

# Somatostatin receptor scintigraphy might be useful for detecting skeleton abnormalities in patients with multiple myeloma and plasmacytoma

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## Abstract

**Purpose** Somatostatin receptor expression has been demonstrated on a number of plasma cell lines. Therefore, we questioned whether somatostatin receptor scintigraphy (SRS) can be used to demonstrate in vivo multiple myeloma (MM) activity.

**Methods** SRS was performed in newly diagnosed ( $n=9$ ) or relapsing ( $n=18$ ) MM patients or in patients with localized plasmacytoma ( $n=2$ ). The results were compared with radiographic findings.

**Results** A positive SRS was demonstrated in 44% of the newly diagnosed patients, in 83% of the relapsed patients and in both patients with plasmacytoma. The SRS findings corresponded with radiographic abnormalities in 40% of the patients. However, in relapsed patients 60% demonstrated increased SRS uptake in areas without new radiographic abnormalities. The positive SRS corresponded with histologically proven disease activity and responded upon treatment. Moreover, immunohistochemical staining of

MM material demonstrated concordant somatostatin receptor sst3 staining in five of six patients.

**Conclusion** These results demonstrate that SRS is a valuable tool to detect disease activity, especially in relapsing MM patients.

**Keywords** Somatostatin receptor scintigraphy · Multiple myeloma · Disease activity

## Introduction

Multiple myeloma (MM) is a clonal B-cell disorder characterized by a monoclonal plasma cell population in bone marrow, with bone pain as a result of skeleton abnormalities, hypercalcaemia and kidney dysfunction [1]. In a minority of the patients the disorder is localized and presents as a solitary plasmacytoma. In 60–70% of the patients skeletal abnormalities are identified by X-ray

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examination and are characterized by typical osteolytic defects [1]. Following treatment with chemotherapy or radiotherapy the osteolytic defects persist and no clear distinction can be made whether vital tumour cells are present in these lesions. Also in relapsing disease the X-ray examination has a limited value unless progressive defects are observed. Therefore, it would be attractive to have scanning methods that identify the metabolic activity of the malignant plasma cells. Previous studies have shown that FDG PET might identify the metabolic activity of the malignant plasma cells. Several studies have demonstrated that in a high percentage of newly diagnosed MM patients osteolytic lesions are FDG PET positive due to their higher metabolic activity [2, 3]. An alternative approach would be the use of tracers that identify tumour-specific receptors. In vitro studies with plasma cell lines have shown that the somatostatin receptor is expressed on malignant plasma cells. It was shown that all MM cell lines express functional somatostatin receptors (sst) and that the subtypes sst2, sst3 and predominantly sst5 were present [4]. It is therefore conceivable that somatostatin receptor scintigraphy (SRS) using  $^{111m}\text{In}$ -pentetreotide may be a good alternative to study the presence of the malignant plasma cells [5]. So far SRS has been used for the detection of neuroendocrine tumours and aggressive malignant lymphoma especially to define the extent of the disease [6, 7]. Based on these findings we performed SRS in patients with MM or plasmacytoma to determine whether SRS can be used as an alternative method to detect disease activity in malignant plasma cell disorders.

## Materials and methods

### Patients

A total of 29 patients were prospectively included in this study (Table 1). The patient group consisted of 22 men and 7 women with a median age of 59 years (range: 40–85 years). MM or plasmacytoma was based on the presence of a monoclonal plasma cell population in the bone marrow biopsy, the presence of a monoclonal Ig protein or free light chains (FLC) in serum according to internationally defined guidelines [1].

In all patients total whole-body radiography was performed. In a selected number of patients an additional CT scan or MRI scan was performed based on clinical symptoms. Patients were treated according to ongoing trials for MM patients younger than 65 years or with melphalan/prednisolone [8–10]. Patients (< 65 years) were treated upfront with three cycles of VAD (vincristine, doxorubicin, dexamethasone) or TAD (thalidomide, doxorubicin, dexamethasone). This was followed by peripheral blood stem

**Table 1** Patient characteristics at presentation or at relapse

Patient No.	Age (years)	Sex	Type of underlying disorder	Paraprotein	SRS
1	63	F	MM	IgA- $\kappa$	+
2	58	F	MM	IgG- $\kappa$	–
3	54	M	MM	IgG- $\lambda$	–
4	57	M	MM	FLC- $\kappa$	+
5	62	M	MM	IgA- $\kappa$	+
6	53	M	MM	IgG- $\kappa$	–
7	52	M	MM	IgG- $\kappa$	+
8	51	M	MM	IgG- $\lambda$	–
9	62	M	MM	IgG- $\kappa$	–
10	60	M	Plasmacytoma	IgA- $\lambda$	+
11	40	M	Plasmacytoma	IgG- $\kappa$	+
12	85	M	MM-R	IgA- $\kappa$	+
13	56	F	MM-R	IgG- $\kappa$	+
14	61	M	MM-R	IgG- $\kappa$	–
15	64	M	MM-R	IgG- $\kappa$	+
16	55	M	MM-R	FLC- $\kappa$	+
17	46	M	MM-R	FLC- $\kappa$	+
18	48	M	MM-R	FLC- $\lambda$	+
19	70	M	MM-R	FLC- $\kappa$	+
20	60	M	MM-R	IgG- $\kappa$	+
21	63	M	MM-R	IgG- $\kappa$	+
22	63	M	MM-R	IgG- $\kappa$	+
23	59	M	MM-R	IgG- $\kappa$	+
24	67	F	MM-R	IgG- $\lambda$	–
25	48	M	MM-R	FLC- $\kappa$	+
26	73	M	MM-R	NS	–
27	65	F	MM-R	FLC- $\kappa$	+
28	60	F	MM-R	FLC- $\lambda$	+
29	64	F	MM-R	NS	+

NS non-secretor, FLC free light chain in serum, MM multiple myeloma, R relapse, SRS somatostatin receptor scintigraphy with a positive (+) or negative (-) scan

collection following high-dose cyclophosphamide plus granulocyte colony stimulation factor. Finally autologous stem cell transplantation was performed with high-dose melphalan and re-infusion of autologous stem cells. The protocol was approved by the Medical Ethics Committee Groningen, The Netherlands and informed consent was obtained from all patients.

### Immunohistochemistry

Bone marrow biopsy or material of extra-osseous localization of MM patients was used for these investigations. In two cases the localization was based on a positive SRS.

Tissue specimens were fixed in phosphate-buffered formaldehyde (12–24 h) and decalcified using a mixture of 10% acetic acid and 4% formaldehyde (24–48 h). After standard tissue processing biopsies were embedded in paraffin wax. Four-micrometer sections were cut and floated onto 3-aminopropylethoxysilane (APES)-coated slides. After dewaxing slides were microwaved in 10 mmol/l citrate buffer, pH 6.0, for 15 min at 750 W, allowed to cool to room temperature and washed three times in triethanolamine-buffered saline. The slides were processed using a Techmate Horizon (Dako, Carpinteria, CA, USA) slide processor. Affinity purified polyclonal rabbit antisera

specifically directed against sst2 (NB100-74537), sst3 (NLS2622) and sst5 (NLS2639) (1 µg/ml, Novus Biologicals, Littleton, CO, USA) were incubated for 1 h and binding was visualized using a streptavidin-biotin complex reagent (StrepABCComplex/HRP Duet, Dako, Carpinteria, CA, USA). Chromogenic substrate was 3,3'-diaminobenzidine. Slides were counterstained with haematoxylin. Positive control of immunostaining was assessed by immunohistochemistry of normal pancreatic islets. However, on bone marrow trephines, satisfactory results were only obtained for the sst3 staining and not for sst2 and sst5. In general, if possible all myeloma

**Table 2** Somatostatin receptor scintigraphy in multiple myeloma patients receiving upfront treatment or at relapse

Patient No.	SRS			Corresponding defects on whole-body radiography (Y/N)	Whole-body radiography		
	Scan pos.	No. of lesions	Uptake ratio		No. lesions > 1cm	No. lesions < 1cm	New lytic lesions at relapse > 1cm
1	+	1	1.5	Y	4	Y	
2	-	0	-	-	3	Y	
3	-	0	-	-	0	N	
4	+	1	2	Y	3	Y	
5	+	1	2.3	N <sup>a</sup>	0	N	
6	-	0	-	-	1	N	
7	+	2	2.5	Y	0	Y	
8	-	0	-	-	0	Y	
9	-	0	-	-	0	N	
10	+	1	2	N <sup>a</sup>	0	N	
11	+	1	1.5	Y	0	N	
12	+	11	2 (1.5–2.5)	N	0	N	0
13	+	2	2 (1.8–2.2)	N	0	N	0
14	-	0	-	-	4	Y	1
15	+	1	2.5	Y	3	N	1
16	+	1	1.5	Y	6	Y	1
17	+	1	2	Y	4	Y	1
18	+	3	3 (2.8–3.2)	Y <sup>b</sup>	3	Y	3
19	+	Diffuse	n.a.	N	0	Y	0
20	+	12	2 (1.5–2.5)	N	3	N	0
21	+	1	1.3	Y <sup>a</sup>	2	Y	1
22	+	1	2	Y	5	Y	1
23	+	3	2 (1.7–2.2)	N	0	N	0
24	-	0	-	-	0	Y	0
25	+	3	2	N	5	N	0
26	-	0	-	-	0	N	0
27	+	1	2	N	5	Y	0
28	+	3	3 (2.6–3.3)	N <sup>b</sup>	3	Y	2
29	+	1	1.4	N <sup>a</sup>	0	Y	0

Lytic lesions larger than 1 cm; osteolytic defects present (Y) or absent (N)

n.a. not available

<sup>a</sup>No abnormalities on whole-body radiography, but defects on MRI or CT scan

<sup>b</sup>Extra-osseous localization

cells were stained. The intensity of the immunostaining of myeloma cells was reported using the following system: 0: no or extremely weak, +: moderate and ++: strong.

#### Octreotide scintigraphy

Whole-body scan SRS was performed 24 h after intravenous injection of 200 MBq  $^{111}\text{In}$ -pentetreotide. A Multispect 2 Siemens double-headed gamma camera (Siemens Medical Systems, USA) was used with a matrix of  $256 \times 256$  and equipped with medium-energy collimator. Patients were positioned supine on the imaging table; subsequently six views were obtained: anterior and posterior of head/neck/thorax, abdomen and the thighs, 10 min/view. The SRS scan and skeletal X-ray were performed within 7 days.

SRS were separately examined by two experienced nuclear physicians using visual examination with special attention to the skeleton. Any focal tracer accumulation exceeding normal regional tracer uptake levels was rated as pathological. Subsequently, regions of interest (ROIs) were visually placed over the area with abnormal uptake and tracer uptake was quantified by comparing the average counts per pixel of the focus in comparison with normal background bone activity assessed from a usually symmetrically placed contralateral background ROI. A simple scoring system was developed to grade the uptake in the pathological sites. Uptake was recognized as ‘slightly

elevated’ if the uptake ratio exceeded 1.5 in the lesion, as ‘moderate’ when the uptake ratio was between 1.5 and 2, and as ‘high’ when over 2. Non-focal intestinal uptake changing over time was considered to be physiological background activity. All scintigraphic results were compared with radiographic findings.

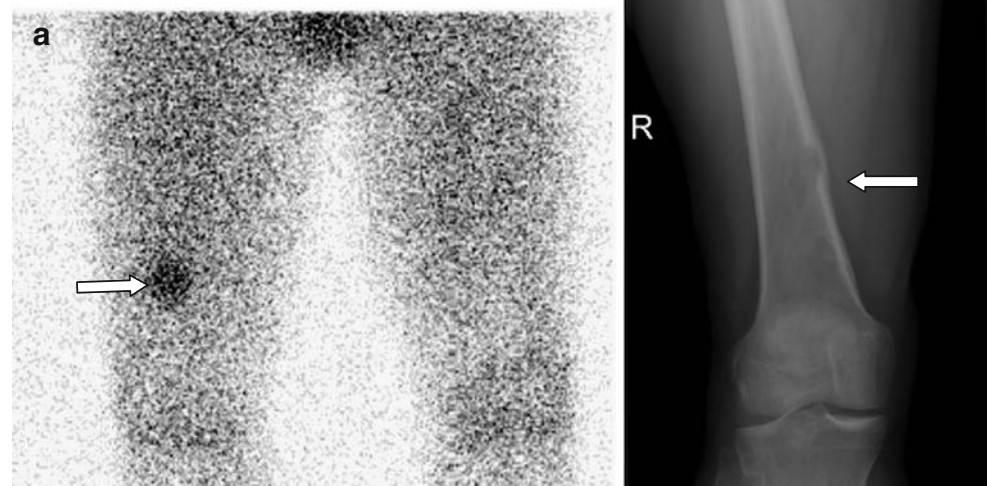
#### Results

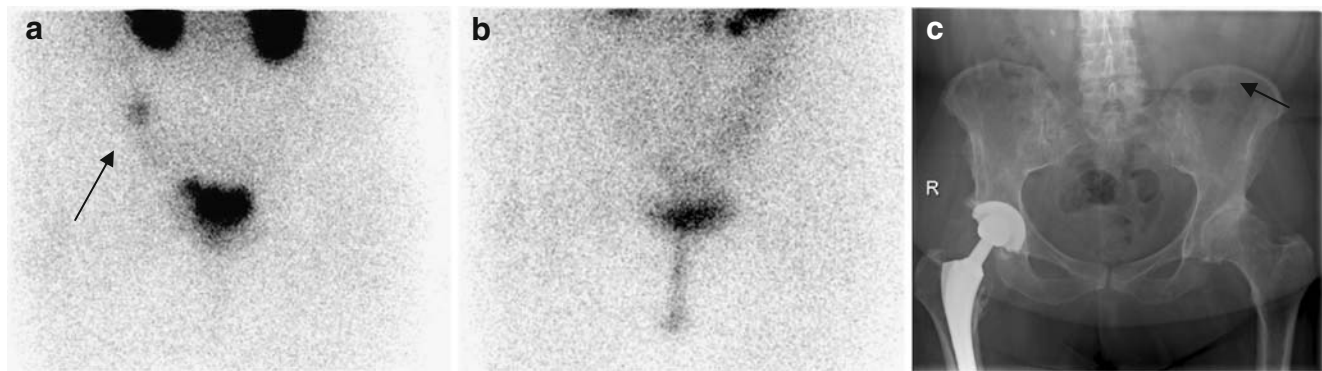
A total of 27 patients with MM and 2 patients with plasmacytoma were studied. Patient characteristics are presented in Table 1. Of the 27 patients with MM, 9 patients had newly diagnosed and 18 patients had relapsing disease. MM showed production of IgG- $\kappa$  ( $n=12$ ), IgG- $\lambda$  type ( $n=3$ ) and IgA- $\lambda$  or IgA- $\kappa$  ( $n=4$ ) types. In eight patients monoclonal FLCs were demonstrated in the serum.

Whole-body radiography demonstrated abnormalities in 14 of the 29 patients.

The type of treatment was dependent on age and whether the patient presented with newly diagnosed or relapsing disease. The newly diagnosed patients (age: 51–63 years) were treated with intensive chemotherapy and autologous stem cell transplantation [9, 10]. Relapsing patients (age: 46–85 years) were treated with variable combinations of dexamethasone, cyclophosphamide, thalidomide or bortezomib. The two patients with solitary plasmacytoma (age: 40 and 60 years) were treated with radiotherapy with and without intensive chemotherapy (Table 2).

**Fig. 1** Elevated SRS uptake in the distal right femur matching with the osteolytic lesion on skeletal X-ray (both white arrows). There is no SRS uptake in the osteolytic lesion of the proximal right femur on skeletal X-ray (small black arrow)





**Fig. 2** Somatostatin receptor scintigraphy of the pelvis posterior view in a patient with multiple myeloma in the left iliac bone, with elevated SRS uptake before treatment (*small black arrow*) (a) and normaliza-

tion after treatment (b). The X-ray shows a persistent matching osteolytic bone lesion (*small black arrow*) (c)

### Octreotide scintigraphy

In all patients SRS was performed. In five patients a second scan was obtained after 3–5 months of treatment. The number of affected areas on the SRS varied between 1 and 12 per patient. The median uptake ratio was 2.0 (range: 1.3–3.5). Based on a comparison with the abnormalities seen by whole-body radiography, we defined that SRS was only positive in lesions with a diameter of more than 1 cm. In four of the nine [44%, 95% confidence interval (CI): 0.12–0.77] newly diagnosed MM patients the SRS was positive, in the other five patients the SRS was normal (Fig. 1). Two of these five patients had distinct abnormalities by whole-body radiography. In both patients with solitary plasmacytoma, a positive SRS was obtained of the affected area which was confirmed by X-ray examination and CT scanning.

SRS was studied in 18 MM patients with relapsing disease. A positive SRS was shown in 15 of 18 (83%, 95% CI: 0.66–1) of these patients. In 6 of the 15 (40%, 95% CI: 0.15–0.60) evaluable patients the increase in SRS

corresponded with new abnormalities on the whole-body radiography, whereas in the other 9 patients (60%, 95% CI: 0.35–0.85) enhanced SRS activity was not accompanied by new abnormalities on the whole-body radiography.

To verify that the increased octreotide uptake was related to disease activity, biopsies were performed of the affected areas (pelvis, clavícula) in four patients (1, 10, 11 and 18). In all four cases histologically proven MM activity was present.

To study the effect of treatment, follow-up scans were performed in five cases. Scans performed after 3–4 months of treatment demonstrated a complete disappearance of lesions in three patients and a decrease in two. These changes corresponded with reduced disease activity including declining paraprotein or FLC levels (Fig. 2, Table 3).

Finally the somatostatin receptor expression *sst3* was studied on biopsy material of patients with MM. It included bone marrow biopsy material and one extra-osseous manifestation of MM. In total six patients were studied: four patients with a positive SRS scan and two patients with a negative scan. Three of four patients with a positive SRS

**Table 3** Follow-up results of SRS scan after 3 months of treatment

Patient No.	Type of paraprotein	Paraprotein level			SRS		Treatment
		Upfront		Follow-up	Upfront	Follow-up <sup>a</sup>	
1	FLC-κ	204	–	2	+	–	VAD
11	IgG-κ	37	–	4	+	–	VAD
12	IgG-κ	17	–	3	+	–	Thalid/dexa
18	FLC-λ	885	–	68	+	+/-	Thalid/dexa
20	FLC-κ	382	–	40	+	+/-	Thalid/dexa

<sup>a</sup> Follow-up scan was performed 3–4 months after start of treatment with thalidomide (*thalid*), dexamethasone (*dexa*) or vincristine, Adriamycin and dexamethasone (*VAD*). Free light chain (FLC) serum level; normal range: FLC-λ 4.4–32 mg/ml; FLC-κ 2.3–20 mg/ml

**Table 4** Immunohistochemistry for somatostatin receptor subtype sstr3

Patient No.	SRS scan	sstr3
1	Positive	Heterogeneous
3	Negative	Heterogeneous
6	Negative	Negative
11	Positive	Moderate
23	Positive	Strong
28	Positive	Strong

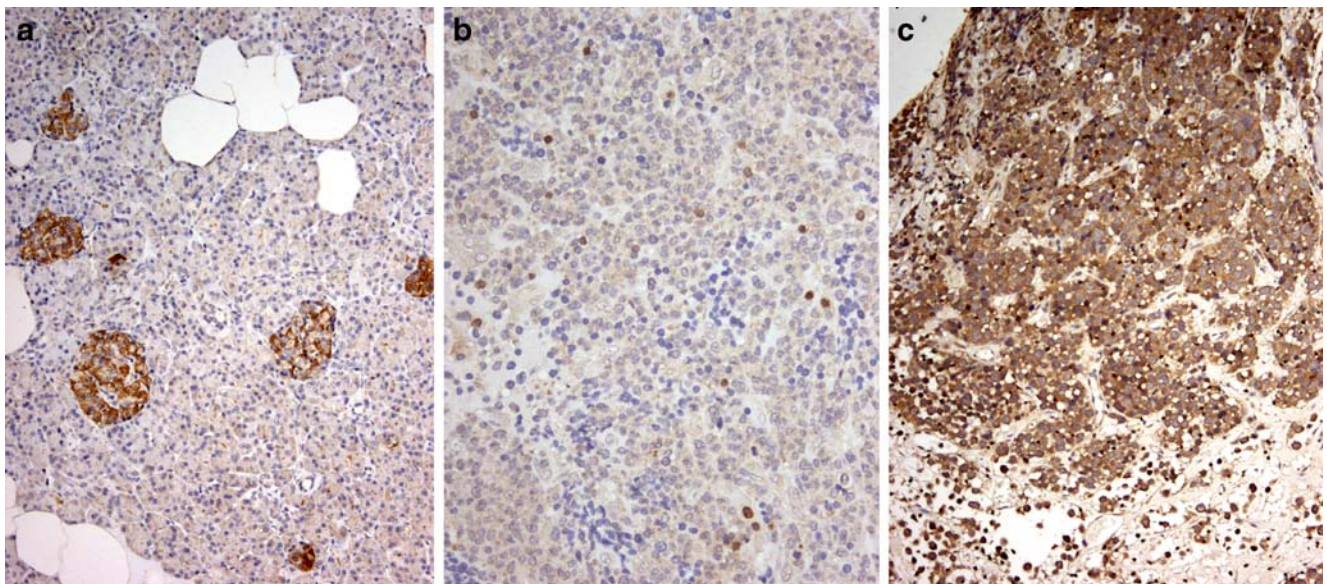
Expression of somatostatin receptor subtype sstr3 was studied on bone marrow material of multiple myeloma patients or extra-osseous manifestation of multiple myeloma. Patient No. reflects the number in Table 1; sstr3 staining was quantified semi-quantitatively as described in the “Materials and methods” section. Patient 1 showed mainly negative tumour cells, but within the tumour individual, strongly positive lymphoid cells

showed positively stained MM cells, two of them showing strongly positive cells. One patient with a positive scan showed few strongly positive cells whereas no immunostaining was observed on the majority of the MM cells. One patient with a negative scan showed entirely negative tumour cells, and the other showed occasionally positive cells (Table 4, Fig. 3). Although the series of patients is very small, we also looked for a possible relationship between the SRS results and tumour load in the biopsies, since negative SRS results might have been caused by a less prominent infiltrate. No such correlation was found (data not shown).

## Discussion

Several methods are available to demonstrate disease activity and bone lesions in patients with MM. Whole-body radiography has been most frequently used so far and demonstrates the characteristic osteolytic lesions in 60–70% of the patients [1]. By using MRI scanning a further increase in skeletal abnormalities can be demonstrated. Recently, alternative techniques have been developed that make use of an increased metabolic activity of the malignant plasma cells. FDG PET as well as  $^{99m}\text{Tc}$ -sestamibi scanning have shown that in 80–90% of the patients abnormal areas of increased uptake are present which are frequently associated with abnormal lesions on whole-body radiography [2, 3, 11, 12]. In addition, there is evidence that the increased uptake of the  $^{99m}\text{Tc}$ -sestamibi correlates with other measurable parameters of disease activity including C-reactive protein, lactate dehydrogenase and  $\beta_2$ -microglobulin [11, 12].

Previous studies have shown that MM cell lines express functional receptors for sst2, sst3 and in particular sst5 and that in vitro growth of myeloma cells can be inhibited by somatostatin and its analogue octreotide [4]. Although the role of these receptors remains enigmatic in lymphoid cells, these findings provided us a rationale to study SRS in the clinical management of myeloma. It has been demonstrated that the currently used radiopharmaceuticals for somatostatin receptor targeting do not bind with high affinity to all presently known somatostatin receptor subtypes. They bind with very high affinity to sst2 and with somewhat lower affinity to sst3 and sst5 but not to sst1 and sst4.



**Fig. 3** **a** Normal pancreatic tissue showing positive islets and negative exocrine tissue (original magnification  $\times 200$ ). **b** Patient 1 with mainly negative but incidentally strongly positive tumour cells (see also the insert; original magnification  $\times 400$ ). **c** Patient 23 with strongly positive tumour cells

The present study demonstrates that SRS is an alternative method to visualize *in vivo* MM activity. Although the number of patients with *de novo* disease is limited, the data in patients with relapsing disease suggest that SRS is more sensitive than other methods. The SRS was abnormal in 82% of the patients, whereas conventional whole-body radiography revealed new lesions in only 33% of the same patients. Histological analysis in six patients proved that the abnormal lesions as revealed by SRS were tumour related. Moreover, in most patients SRS-positive areas stained at least for the somatostatin receptor subtype sst3. Unfortunately, immunohistochemistry for sst2 and sst5 which was most widely expressed in myeloma cell lines was unsatisfactory [4].

Patients responsive to treatment demonstrated total or partial normalization of the abnormal uptake after 3–4 months of treatment, which correlated with a decline of other disease-related parameters. A remarkable finding was the fact that a positive SRS was more frequently noticed in relapsing MM patients than in upfront patients. It is unlikely that the difference is linked to the number of patients studied. Since we identified several MM cases with histologically massive, diffuse infiltrates that were mainly negative in immunohistochemistry, it is also unlikely that the differences in detection rate by SRS were caused by differences in growth pattern. It is more conceivable that an enhanced somatostatin receptor expression is shown in a more advanced state of the disease. This would be in line with the strong positive somatostatin receptor expression on MM cell lines which reflects also a more aggressive type of MM. Also in two patients with plasmacytoma a localized abnormal SRS could be shown. Although the number of patients studied is limited, these findings suggest that SRS might be a good alternative that verifies whether a localized disease is present. However, the skeletal abnormalities require a certain diameter. In our hands defects  $\geq 1$  cm were in general noticed by SRS. Smaller lesions were in general not shown on SRS. Improved localization of the abnormal SRS might further be obtained by combining it with the SPECT/CT scan. Also  $^{99m}\text{Tc}$ -labelled somatostatin is a preferable diagnostic radionuclide for higher scan quality because of favourable decay properties (6 h half-life, gamma radiation of 140 KeV) that allow administration of a large dose, to yield high-resolution images, as well as lower cost and easy on-site availability by the  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator in the clinic. PET labelled somatostatin analogues like  $^{68}\text{Ga}$ -DOTATOC or  $^{68}\text{Ga}$ -DOTANOC are also an interesting option, due to the higher resolution of PET camera systems.

In summary, the results demonstrate that SRS is a valuable tool to detect tumour activity in MM especially in patients with relapsing disease.

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