid infusion, resulted in the absence of serious kidney toxicity in any of our patients. Such renal toxicity has been reported in patients treated with [^{90}Y-DOTA^0,Tyr^3]octreotide, especially if no amino acids were coadministered.[18-20]

We found tumor size reductions, including MR, in 46% of our patients. MR was included as a separate response class because of the usual slow growth of GEPNETs, and their often partly cystic appearance, making major tumor size reductions less likely than in fast growing solid tumors after, for instance, chemotherapy or external-beam radiation. PR and CR were observed in 30% of patients. This percentage compares favorably to recent chemotherapy studies in GEPNETs, which mostly report CR and PR in less than 20% of patients. Also, the duration of the response, progression-free survival and OS are more favorable after ^{177}Lu-octreotate (Table 4).

Antiproliferative treatment options for patients with inoperable GEPNETs are limited. Somatostatin analogs, interferon-alfa, and their combination have their specific merit in reducing symptomatology from hormonal overproduction by GEPNETs. However, CT-assessed

Table 3. Significant Factors Predicting Disease-Specific Survival in Patients (n = 310)

Factor	No. of Patients	Survival (months)	*P*
Treatment outcome			
PD	61	11	
SD	107	> 48	< .001
Remission	142	> 48	
Liver involvement			
Extensive	85	25	
Moderate	191	> 48	< .001
None	34	> 48	
KPS ≤ 70			
Yes	39	16	
No	271	> 48	.001
Baseline weight loss			
Yes	75	30	
No	235	> 48	.001
Presence of bone metastases			
Yes	68	37	
No	242	> 48	.004
Tumor type gastrinoma/ insulinoma/VIPoma			
Yes	19	33	
No	291	> 48	.04

NOTE. Significance levels pertain to Cox regression with analysis of more factors than are listed in the Table, and which are listed in Table 1 and are marked with an asterisk.

Abbreviations: PD, progressive disease; SD, stable disease; KPS, Karnofsky performance status; VIPoma, vasoactive intestinal peptide-secreting tumor.

Table 4. Results of Recent Chemotherapy Reports Compared With Treatment With ^{177}Lu-Octreotate

Regimen	Tumor Type	No. of Patients	PR/CR (%)	Median PFS (months)	Median OS (months)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng (1999)[21]
Dacarbazine	Carc	56	16	NA	20	Bukowski (1994)[22]
Dacarbazine	Carc	7	14	NA	NA	Ritzel (1995)[23]
FU + IFN-α	Carc/PNET	24	21	8	23	Andreyev (1995)[24]
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt (1995)[25]
Paclixatel	Carc/PNET	24	4	3	18	Ansell (2001)[26]
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki (2004)[27]
Doxorubicin + FU	Carc	85	13	5	16	Sun (2005)[28]
STZ + FU	Carc	78	15	5	24	Sun (2005)[28]
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux (2006)[29]
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta et al (2007)[30]
^{177}Lu-octreotate	Carc/PNET	310	30	32	46	Present results

Abbreviations: STZ, streptozotocin; FU, fluorouracil; IFN-α, interferon-α; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available.

responses are rare, occurring in less than 5% to 10% of cases.[31-33] Other, nonsystemic, local ablative therapies for liver metastases are radiofrequency ablation (RFA), and liver embolization or chemoembolisation. Studies in usually small patient series report objective response rates of 30% to 80% with response durations of 6 to 42 months.[34] Recent single center overviews in larger series of over 50 patients report symptomatic relief, with a mean duration of 11 months, in 70% of patients after RFA, but no data on objective responses,[11] whereas an objective response was found in 37% of patients after chemoembolization, with a median duration of 14 months.[35] Serious procedure-related morbidity was reported in 5% of patients after RFA, and in 10% of patients after chemoembolization. Clearly, these serious adverse effects are fewer in our patients treated with ^{177}Lu-octreotate, and also the response duration is longer. Also, it is of note to realize that both methods, RFA and chemoembolization, are performed only if major tumor load is restricted to the liver. In addition to other criteria relating to tumor size and number, intact portal bloodflow, and tumor localization in relation to blood vessels have to be met.

Treatment with the radiolabeled somatostatin analog [^{90}Y-DOTA^0,Tyr^3]octreotide has been and is still performed in a number of centers. PR and CR have been reported in 8% to 33% of patients, mostly in small patient groups.[19,36-39] Differences in treament outcome evaluation (Response Evaluation Criteria in Solid Tumors, WHO, versus Southwest Oncology Group criteria), but especially patient inclusion bias, may account for this. In the present analysis, the two significant factors predicting favorable treatment outcome were high patient performance score and high uptake on the pretreatment OctreoScan. It is obvious that different studies can only be reliably compared if stratification for these factors is applied. From the published data, such stratified comparison cannot be performed. In our own institution, CT-assessed CR/PR occurred in only 8% of patients after treatment with [^{90}Y-DOTA^0,Tyr^3]octreotide.[39] Also, when we compared the residence time in tumors for [^{177}Lu-DOTA^0,Tyr^3]octreotide and [^{177}Lu-DOTA^0,Tyr^3]octreotate in the same patients in a therapeutical setting, we found a factor of 2.1 in favor of [^{177}Lu-DOTA^0,Tyr^3]octreotate.[40] Therefore, we think that ^{177}Lu-octreotate is the radiolabeled somatostatin analog of choice when performing PRRT.

In a small number of patients who had inoperable pancreatic NETs that had not metastasized, tumor shrinkage subsequent to treatment with ^{177}Lu-octreotate made these patients candidates for surgery. This neoadjuvant use of PRRT, although applicable in select cases only, is of great interest, as it may cure such patients.

An important feature of the tumor response after treatment with ^{177}Lu-octreotate that we observed, is that the eventual maximal shrinkage of the tumor may take months after completing the therapy. This is most likely due to the slow growing nature of these tumors; radiation biology axioms state that radiation damage to the DNA usually results in cell death only after their reproductive integrity is tested by one or more attempts at mitotic division.[41] Therefore, if such attempts at cell division are few, tumor size reduction will be slow.

Time to progression in patients having CR, PR, MR, or SD was significantly shorter for patients having high tumor load in the liver or having bone metastases. These are well-known prognostic factors of poor disease evolution. More puzzling is the fact that patients with gastrinoma, VIPoma, or insulinoma had significantly shorter response durations than other patients. A faster growth pattern of tumor cells must be assumed, but direct comparisons for tumoral growth between these tumors and other NETs, like carcinoids, are lacking.

Median OS was shorter in patients having a poor PS and those having extensive liver involvement. This implies that treatment with ^{177}Lu-octreotate should preferably be started early in the disease evolution. Because neuroendocrine tumors can be clinically stable for years, however, it is, in our opinion, good clinical practice to wait for signs of disease progression if the tumor load is moderate. Such signs should not be restricted to CT-assessed tumor growth, but also include rises in serum tumor markers, increase in symptoms, or involuntary weight loss. In patients with limited tumor load and in whom cure is potentially possible, treatment should be initiated without further delay, and the same holds true for patients with extensive tumor load, hepatomegaly, or significant weight loss, when waiting for formally assessed tumor progression would place these patients in an unfavorable starting position for treatment or would even qualify them as ineligible.

We found OS and disease-specific survival at and above 48 months. Because the treatment with ^{177}Lu-octreotate is still open for

Table 5. Survival Data in Patients With Neuroendocrine Tumors

Study	Study Population	Period	No. of Patients	Specific Intervention	Median OS From Referral (months)	Median OS From Diagnosis (months)	Comments
Clancy et al[9]	WDEC	1997-2003	137	—		72	Mean Alk Phos 155 U/L
	This study		310			128	Mean Alk Phos 214 U/L
	WDEC, Alk Phos < 127		67		51		
	This study		139		> 48		
	WDEC, Alk Phos > 127		46		19		
	This study		167		37		
Janson et al[10]	Carcinoid	1978-1993	256	—		92	19% had no lesions on imaging studies (K. Oberg, personal communication, 2007)
Idem, update		1993-2005	304	—		115	
	This study		188			155	
Quaedvlieg et al[5]	Dutch patients with carcinoid liver metastases at diagnosis	1992-1997	58	—		43	
	This study		100			97	
Chu et al[12]	PNET with liver metastases	1970-2001	29	—	25		Concomitant chemotherapy in most
	This study		76		44		
Mazzaglia et al[11]	Carcinoid liver metastases	1996-2005	35	RFA	47	82	Concomitant chemo/biotherapy in most
	This study		172		> 48	154	
	PNET liver metastases		18	RFA	35	54	
	This study		76		44	94	
Gupta et al[13]	Carcinoid liver metastases	1992-2000	69	(Chemo)-Embol	34		
	This study		172		> 48		
	PNET liver metastases		54	(Chemo)-Embol	23		
	This study		76		44		
Ho et al[14]	Carcinoid/PNET liver metastases	1991-2005	46	(Chemo)-Embol	33		
	This study		276		45		

Abbreviations: OS, overall survival; WDEC, well-differentiated endocrine carcinoma; Alk Phos, serum alkaline phosphatase concentration; RFA, radiofrequency ablation; PNET, pancreatic neuroendocrine tumor; Embol, embolization.

new patients, and median follow-up in relation to survival is relatively short, we also analyzed our local Dutch patients separately, with subgroups that had longer follow-up. Also in these analyses, OS and disease-specific survival time were consistently at or above 48 months (data not shown). Comparing survival data in our group, either from time of diagnosis or from time of referral, with data from different epidemiologic studies or studies pertaining to a specific intervention, and limiting our data to similar subgroups of patients, we found a benefit in OS for patients treated with ^{177}Lu-octreotate, which ranged from 40 to 72 months from diagnosis (Table 5). Of course, our patients were selected on the basis of a positive somatostatin receptor status of their tumors. In theory, not including patients with poorly differentiated, somatostatin receptor–negative tumors in our series could have caused a selection bias. We therefore also calculated OS for the subgroups listed in Table 5 with the addition of fictitious patients with a survival of 6 months from diagnosis, assuming their incidence at 5% of patients. (The incidence of poorly differentiated NETs is estimated at < 3% for foregut NETs[42]). Even with these assumptions, the survival benefit for patients treated with ^{177}Lu-octreotate was 23 to 69 months (data not shown). We are aware that comparisons with historical controls should be interpreted with caution, but we also think that such a consistent difference with many other reports in similar patient groups cannot be ignored, and is most probably caused by a real difference in survival.

In conclusion, the therapy with ^{177}Lu-octreotate has few serious adverse effects and can be regarded safe. Tumor response rates and progression-free survival compare favorably to the limited number of alternative treatment modalities in patients with inoperable or metastasized GEPNETs. Compared to historical controls, there is a benefit in OS of several years from time of diagnosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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