Frequency and characterization of gastro–entero–pancreatic neuroendocrine tumor patients with high-grade of uptake at somatostatin receptor scintigraphy

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Abstract

Recent studies suggest that the somatostatin receptor scintigraphy (SRS) grade of uptake is a predictor of response to peptide receptor radionuclide therapy (PRRT). To identify and characterize patients with well-differentiated (WD) neuroendocrine neoplasm (NEN) displaying a high-grade uptake at SRS. Patients with WD-NEN, whose SRS films were available for review, were retrospectively included. SRS was reviewed by three independent readers and classified into four subgroups based on a modified Krenning's scale (mKS): no uptake (group-0), homogeneous grade 1–2 uptake (group-1), homogeneous grade 3–4 (group-2), and heterogeneous grade 1–4 (group-3). A simplified scale (sS) of SRS was also used to look for characteristics of patients with high-grade uptake. One hundred and six WD-NEN patients were enrolled. Group-0, group-1, group-2, and group-3 were found in 17, 8, 33, and 42% of cases respectively. High-grade uptake at sS (75% of cases) was correlated with older age, functioning NEN, high chromogranin-A level, and grade 1 (G1) NEN based on mitotic count. Based on the mKS or sS scales, no difference on survival was found. Thirty-three to seventy-five percent of metastatic NEN patients can be considered candidates for PRRT based on homogeneous or heterogeneous high-grade uptake. Functioning G1 NEN patients could be the best candidates for PRRT. Randomized trials are expected to confirm this result.

Key Words
- Well-differentiated neuroendocrine tumor
- Carcinoid
- Somatostatin receptor scintigraphy
- Computed tomography
- Prognosis
- Predictor

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Introduction

Functional imaging has become critical for gastro–entero–pancreatic neuroendocrine neoplasm (GEP NEN) (Krenning *et al*. 1994, Baudin 2007). Somatostatin receptors (sst) are expressed by these tumors, and somatostatin receptor scintigraphy (SRS) improves the staging of well-differentiated (WD) GEP NEN (Krenning *et al*. 1994, Gibril *et al*. 1996, Lebtahi *et al*. 1997, Leboulleux *et al*. 2008). Further developments of SRS staging include the use of positron emission tomography (PET)-dedicated tracers (Ambrosini *et al*. 2008, Srirajaskanthan *et al*. 2010) and the use of tracers with higher affinity for sstr (Krenning *et al*. 1999, Carrasquillo & Chen 2010).

Peptide receptor radionuclide therapy (PRRT) that uses radiolabeled somatostatin analogs has been recently developed in GEP NEN. Several groups have reported sustained objective responses, using either 90Y-DOTATOC (90Y-DOTA0, Tyr3-octreotide; Otte *et al*. 1998) or 177Lu-DOTATATE (177Lu-DOTA0, Tyr3-octreotate; Kwekkeboom *et al*. 2005, 2008), triggering the development of phase III studies. The intensity of SRS uptake in the tumors predicts tumor response (Kwekkeboom *et al*. 2008), and an objective response to 177Lu-DOTATATE was observed in 75 and 41% of the patients with grades 4 or 3 uptake respectively but in only 25% of the patients with a grade 2 uptake (Kwekkeboom *et al*. 2005). SRS has also a prognostic role, with a better 5-year survival in positive SRS patients than in matched SRS-negative patients (55 vs 30% respectively; Asnacios *et al*. 2008). This prognostic role was suggested in a prospective series of 38 patients with GEP NEN that were selected for a wait-and-see policy only and classified as positive or negative for their respective SRS or PET status (Garin *et al*. 2009, Binderup *et al*. 2010*a*). More precisely, high-grade of SRS uptake was recently found to carry prognostic information (Imhof *et al*. 2011). However, in the absence of randomized study, the respective prognostic or predictive role of SRS on PRRT tumor response has not been clearly ascertained. Furthermore, definition of the best candidates for PRRT is urgently needed. Indeed, in the recently published ENETS or NANETS guidelines for the management of metastatic NEN, PRRT is recognized as a second- or third-line medical alternative, and its indication requires a better rationale (Pavel *et al*. 2012). Individualization of NEN patients with high uptake at SRS as well as their in-depth characterization will help rationalize therapeutic strategies. Recently, two studies demonstrated that proliferative index may help to refine the population of patients in whom an informative SRS could be expected (Binderup *et al*. 2010*a*, Abgral *et al*. 2011). A more precise characterization of GEP NEN patients that express grade 3–4 uptake at SRS is expected, still.

In order to better characterize the number of grade 3–4 patients eligible for PRRT and their characteristics, we conducted a single-center retrospective study to determine the percentage of patients with high uptake at SRS and their characteristics. In addition, we investigated the value of SRS grading to predict overall survival (OS).

Materials and methods

Inclusion criteria

Approval from our institutional review board was obtained for the study. The files of 318 consecutive WD GEP NEN patients referred to our institution between January 2001 and December 2005 were retrospectively analyzed.

Inclusion criteria were i) WD GEP NEN according to WHO 2010 classification (Rindi *et al*. 2010), confirmed by an experienced pathologist; ii) absence of second cancer, except for prostate, cervical uterine, and skin cancer in complete remission; iii) at least one evaluable tumor target, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.0); and iv) availability of SRS films for review.

The following parameters were collected at the time of SRS: age; gender; primary location (classified into six categories: small intestine, pancreas, lung, thymus, others, and unknown); presence of hormone-related clinical symptoms (functioning NEN), ENET, and UICC TNM stage (Rindi *et al*. 2006, Sobin *et al*. 2009); WHO 2010 classification; number of tumor organs; metastatic location (liver, lung, bone, and abdomen); and time interval between initial diagnosis and SRS. The maximum diameter of liver metastases (LM) was determined on conventional imaging (computed tomography (CT) and magnetic resonance imaging (MRI)) at the time of SRS. In addition, all previous treatments were recorded.

Somatostatin receptor scintigraphy

The SRS was performed at initial staging or during follow-up. SRS was performed after i.v. injection of 170–220 MBq Indium-111-DTPA-Phe1-octreotide (Octreo-Scan; Mallinckrodt Medical, Petten, The Netherlands). Treatment with somatostatin analogs at the time of SRS

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was recorded. Digestive artifacts were reduced with an adequate colonic preparation (64 g macrogol 4000 in the evening after the injection and again the next morning before 24-h imaging). Acquisition was performed using both 111In photopeaks (171 and 245 keV) and a large field of view double head gamma camera equipped with a medium-energy collimator (Axis; Philips Medical Systems, Best, The Netherlands), in accordance with recommendations (Balon *et al.* 2001). Four static anterior and posterior spot views covering the abdomen and pelvis were acquired at 4 h and 16 static anterior and posterior spot views covering the whole body were acquired at 24 h, and when needed, also at 48 h (256×256 word matrix, at least 10 min per view or 30 000 preset counts for the head and neck and 500 000 for the rest of the body). Abdominal single-photon emission CT (SPECT) was at 24 h (64 projections, 128×128 word matrix, 1 min per projection, and iterative reconstruction (ordered subset expectation maximization (OSEM) with eight subsets and two iterations). When necessary, additional lateral views of the head and lateral views or SPECT of the chest were also performed.

SRS analysis

To analyze the uptake grade, SRS results were reviewed based on films by three senior nuclear medicine physicians (S L, J L, and E B) blinded from patient and NEN characteristics, including results of conventional imaging. Films were preferred due to local logistical organization. Reviewers first analyzed the images independently and then met to reach a consensus in case of discordance. The location and uptake grades were analyzed visually on a gray scale from planar pictures (and abdominal tomography, when available). Locations of the foci were ascribed to the following region: liver, abdomen (except liver), lung, bone, and neck mediastinum.

The uptake in each focus was first graded according to the Krenning's scale as follows: grade 0 in the absence of any uptake, grade 1 in case of uptake below normal liver uptake, grade 2 in case of uptake equal to normal liver uptake, grade 3 in case of uptake higher than normal liver uptake, and grade 4 in case of uptake comparable to spleen uptake (Kwekkeboom *et al.* 2005). To better qualify SRS results according to the homogeneous or heterogeneous uptake, we further refined the classification of SRS uptake and assigned SRS results in a four-group stratification named 'modified Krenning's scale (mKS) classification' defining the groups as follows: group 0, no uptake; group 1, homogeneous grade 1–2 uptake (only grade 1 or grade 2 foci was present in a given patient); group 2, homogenous grade 3–4 uptake (only grade 3 or grade 4 foci was present in a given patient); and group 3, heterogeneous grade 1–4 uptake (heterogeneous foci of uptake were present in a given patient). Patients belonging to the group 2 with grade 3 or grade 4 foci were considered as best candidates for PRRT.

Finally, we used a simplified classification (sS) with two subgroups: a high uptake group that exhibited grade 3–4 uptake (homogeneous or heterogeneous) and a low-uptake group, exhibiting either homogeneous grade 1–2 uptake or no uptake at all.

NEN characterization

The serum chromogranin A (CgA) level was measured within 3 months of the SRS, using the Elisa kit Chromoa (Cisbio Bioassays, Bagnols-sur-Cèze, France) in which the upper normal limit (UNL) is below 100 ng/ml. These levels were used to classify patients in four subgroups (normal, below 2 UNL, between 2 and 5 UNL, and above 5 UNL).

Pathological classification including proliferative index was determined according to the WHO 2010 classification (Kloppel *et al.* 2009). The mitotic count was estimated after examination of at least 10 fields (10 high-power field (HPF)) colored by hematoxylin and eosin with the microscope Zeiss Axioplan (objective 40×/0.7, eye used 10×, every field corresponding to a surface of 0.33 mm^2). For each group of patients, we evaluated mitotic count results as median or within two categories (G1 <2/10 HPF or G2 ≥2/10 HPF). The Ki67 index, expressed in percentage (%), was determined using staining of 2000 cells with a specific anti-Ki67 antibody (clone MIB1, Dako A/S, Glostrup, Denmark). For each group of patients, we evaluated Ki67 results as median or within two categories (G1 ≤2% or G2 >2%). All patients underwent a thoraco–abdominal–pelvic spiral CT as part of the routine follow-up (GE Medical Systems, Milwaukee, WI, USA), and images were obtained before a monophasic injection of 100 ml monoionic contrast material (Xenetix 300; Guerbet, Roissy, France), at early arterial phase and portal time (Paulson *et al.* 1998). Scanning was performed at 120 kV and 270 mA. Contiguously reconstructed sections (pitch of 1:1) were obtained with 5 mm collimation. Results were classified according to ENETS (Rindi *et al.* 2006, 2007) and UICC TNM (Sobin *et al.* 2009). Patients in whom CT was available at the time of SRS were locally reviewed by one investigator (C C) to determine the maximum diameter of LM, and patients were classified

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Table 1 NEN characteristics of patients according to SRS results and sS classification (univariate analysis).

Characteristics	Total (*n* (%))	High uptake (*n* (%))[a]	Low-uptake (*n* (%))[a]	
n	106	79	27	***P***
Age: median	58 years (22–81)	59 years	53 years	0.08
Time since diagnosis: median (range)	1 (0–27)	0.9 (0–9)	1.5 (0–27)	NS
Male	58 (55%)	43 (54%)	15 (55%)	NS
Primary				
Small intestine	33 (31%)	27 (34%)	6 (22%)	NS
Pancreas	36 (34%)	29 (37%)	7 (26%)	NS
Lung	16 (15%)	9 (11%)	7 (26%)	NS
Thymus	6 (6%)	4 (5%)	2 (7%)	NS
Others	6 (5.5%)	5 (6%)	1 (4%)	NS
Unknown	9 (8.5%)	5 (6%)	4 (15%)	NS
Number of tumoral region at conventional imaging				
1	43 (41%)	32 (41%)	11 (41%)	NS
2	48 (45%)	36 (46%)	12 (44%)	
≥3	15 (14%)	11 (14%)	4 (15%)	
Functioning tumors	47 (44%)	40 (50%)	7 (26%)	0.02
Genetics (NEM1)	3 (3%)	3 (4%)	0	NS
Metastasis location				
Absence	8 (7.5%)	5 (6%)	3 (11%)	NS
Liver metastases	88 (83%)	68 (86%)	20 (74%)	NS
Abdomen but liver	35 (33%)	29 (37%)	6 (22%)	NS
Bone	20 (19%)	17 (22%)	8 (30%)	NS
Lung	25 (23.5%)	13 (16%)	7 (26%)	NS
CgA				
n evaluable	105	78	27	
Median (range) (ng/ml)	286 (29–43 000)	369 (33–43 000)	183 (29–3960)	NS
CgA <2 UNL	41 (39%)	25 (32%)	16 (59%)	
CgA ≥2 UNL	64 (61%)	53 (68%)	11 (41%)	0.012
Mitotic count				
n evaluable	91	65	26	
Median (range)/10 HPF	2 (0–30)	1 (0–30)	2 (0–20)	NS
G1 mitotic count <2	42 (46%)	35 (54%)	7 (27%)	0.02
G2 mitotic count ≥2	49 (54%)	30 (46%)	19 (73%)	
Ki67				
n evaluable	77	56	21	
Median (range) (%)	2 (0–60)	2% (0–30)	2% (0–60)	NS
G1 Ki67 ≤2	42 (55%)	31 (55%)	11 (52%)	NS
G2 Ki67 >2	35 (45%)	25 (45%)	10 (48%)	
Previous treatments				
None	21 (20%)	17 (22%)	4 (15%)	NS
Surgery	55 (52%)	39 (49%)	16 (59%)	NS
Somatostatin analog	29 (27%)	23 (29%)	6 (22%)	NS
Extern radiation beam	9 (8.5%)	4 (5%)	5 (19%)	0.03
Liver chemoembolization	20 (19%)	17 (22%)	3 (11%)	NS
Chemotherapy	35 (33%)	24 (30%)	11 (41%)	NS
Interferon	2 (2%)	0	2 (7%)	NS
Number of treatment lines				NS
0	21 (20%)	17 (22%)	4 (15%)	
1	42 (39.5%)	32 (40%)	10 (27%)	
≥2	43 (40.5%)	30 (38%)	13 (48%)	
Maximum size of liver metastases				
n evaluable	80	19	61	
1–≤2.5 cm[b]	31	12 (60%)	19 (38%)	
>2.5 cm	49	7 (40%)	42 (62%)	0.01

[a]Percentages in brackets refer to the total number of high- or low-grade of uptake.
[b]In the subgroup of patients with maximum liver metastasis below 2.5 cm, four patients (21% of the low-grade group), or seven patients (11% of the high-grade group), had a maximum diameter <1 cm.

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into two categories of size: max LM $\leq$2.5 and $>$2.5 cm. In the subgroup of patients with LM $\leq$2.5 cm, the patients with LM below to 1 cm were looked for.

Statistical and survival analysis

Clinical, genetic, pathological, and therapeutic parameters and grade of SRS given by the sS classification were correlated. Qualitative variables were analyzed by the χ^2 test or the Fisher exact test. Quantitative variables were analyzed either by an ANOVA test or a nonparametric Kruskal–Wallis test, depending whether results were normally distributed or not. The differences were considered as statistically significant if $P<0.10$ for univariate analysis or $P<0.05$ for multivariate analysis. Inter-observer concordance for the classification of SRS uptake was analyzed based on concordance or disagreement of the three readers for the attribution of grade of uptake.

The OS was defined as time from SRS to death for each group, defined according to either the mKS or the sS classifications. Living patients were censored at their date of last follow-up, using the 01/02/11 as the last point date. Survival rates were estimated by Kaplan–Meier method and were given with the Rothman 95% CI. Median follow-up was estimated by the inversed Kaplan–Meier method.

Results

Population under study

Among the 318 consecutive patients with GEP NEN, seen at our institution for the first time between January 2001 and December 2005, 212 were excluded for the following reasons: 7 patients for a second cancer, 57 patients for the absence of tumor target, and 148 patients because SRS films were not available for review.

Overall, 106 patients were enrolled in this study. Their clinical, pathological, and therapeutic characteristics are summarized in Table 1.

In brief, primary tumors were mainly located in the pancreas (34%) and small intestine (31%). Forty-seven patients had functioning NEN, including carcinoid syndrome in 39 cases, insulinoma in one case, glucagonoma in one case, gastrinoma in three cases, and paraneoplastic Cushing's syndrome in three cases. Distant metastases (stage IV ENET or UICC) were present in 93% of patients, with LM in 83% of the cases. All patients were RECIST evaluable. The vast majority of patients with LM were RECIST evaluable on the liver targets but 11 and 21% of the cases in the high- or low-uptake group whose LM were strictly below 1 cm. Median serum CgA level, available in 105 patients, was 286 ng/ml (range, 29–43 000) and CgA was above 2 UNL in 61% of the patients. The median mitotic index value, available in 91 patients, was 2/10 HPF (range, 0–30), classified G1 in 46% of cases. Median Ki67 staining, available in 77 patients, was 2% (range, 0–60), classified G1 in 43% of the patients. Twenty percent of the patients were treatment naïve and 52% underwent a surgical resection. Only 40% of the patients had received a treatment during the 2 months preceding SRS, including somatostatin analog in 22% and chemotherapy in 11%.

Concordance for SRS reading

Disagreement between the three readers was analyzed. For the mKS classification, in 12 patients, at least one spot of uptake was discordant: mostly in the heterogeneous group (nine times) affecting the final four subgroups' classification in five patients (5%). Overall, 2% (2/106) of the patients had a discordant sS classification (low/high uptake).

SRS uptake and characterization

The results of SRS are summarized in Table 2. Somatostatin analogs were given 1 month before SRS in 12 patients (including two patients classified in the low-uptake group) or within the month of SRS in seven patients

Table 2 Results of SRS.

SRS	No. of patients (%)
Region of uptake	
Liver	63 (59.4%)
Abdomen	46 (43.4%)
Bone	27 (25.5%)
Lung	9 (8.5%)
Cervicomediastinal	29 (27.4%)
Number of region of uptake	
0	18 (17%)
1	37 (34.9%)
2	26 (24.5%)
$\geq$3	26 (24.5%)
mKS classification	
0	18 (17%)
1–2 Homogeneous	9 (8%)
3–4 Homogeneous	35 (33%)
3–4 Heterogeneous	44 (42%)
sS classification	
High uptake group	79 patients (75%)
Low-uptake group	27 patients (25%)

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(all classified in the high uptake group) including two in whom SMS analog therapy was given within 2 weeks of SRS. In 83% of the cases, abdominal tomography was available. Foci of uptake were mainly located in the liver (60%), or in the abdomen outside the liver (43%). Most patients (60%) had one or two regions of uptake.

According to the mKS classification, SRS uptake was classified as grade 0 in 18 cases (17%), homogeneous grade 1–2 in 9 (8%), homogeneous grade 3–4 in 35 (33%), and heterogeneous in 44 cases (42%). According to the sS classification, 79 patients (75%) belonged to the high uptake group and 27 patients (25%) to the low-uptake group.

The results of correlation between sS classification and analyzed parameters are shown in Table 1. At univariate analysis, high uptake was found associated with older age ($P=0.08$), functioning symptoms ($P=0.02$), CgA level above 2 UNL ($P=0.03$), G1 mitotic count ($P=0.05$), less external beam radiation ($P=0.03$), and maximum diameter of LM above 2.5 cm ($P=0.01$). Patients with functioning NEN, high CgA levels, and G1 mitotic count had high uptake in 85% (40/47), 83% (53/64), and 83% (35/42) respectively. By contrast, patients with non-functioning NEN, normal CgA, or G2 mitotic count had high uptake in 68% (39/57), 61% (25/41), and 61% (30/49) respectively. Abdomen CT and/or MRI was available in 80 patients, patients with maximum size of LM above 2.5 cm had high uptake in 62% of patients with high uptake in contrast with 40% in case of maximum diameter was below 2.5 cm (cf. Table 1). In a multivariate analysis, only high CgA level remained significantly associated with high uptake ($P=0.005$), and with previous external beam radiation ($P=0.04$). No correlation was found between SRS uptake and prescription of somatostatin analog therapy. No significant correlation was found between any clinical parameter and results of the SRS when ascribed in four subgroups of the mKS.

Seventeen patients underwent PRRT subsequently. Seven or nine patients with homogeneous or heterogeneous had G3–4 uptake at SRS respectively. The number of patients was too low to allow any comparison.

SRS results as a prognostic parameter

With a median follow-up of 9 years after SRS (range, 1.2–22.7), the OS was 4.2 years; the 5-year survival rate was 45% (range, 36–54%). No difference in OS was observed between the four groups of the mKS classification or between the two subgroups of sS classification (Figs 1 and 2).

Discussion

Owing to the low number of randomized studies in NEN, retrospective analyses may still provide new insights for the characterization of patients who express a predictor of response for a given therapy. This was the aim of our study, which was undertaken based on the promising results of high SRS uptake as a predictor of response to PRRT (Kwekkeboom *et al*. 2005, 2008).

Our study provides new data in two directions. First, we could estimate the percentage of patients with metastatic NEN eligible for PRRT based on the grade of SRS uptake. To the best of our knowledge, this is the first estimation based on consecutive recruitment in one single specialized center. This percentage ranged between 33% (if only patients with homogeneous grade 3–4 uptake were considered) to up to 75% (if patients with heterogeneous uptake including grade 3–4 uptake at SRS were also taken into account). Randomized studies are needed to demonstrate which SRS high-grade definition, either homogeneous or heterogeneous, is the best predictor of response to PRRT. Owing to the limited number of patients who underwent PRRT in our study, we were not able to progress in that field.

A refined mKS was used to take into account both the intensity and the heterogeneity of uptake. Indeed, both pieces of information's are available in routine practice and best reflect the SRS results. In this study, heterogeneous uptake at SRS was found in 42% of the patients, which constituted the most frequent SRS result. We are well aware that the interpretation of SRS uptake heterogeneity is complex. It likely reflects the heterogeneity in the tumor biology in a given patient, including heterogeneity in sstr density or subtype expression (Papotti *et al*. 2001, Kulaksiz *et al*. 2002, Volante *et al*. 2008). This biological heterogeneity has already been described in the setting of radioiodine uptake in metastases from differentiated thyroid carcinoma in which dosimetric approaches have demonstrated heterogeneity of uptake among metastases in a given patient (Sgouros *et al*. 2004, 2011). This may explain the limited therapeutic success of radioiodine treatment in patients with uptake in some metastatic lesions. SRS heterogeneity may also reflect technical issues related to the size of each tumor focus, their anatomical location, and/or the physical modality of detection, may also have some influence. The absence of uptake at SRS in NEN, in 17% of patients, is in the 6–33% range of previous studies (Krenning *et al*. 1993, Panzuto *et al*. 2003, Dromain *et al*. 2005), and in up to 80% in case of localized duodenopancreatic tumors of <2 cm in size

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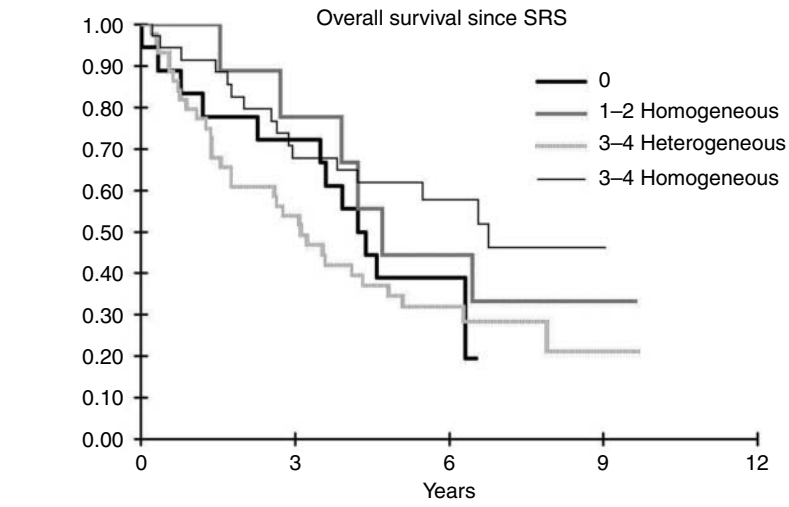

	Median follow-up	Median survival:	5-year survival
All patients	7 years (1–10)	4.2 years	45% (36–54%)
0	5 years (5; 7)	4.2 years	39% (20–61%)
1–2 Homogeneous	8 years (8; 10)	4.7 years	33% (12–65%)
3–4 Heterogeneous	7 years (1; 10)	3.1 years	32% (20–47%)
3–4 Homogeneous	6 years (1; 9)	6.8 years	62% (45–76%)

Figure 1
Kaplan–Meier survival of patients after the SRS according to mKS classification.

(Alexander *et al*. 1998). The influence of the size was again confirmed in our study as a positive correlation was found between the maximum diameter of LM and high uptake at SRS. Again, negative SRS results may be explained by insufficient resolution capacity and/or small tumor foci, especially when SPECT CT is used. However, with the recent introduction of high-resolution CT and PET-dedicated tracers, progress regarding SRS sensitivity has been made. Low or inappropriate expression of sst subtypes could also play a role (Janson *et al*. 1998, Hofland *et al*. 2003, Volante *et al*. 2007). Finally, despite its limitations, visual interpretation of SRS remains a standard and is an easily applicable technique in routine practice and has already been used in clinical studies (Krenning *et al*. 1996, Kwekkeboom *et al*. 2005). Interestingly, the rate of discrepancy in the interpretation of SRS grade between three proofreaders was low, suggesting that our approach is robust and acceptable in the majority of cases.

Secondly, to better anticipate the profile of metastatic NEN patients eligible for PRRT, we sought for correlations between high-grade of uptake, as defined by the sS, and characteristics of this group of patients. At univariate analysis, older age, presence of functioning symptoms, high level of CgA, LM maximum diameter above 2.5 cm, G1 mitotic count, and less external beam radiation were correlated with high-grade of uptake ($P=0.03$). Indeed, more than 80% of NEN patients with high CgA levels, maximum diameter above 2.5 cm, G1, or functioning NEN experienced high uptake at SRS, which contrasted with the <60–70% high SRS uptake in patients who did not exhibit any of these characteristics. The role of tumor burden is more difficult to interpret in the absence of true quantification of tracer uptake in each metastasis, in our study. These characteristics define patients with a very-WD, functioning, low proliferative phenotype, named G1 NEN in the recent WHO 2010 classification, and who are considered for PRRT when systemic therapy is

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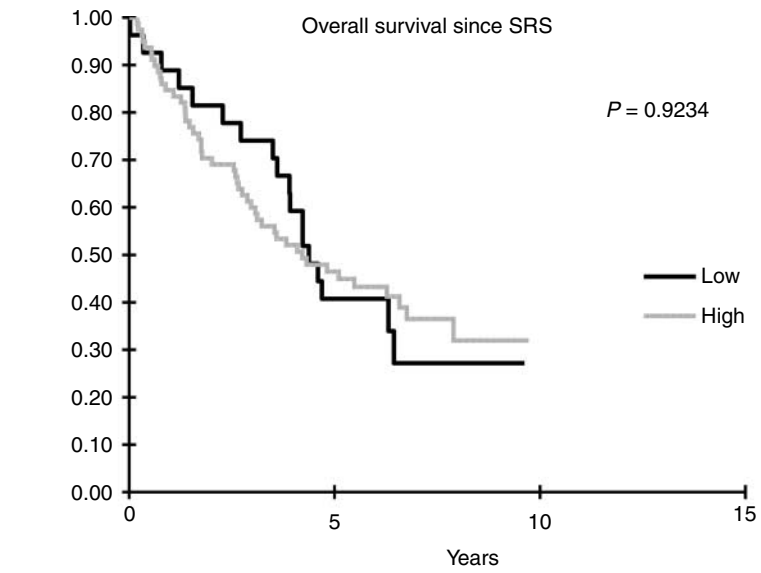

	Median follow-up	Median survival:	5-year survival
All patients	7 years (1–10)	4.2 years	45% (36–44%)
Low	7 years (5–10)	4.4 years	41% (25–59%)
High	7 years (1–10)	4.2 years	45% (34–56%)

Figure 2
Kaplan–Meier overall survival of 106 patients after the SRS: comparison high/low-uptake (sS classification).

required. By contrast, patients with tumors displaying high proliferative capacity could be considered as best candidates for chemotherapy (Brizzi *et al*. 2009, Turner *et al*. 2010, Salazar *et al*. 2012).

Our study confirms the results of previous more limited studies that have reported, in 48–88 patients, correlations between SRS uptake and different NEN characteristics, such as good performance status (Krenning *et al*. 1994), presence of a functioning NEN (Taal *et al*. 1996, Stokkel *et al*. 2011), high level of CgA (Kalkner *et al*. 1995, Asnacios *et al*. 2008, Namwongprom *et al*. 2008, Stokkel *et al*. 2011), or low proliferative index (Adams *et al*. 1998, Ezziddin *et al*. 2006). Indeed, Binderup *et al*. (2010*a*) but also Abgral *et al*. (2011) previously reported a lower performance of SRS in case of a Ki67 index measured above 15 or 10% respectively. In addition, Binderup *et al*. (2010*b*) reported a lower performance of the PET with fluorodeoxyglucose (PET FDG) but not SRS in case of a Ki67 threshold below 2%, in 85 patients. In our study, taking into account the threshold of 2 and the results of the mitotic count that distinguishes G1 from G2 NEN, we found in 91 patients a greater percentage of grade 3–4 uptake at SRS in case of a low mitotic count below 2. Of note, SRS uptake was defined as positive or negative in most previous studies and a strict definition of a positive SRS based on the Krenning's scale was used in only four of these studies (Taal *et al*. 1996, Ezziddin *et al*. 2006, Asnacios *et al*. 2008, Stokkel *et al*. 2011). Indeed, a grade 2 uptake at SRS was considered as a cutoff of positivity in these four studies, which does not seem optimal as a predictor of response to PRRT. None of these studies evaluated the high-grade 3–4 of uptake using Krenning's scale. Taken together, these results suggest again that very-WD functioning G1 NEN could be considered best candidates for PRRT. We also found a deleterious association between external radiation therapy and low-uptake at SRS that could reflect a higher tumor burden. Finally, although withdrawal of ongoing therapies at the time of SRS is considered optimal, the use of long-acting somatostatin analogs makes this situation impossible in routine practice. Of note, ongoing therapies were not found to play a major role in SRS grade of uptake.

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SRS grade of uptake has been proposed as a prognostic parameter of NEN (Asnacios *et al*. 2008, Garin *et al*. 2009). It could overcome current limitations regarding limited sampling for pathological analyses in metastatic NEN. However, previous results were based on a limited number of selected patients and/or matched subgroups of patients, which do not reflect the real-life situation. In our study, we took into account both the grade of uptake and its homogeneity, in a cohort of unselected patients. Using this approach, which reflects the common clinical situation in a large specialized center, we were unable to confirm a prognostic role for SRS. Owing to the number of biological but also methodological variables that affect SRS interpretation, these results are not surprising. Indeed, a negative SRS may reflect both a low tumor burden and or a negative sstr expression. This situation is already improving as PET combined with high-resolution CT technology increases the sensitivity of SRS and allows quantification of the tracer uptake in tumors. It is also expected that, in subgroup of patients in whom an accurate prognostic characterization is urgent, the number of targets depicted at conventional imaging, PET FDG, and SRS, will help to further refine the prognosis (Garin *et al*. 2009, Binderup *et al*. 2010*b*, Abgral *et al*. 2011).

We acknowledge limitations in our study, which include its retrospective nature, films reviews were used which cause the exclusion of a significant number of patients, which may have biased the results; the fact that only results of Indium-111-DTPA-Phe1-octreotide scintigraphy were analyzed and not tumor response to PRRT and finally, SRS results were not matched with a precise analysis of tumor burden.

In conclusion, our study shows that 33% of the patients seen in a tertiary referral centers could be considered as best candidates for PRRT, based on a high homogeneous grade of uptake at SRS. Characteristics of this subgroup of patients are compatible with a functioning G1 NEN phenotype. Randomized studies are still needed to better define predictors of response to PRRT.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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