Bone marrow absorbed doses and correlations with hematological response during $^{177}$Lu-DOTATATE treatments are influenced by image-based dosimetry method and presence of skeletal metastases.

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Abstract

This study aimed to compare different image-based methods for bone marrow dosimetry and study the dose-response relationship during treatment with $^{177}$Lu-DOTATATE in patients with and without skeletal metastases. **Methods.** This study included 46 patients with advanced neuroendocrine tumors treated with at least two fractions of $^{177}$Lu-DOTATATE at Sahlgrenska University Hospital. High- and low-uptake compartments were automatically outlined in planar images collected at 2, 24, 48, and 168 hours post injection (h.p.i.). The bone marrow absorbed doses were calculated from the cross-doses of the high- and low-uptake compartments and the self-dose, using the time-activity concentration curve for the low-uptake compartment. This time-activity concentration curve was adjusted using a fixed constant of 1.8 for the planar dosimetry method, and using the activity concentrations in vertebral bodies in single-photon emission computerized tomography (SPECT) images at 24 h.p.i of $^{177}$Lu-DOTATATE in four hybrid methods: the L4-SPECT used the activity concentration in the lumbar vertebra L4; while, V-SPECT, L-SPECT, and T-SPECT used the median activity concentration in all visible vertebrae, lumbar vertebrae, and thoracic vertebrae, respectively. **Results:** Using the planar method, L4-SPECT, V-SPECT, L-SPECT, and T-SPECT, the estimated median bone marrow absorbed doses (range) were 0.19 (0.12–0.33), 0.36 (0.15–1.44), 0.40 (0.19–1.71), 0.39 (0.21–1.60), and 0.46 (0.18–2.12) Gy/7.4 GBq, respectively. For all methods, the bone marrow absorbed dose significantly correlated with decreased platelet counts. This correlation increased after treatment fraction two: planar method ($r_s = -0.49$), L4-SPECT ($r_s = -0.61$), V-SPECT ($r_s = -0.63$), L-SPECT ($r_s = -0.63$), and T-SPECT ($r_s = -0.57$). A separate analysis revealed an increased correlation for patients without skeletal metastases using the planar method ($r_s = -0.67$). In contrast, hybrid methods had poor correlations for patients without metastases and stronger correlations for patients
with skeletal metastases ($r_s = -0.61$ to $-0.74$). The mean bone marrow absorbed doses were 3-69% higher for patients with skeletal metastases than those without. **Conclusion:** The estimated bone marrow absorbed doses by image-based techniques and its correlation with platelets are influenced by the choice of measured vertebrae and the presence of skeletal metastases.
INTRODUCTION

Peptide receptor radionuclide therapy with $^{177}$Lu-DOTATATE is a valuable treatment option for metastatic neuroendocrine tumors that positively impacts survival parameters and has only minor side-effects (1,2). However, treatment is restricted due to limitations imposed by irradiation of the kidneys and bone marrow. Current evidence indicates that kidneys can tolerate mean absorbed doses above the general dose-limit of 23 Gy, and that patients can receive more than the standard of four fractions of 7.4 GBq (3-5). Recent studies have also reported the use of retreatment for patients with progressed disease (6,7). If higher renal mean absorbed doses are accepted, higher total activity will be administered and bone marrow toxicity might become the dose-limiting factor.

A dose limit of 2 Gy to the bone marrow is based on treatments with $^{131}$I and blood-based dosimetry (8,9). In a recently published study, blood-based dosimetry was performed for $^{177}$Lu-DOTATATE treatments in 200 patients and showed no correlation with hematological toxicity (10). Bergsma et. al has presented the only correlation for $^{177}$Lu-DOTATATE using blood-based dosimetry for a small selected subpopulation (11). It remains unclear if this method is valid for bone marrow dosimetry for $^{177}$Lu-DOTATATE (12).

Image-based bone marrow dosimetry and its correlation with toxicity is challenging due to problems quantifying the activity concentrations in small dispersed bone marrow cavities, which may be infiltrated with metastases. Additionally, the bone marrow is mixed with adipose tissue, with a fraction that differ between vertebrae and with age and gender (13-15). Moreover, toxicity is dependent on the bone marrow status, which can be affected by several factors such as age and previous treatments. While most patients receiving peptide receptor radionuclide therapy experience minor side effects, 10% develop severe hematological toxicity and 1–2% develop
myelodysplastic syndrome and acute leukemia (16-20). Personalized bone marrow dosimetry should be included as a factor to prevent bone marrow toxicity during treatment and as a risk factor for myelodysplastic syndrome and acute leukemia (16). However, the significance of image-based bone marrow dosimetry as a predicting factor for bone marrow toxicity is unclear.

Our research group previously published a planar image-based method for bone marrow dosimetry showing a statistical significant correlation between the bone marrow absorbed dose and hematological toxicity (21). This method uses a fixed ratio between the activity concentration in bone marrow and in low-uptake organs, without accounting for individual ratios, which may reduce its accuracy. Moreover, the method doesn’t account for the cross-irradiation of infiltrating metastases, and thus may underestimate the bone marrow absorbed dose in patients with skeletal metastases.

Here, we aimed to further develop this methodology into a hybrid planar and single-photon emission computerized tomography (SPECT) image method, enabling more personalized dosimetry. Since the active bone marrow varies within vertebrae, we determined the activity concentration in vertebrae using several methods. We also investigated whether the bone marrow absorbed dose correlated with hematological response early during treatment. Finally, we investigated if skeletal metastases influence the dose-response relationship by dividing patients into: all patients, patients without skeletal metastases, and patients with skeletal metastases.
MATERIALS AND METHODS

The patients were included in the ILUMINET-study (EUDRACT no. 2011-000240-16.), which is a collaboration between Sahlgrenska University Hospital Gothenburg and Skåne University Hospital, Lund, Sweden. This prospective study was approved by the regional Ethics Review Board in Gothenburg, and was performed in accordance with the Declaration of Helsinki and national regulations.

Patients and Therapy

This cohort study included 46 patients diagnosed with advanced neuroendocrine tumors treated with at least two fractions of $^{177}$Lu-DOTATATE at Sahlgrenska University Hospital between 2011 and 2017 (Table 1). The mean administered activity for this cohort was 7.5 GBq (6.8–8.0 GBq) $^{177}$Lu-DOTATATE per treatment fraction. Fractions were administered approximately 8 weeks apart until reaching a mean renal biological effective dose of 27 ± 2 Gy, or until the patient exhibited a persisting hematological response or disease progression. Each fraction was co-administered with an intravenous infusion of kidney-protective amino acids (2.5% lysine and 2.5% arginine in 1 L 0.9% NaCl; infusion rate 250 mL/h). Infusions of $^{177}$Lu-DOTATATE and amino acids were administered over 30 min and 4 h, respectively. Weekly blood samples were drawn to detect treatment-related toxicity and the relative nadir values of the number of platelets counts versus baseline were used to evaluate dose-response relationships.

Image Acquisition

During each treatment fraction, we collected four planar images at 2, 24, 48, and 168 hours post injection (h.p.i.), and acquired a SPECT/CT at 24 h.p.i. Imaging was performed using a
Tandem Discovery Pro, Tandem Discovery, Infinia, or Millennium VG (General Electric Medical Systems, Milwaukee, WI, USA) and a Picker IRIX (Marconi, Phillips, Netherlands). Planar whole-body scintigraphy (anterior and posterior) was performed with a scanning time of 10 cm/min. The camera was equipped with a medium-energy general purpose collimator, and the energy window was set at 208.4 keV ± 10%. No scatter correction was applied. Using the same energy settings, SPECT imaging was performed with a 30-s frame duration for 120 projections. SPECT reconstructions were completed using the Monte Carlo-based reconstruction code SARec in the image platform PhONSAi (22). Scintigraphies of a Petri dish containing $^{177}$Lu placed at different depths in a tissue-equivalent phantom were used to determine the sensitivity and effective attenuation coefficient of the gamma cameras.

The Planar Two-Compartment Method

For each patient, the whole body was divided into a high- and a low-uptake compartment. This was performed by creating a whole-body region of interest in filtered geometric mean images produced from the acquired anterior and posterior planar images. This whole-body region of interest was applied in unfiltered images, and an automated threshold-based segmentation tool in the image platform PhONSAi was used to segment the whole body into the two compartments (Fig. 1) (21,23). The algorithm uses the optimal threshold value for segmentation, according to previous work (21). Segmentation produced a high-uptake compartment comprising the liver, spleen, kidneys, and tumor, and a low-uptake compartment comprising the rest of the body.

Dose Calculation: The Planar Two-Compartment Method
The bone marrow absorbed dose was calculated as the sum of the self-dose from the bone marrow itself plus the cross-doses from the high- and low-uptake compartments (eq. 1). Activity in the planar images was quantified using the conjugate view formula, using the body thickness measured over the abdomen from CT images and a general organ thickness of 8 cm (21). Time-activity curves were obtained using the activities quantified from the planar images. For the low-uptake compartment, we used a bi-exponential fit. For the high-uptake compartment, we used a linear fit between the first two time-points, and an exponential fit between the second and fourth. The time-activity concentration curve for bone marrow was created by dividing the activity in the low-uptake compartment by the mass of the low-uptake compartment. In a previous work, a ratio of 1.8 was found between the SPECT-derived activity concentration in the bone marrow in lumbar vertebrae L4 and the activity concentration in the surrounding tissue, which was assumed to represent the low-uptake compartment (23). This ratio was used for each patient.

From the time-activity curves, we determined the time-integrated activity. This was used to calculate the bone marrow absorbed dose \( D_{BM} \) together with the S-factors for each compartment, according to equation 1:

\[
D_{BM} = \bar{C}_{BM} \times \phi_{BM-BM} \times \Delta \times 1.8 + \bar{A}_{low} \times S_{BM-low} + \bar{A}_{high} \times S_{BM-high} \tag{Eq. 1}
\]

In this equation, \( \bar{C}_{BM} \) is the time-integrated activity concentration in bone marrow; \( \phi_{BM-BM} \) is the absorbed fraction for self-irradiation, which was set to 1; \( \Delta \) is the energy released per disintegration, which was set to 147 keV (24); \( \bar{A}_{low} \) and \( \bar{A}_{high} \) are the time-integrated activities in the low- and high-uptake compartments, respectively; \( S_{BM-low} \) and \( S_{BM-high} \) are the cross-dose S-factors calculated using specific absorbed fractions for all emitted gamma energies for adult males and
females (25) and weighted based on the masses of the organs included in the low- and high-uptake compartments, respectively, using previously reported average organ masses for males and females. The mean absorbed doses were estimated for treatment fractions one and two.

The Hybrid Methods

In CT images, a spherical volume of interest was created in the middle of the body of each visible vertebra (Fig. 2a–c), representing the bone marrow. To reduce partial volume effects and minimize cross-contamination from surrounding high-uptake regions, the spheres were smaller than the vertebra, having a volume of 0.7 cm³, and were centrally placed within the vertebrae. These spheres were then transferred to the reconstructed SPECT image, and the activity concentration was calculated within the spheres for each patient. To generate a time-activity concentration curve for the bone marrow, we divided the activity in the low-uptake compartment by the mass of the low-uptake compartment, and adjusted the curve using the activity concentration in the spheres. The mass of the low-uptake compartment was determined as the patient-specific weight minus the mass of the high uptake compartment which was calculated as the area of the high-uptake compartment multiplied with the abdominal thickness. A density of unity was assumed for the two compartments. We investigated four variations of this hybrid method. The L4-SPECT method used the activity concentration in L4 (L5 if L4 was infiltrated with metastasis and thereafter L3 and L2). The V-SPECT, L-SPECT, and T-SPECT methods used the median value of the activity concentration in all visible vertebrae, lumbar vertebrae, and thoracic vertebrae, respectively.

We examined the dose-response for three patient groups: all patients, patients without skeletal metastases (Fig. 2a–c), and patients with skeletal metastases (Fig. 2d–e). We also determined the activity distribution in the vertebrae in patients without skeletal metastases. Due to
the reported difference in adipose tissue between females and males in L1-L4, we determined the mean activity concentrations in these vertebrae for females and males (14,15).

**Absorbed Dose Calculation: The Hybrid Methods**

The bone marrow absorbed dose for the hybrid methods \(D_{BM,SPECT}\) was calculated according to equation 2. The planar method used a general ratio between the low-uptake compartment and the bone marrow. In contrast, here the time-activity concentration curve created for the low-uptake compartment was adjusted using the activity concentration determined from the spheres in the SPECT/CT for each patient.

\[
D_{BM,SPECT} = \tilde{C}_{BM,SPECT} \cdot \phi_{BM-BM} \cdot \Delta + \bar{A}_{low} \cdot S_{BM-low} + \bar{A}_{high} \cdot S_{BM-high} \quad \text{Eq. 2}
\]

In this equation, \(\tilde{C}_{BM,SPECT}\) is the time-integrated activity concentration calculated from the adjusted time-activity curve for the low-uptake compartment. The other parameters have been described in Eq.1. The absorbed doses were estimated for treatment fractions one and two.

**Statistical Analysis**

The dose-response relationships were examined by Spearman correlation \(r_s\). P-values < 0.05 were considered significant. The comparison of the absorbed doses estimated with the planar and hybrid methods, the comparison of absorbed doses between patients with and without skeletal metastases and the comparison of activity concentrations in the lumbar vertebrae in men and women were performed using Wilcoxon rank sum test.
RESULTS

Bone Marrow Absorbed Dose

In the first treatment fraction using the planar method and the L4-SPECT, V-SPECT, L-SPECT, and T-SPECT the median absorbed doses for patients without skeletal metastases was 0.19 (0.12-0.32), 0.32 (0.15-0.5), 0.39 (0.18-0.62), 0.34 (0.21-0.67) and 0.46 (0.18-0.86) Gy/7.4 GBq, respectively (Figure 3). For patients with skeletal metastases the corresponding median absorbed doses was 0.18 (0.12-0.29), 0.39 (0.16-1.4), 0.44 (0.23-1.7), 0.42 (0.21-1.6), and 0.45 (0.27-2.1) Gy/7.4 GBq, respectively. The results show that the planar method had similar range in absorbed doses for patients with or without metastases. In contrast, when skeletal metastases were present the hybrid methods had higher range in absorbed doses and the median absorbed dose was increased by 13-22% (L4-SPECT, V-SPECT, L-SPECT).

The absorbed doses estimated using the hybrid methods were significantly higher from the absorbed dose estimated using the planar method for the whole patient cohort, the patients with skeletal metastases, and the patients without skeletal metastases. Absorbed doses for patients with skeletal metastases were significantly higher than absorbed doses for patients without metastases using L4-SPECT.

When we studied the activity distribution among vertebrae in the 22 patients who did not suffer from skeletal metastases, the highest activity concentration was observed between T10 and L1, while the lowest values were for T5–T7 and L4–L5 (Table 2). This also reflects the tendency for higher absorbed doses using T-SPECT, which mainly uses the median of T8-T12. The 22 patients were also grouped according to gender. The mean activity concentration in L1-L4 was 1.13 times higher in males but this difference was not statistically significant.
Dose-Response Relationship

When including all patients, significant dose-response relationships were established after the first treatment fraction between the bone marrow absorbed dose and the relative decrease in platelet counts using the planar method ($r_s = -0.42$, $P < 0.001$), L4-SPECT ($r_s = -0.45$, $P < 0.01$), V-SPECT ($r_s = -0.48$, $P < 0.001$), L-SPECT ($r_s = -0.57$, $P < 0.0001$), and T-SPECT ($r_s = -0.44$, $P < 0.01$) (Fig. 3). The correlations increased for fraction two using the cumulative absorbed dose: planar method ($r_s = -0.49$, $P < 0.001$), L4-SPECT ($r_s = -0.61$, $P < 0.0001$), V-SPECT ($r_s = -0.63$, $P < 0.0001$), L-SPECT ($r_s = -0.63$, $P_2 < 0.0001$), and T-SPECT ($r_s = -0.57$, $P < 0.0001$).

We then performed a separate analysis of patients with and without skeletal metastases. For patients without skeletal metastases, the planar method showed stronger significant dose-response relationships after treatment fractions one and two ($r_s = -0.58$ and $r_s = -0.67$, respectively) (Fig. 4C); while, no statistically significant correlation was established using the planar method for patients with skeletal metastases (Fig. 4B). Using the hybrid methods, a significant correlation could be established in patients without skeletal metastases using L-SPECT ($r_s = -0.57$) in treatment fraction one and in treatment fraction two using L4-SPECT ($r_s = -0.49$), V-SPECT ($r_s = -0.51$), and L-SPECT ($r_s = -0.45$). For patients with skeletal metastases, significant dose-response relationships were established after treatment fractions one and two using L4-SPECT ($r_s = -0.50$ and $r_s = -0.61$, respectively), V-SPECT ($r_s = -0.53$ and $r_s = -0.70$, respectively), L-SPECT ($r_s = -0.57$ and $r_s = -0.74$, respectively), and T-SPECT ($r_s = -0.48$ and $r_s = -0.71$, respectively) (Fig. 3B). All dosimetry and response data is available as supplemental tables (Table S1 and Table S2).
DISCUSSION

The present study aimed to update a bone marrow dosimetry method based on planar images into a hybrid methodology that incorporates SPECT/CT for patient-specific determination of activity in bone marrow. We expected this would lead to an improved correlation between the bone marrow absorbed dose and platelet response. However, this improvement was only partly achieved. When using the planar method, the predictive ability showed a modest correlation after the first fraction and stronger correlation for fraction two. There was also a strikingly better response prediction for patients without metastases than those with metastases. This suggested that the planar methodology is suitable for patients without skeletal metastases, but less so for patients with metastases. The same should be true for blood-based dosimetry. In a recent prospective study including 200 patients with neuroendocrine tumors treated with $^{177}$Lu-DOTATATE, 22% of patients had to stop treatment due to bone-marrow-related events even though none had reached the 2-Gy dose limit (10). The authors used blood-based dosimetry, which showed low mean specific absorbed doses (0.12 Gy/7.4 GBq), and concluded that the dosimetry method did not predict toxicity. This might reflect the inability of a blood-based methodology to take into account the impact of infiltrating skeletal metastases and to correctly estimate the individual variations in bone marrow activity concentration.

The planar method yielded a median bone marrow absorbed dose of 0.18 Gy/7.4 GBq, while the hybrid methods yielded absorbed doses between 0.32 and 0.46 Gy/7.4 GBq, which is comparable to other published bone marrow dosimetry data (3,10,11,26-29). The low absorbed doses for the planar method are due to an underestimate of the ratio between bone marrow and the low uptake compartment. The former estimate was determined from SPECT/CT in 15 patients as the ratio between the activity concentration in L4 and the surrounding tissue (23). In this study we
were able to compare the true ratio between L4 and the low uptake compartment which resulted in an almost two times higher ratio. Using this factor will result in comparable median absorbed dose between the planar and the L4-SPECT method in patients without metastasis, i.e. 0.32 Gy/7.4 MBq.

To measure the activity concentration in vertebrae for dosimetry is appealing; however, the low activity concentration in vertebrae is challenging due to the risk of cross-contamination of scattered photons from surrounding high uptake organs and tumors. To minimize this effect, we used the Monte Carlo-based reconstruction code SARec (22) for generating the SPECT images. This method reduces the influence of scattered photons and improves the recovery compared with OSEM reconstructions with and without recovery corrections (22). Nevertheless, the highest activity concentrations were observed in the vertebrae closest to the high uptake organs. Studies using magnetic resonance imaging demonstrated that the fraction between bone marrow and fat varies throughout the vertebral column, and with gender and age (13-15). These studies found that the bone marrow fat fraction is larger in the lumbar vertebrae than in the thoracic vertebrae, consistent with our results of lower activity concentrations in the lumbar vertebrae. Furthermore, Baum et al. reported that the bone marrow fat fraction (L1-L4) is 1.2 times higher in females versus males in their sixties. Here, the majority of patients were over sixty years old and males had a 1.13 times higher activity concentration; however, the difference was not statistically significant. Still, these results indicated that the variation in activity concentrations in the vertebrae might reflect the fat fraction and not cross-contamination.

Due to the variable activity concentrations, we used different vertebrae to investigate the influence on the absorbed dose and the dose-response relationship. Previous studies mainly used L4 (26,30). When we used this single vertebra, we had to choose L5 or L3 in 15% of the patients due to skeletal metastases in L4. In contrast to the planar method, there was no dose-response correlation for patients without metastases and a rather strong correlation for patients with
metastases using L4-SPECT. Similar results, with stronger correlations, were obtained when we used the median activity concentration in all, lumbar, or thoracic vertebrae. Thus, the hybrid methods might better reflect the influence of infiltrating bone marrow metastases on the absorbed dose. The absorbed doses were also higher in patients with metastases (except from when using the planar method and T-SPECT), despite excluding metastases in the L4-SPECT method and using the median value to reduce the impact of metastases in the estimate. We demonstrated here that the platelet response is influenced by infiltrating metastases and previously that the absorbed dose to the spleen influences the platelet response by acting as a reservoir for platelets (31). In addition, age, gender, and pretreatment must be incorporated when modelling platelet response and developing predictive models for toxicity.

**CONCLUSION**

The bone marrow absorbed doses differed between the methods studied and for patients with and without metastases. Nevertheless, image-based dosimetry methods demonstrated that increased absorbed doses result in higher platelet toxicity.

**DISCLOSURE**

No potential conflicts of interest relevant to this article exist.
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KEY POINTS

Question: Is the bone marrow absorbed dose and its correlation with hematological response during $^{177}$Lu-DOTATATE treatments influenced by image-based dosimetry method and the presence of skeletal metastases?

Pertinent Findings: In a cohort study of 46 patients treated with $^{177}$Lu-DOTATATE it was established that a planar image-based method for bone marrow dosimetry was not influenced by skeletal metastases whereas hybrid dosimetry methods, based on planar and SPECT images, was influenced by skeletal metastases as well as the used vertebrae for SPECT quantification. Nevertheless, all methods demonstrated statistically significant dose response correlations; the planar method demonstrated the best correlation for patients without skeletal metastasis, and the hybrid methods had the highest dose response correlation for all patients and the cohort of patients with skeletal metastasis.

Implications for Patient Care: Different dosimetry methods might be required for individual prediction of hematological toxicity in patient with and without skeletal metastases.
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FIGURE 1. Resulting segmentation of two compartments in a planar image. The high-uptake compartment (blue) comprises the high-uptake organs (liver, spleen, kidneys, and tumors), and the low-uptake compartment comprises the rest of the body.
FIGURE 2. The location of the spherical volume of interests in the vertebrae. A-C) the volumes of interest in the SPECT/CT images of a patient without skeletal metastases. D-F) The spherical volumes of interest in the SPECT/CT images of a patient with skeletal metastasis in thoracic vertebra 7.
FIGURE 3. Median bone marrow absorbed doses after treatment fraction one estimated using the planar method and the four hybrid methods for (A) all patients, (B) patients with skeletal metastases, and (C) patients without skeletal metastases.
FIGURE 4. The r-values for the dose-response relationships between the bone marrow absorbed dose and the decrease in platelet counts when using the planar method and the hybrid methods for treatment fractions one and two. (A) The r-values when all patients are included. (B) The r-values for patients with skeletal metastases. (C) The r-values for patients without skeletal metastases. *P < 0.05, **P < 0.01, ***P < 0.001.
Figure 5. The total bone marrow absorbed doses versus the response of platelet counts after two treatment fractions using the planar method (A-C) and the hybrid method L-SPECT (D-F). The patients are divided into the three groups; all patients, patients with skeletal metastasis, and patients without skeletal metastasis. The dotted lines represent the linear regressions, for illustrative purposes.
TABLE 1. Patient Characteristics.

| Characteristic                  |         |         |
|--------------------------------|---------|---------|
| Gender: no. (%)                |         |         |
| Female                         | 22 (47.8)|         |
| Male                           | 24 (52.2)|         |
| Age: median [Range]            |         |         |
| All patients                   | 64 [35-84]|         |
| Female                         | 63.5 [44-84]|         |
| Male                           | 64 [35-78]|         |
| Primary tumour: no. (%)        |         |         |
| Small intestine                | 28 (60.9)|         |
| Pancreas                       | 7 (15.2)|         |
| Lung                           | 3 (6.5)|         |
| Colorectal                     | 2 (4.3)|         |
| Other/unknown                  | 6 (13.0)|         |
| Ki67 index: no. (%)            |         |         |
| 0-2%                           | 21 (46.7)|         |
| 3-20%                          | 25 (53.3)|         |
| >20%                           | 0       |         |
| Skeletal metastases: no. (%)   |         |         |
| All patients                   | 24 (52.2)|         |
| Female                         | 9 (40.9)|         |
| Male                           | 15 (62.5)|         |
| Baseline platelets (10^9/L): median [Range] |         |         |
| All patients                   | 241 [128 – 519]|         |
| Female                         | 250.5 [128 – 503]|         |
| Male                           | 264 [150 – 519]|         |
| Previous treatments: no. (%)   |         |         |
| Somatostatin analogues         | 33 (71.7)|         |
| Surgery                        | 42 (91.3)|         |
| Everolimus and/or sunitinib    | 5 (10.9)|         |
| Chemotherapy                   | 11 (23.9)|         |
| Loco-regional therapy          | 30 (65.2)|         |
| PRRT                           | 5 (10.9)|         |
| 131I-MIBG*                     | 1 (2.2)|         |
| Performance status (ECOG): no. (%) |         |         |
| 0                              | 28 (60.0)|         |
| 1                              | 17 (37.8)|         |
| 2                              | 1 (2.2)|         |
| 3-4                            | 0       |         |

*metaiodobenzylguanidine
**TABLE 2.** Median activity concentration in each vertebra among 22 patients without skeletal metastases.

| Vertebra | Median Activity concentration and range (kBq/mL) | No. Patients |
|----------|-----------------------------------------------|--------------|
| T5       | 14.4                                          | 1            |
| T6       | 20.2 (8.7 - 27.7)                             | 3            |
| T7       | 21.3 (10.5 - 37.9)                            | 5            |
| T8       | 25.8 (6.6 - 41.1)                             | 9            |
| T9       | 28.1 (14.6 - 64.6)                            | 15           |
| T10      | 37.1 (14.8 - 86.0)                            | 21           |
| T11      | 47.8 (10.4 – 77.4)                            | 22           |
| T12      | 41.0 (16.1 – 70.5)                            | 22           |
| L1       | 38.4 (15.1 – 79.2)                            | 22           |
| L2       | 35.6 (19.0 – 81.4)                            | 22           |
| L3       | 28.2 (11.7 – 56.3)                            | 22           |
| L4       | 23.9 (11.7 – 46.0)                            | 22           |
| L5       | 24.2 (7.7 – 51.4)                             | 21           |
Table S1. Patient and dosimetry data for the first treatment cycle.

| No. | Age | Gender | Skeletal metastases | Dosimetry method (Gy/7.4 Gy) | Relative platelet counts |
|-----|-----|--------|----------------------|------------------------------|-------------------------|
|     |     |        |                      | Planar | V-SPECT | L-SPECT | T-SPECT | L4-SPECT |             |
| 3   | 59  | f      | 0                    | 0.12   | 0.19    | 0.21    | 0.18    | 0.15    | 0.71       |
| 4   | 46  | m      | 1                    | 0.14   | 0.25    | 0.22    | 0.30    | 0.16    | 0.77       |
| 5   | 52  | m      | 0                    | 0.17   | 0.40    | 0.25    | 0.49    | 0.25    | 0.96       |
| 6   | 35  | m      | 1                    | 0.17   | 0.31    | 0.27    | 0.35    | 0.19    | 0.57       |
| 7   | 55  | m      | 1                    | 0.19   | 1.02    | 1.02    | 0.95    | 0.86    | 0.64       |
| 8   | 59  | m      | 0                    | 0.16   | 0.39    | 0.38    | 0.41    | 0.32    | 0.62       |
| 9   | 54  | f      | 1                    | 0.23   | 0.97    | 0.80    | 1.22    | 0.71    | 0.38       |
| 10  | 68  | m      | 0                    | 0.17   | 0.38    | 0.33    | 0.57    | 0.26    | 0.70       |
| 11  | 77  | f      | 0                    | 0.19   | 0.28    | 0.30    | 0.28    | 0.17    | 0.58       |
| 12  | 64  | m      | 1                    | 0.14   | 0.39    | 0.41    | 0.37    | 0.41    | 0.80       |
| 13  | 66  | m      | 1                    | 0.14   | 0.55    | 0.55    | 0.58    | 0.43    | 0.35       |
| 16  | 43  | m      | 0                    | 0.21   | 0.60    | 0.67    | 0.60    | 0.34    | 0.45       |
| 17  | 77  | f      | 0                    | 0.16   | 0.43    | 0.43    | 0.48    | 0.39    | 0.70       |
| 18  | 79  | f      | 1                    | 0.22   | 1.72    | 1.61    | 2.14    | 1.45    | 0.65       |
| 19  | 68  | f      | 1                    | 0.20   | 0.77    | 1.29    | 0.61    | 0.77    | 0.53       |
| 20  | 57  | f      | 0                    | 0.21   | 0.49    | 0.33    | 0.58    | 0.22    | 0.59       |
| 21  | 54  | f      | 0                    | 0.13   | 0.29    | 0.29    | 0.25    | 0.35    | 0.91       |
| 22  | 61  | f      | 0                    | 0.21   | 0.38    | 0.34    | 0.50    | 0.34    | 0.41       |
| 23  | 71  | m      | 1                    | 0.19   | 0.45    | 0.58    | 0.41    | 0.52    | 0.47       |
| 24  | 67  | f      | 1                    | 0.17   | 0.39    | 0.36    | 0.42    | 0.36    | 0.78       |
| 25  | 68  | f      | 0                    | 0.19   | 0.37    | 0.40    | 0.36    | 0.32    | 0.61       |
| 26  | 69  | f      | 1                    | 0.18   | 0.39    | 0.29    | 0.42    | 0.29    | 0.85       |
| 27  | 61  | f      | 0                    | 0.14   | 0.41    | 0.47    | 0.39    | 0.46    | 0.66       |
| 28  | 65  | f      | 1                    | 0.24   | 0.66    | 1.04    | 0.58    | 0.52    | 0.45       |
| 29  | 78  | m      | 1                    | 0.28   | 1.62    | 1.29    | 1.78    | 1.33    | 0.73       |
| 30  | 44  | f      | 1                    | 0.19   | 0.31    | 0.34    | 0.28    | 0.36    | 0.78       |
| 31  | 70  | m      | 1                    | 0.25   | 0.47    | 0.45    | 0.48    | 0.39    | 0.56       |
| 32  | 47  | m      | 1                    | 0.12   | 1.39    | 1.39    | 1.92    | 0.42    | 0.61       |
| 33  | 70  | f      | 0                    | 0.12   | 0.26    | 0.29    | 0.19    | 0.21    | 0.89       |
| 34  | 50  | f      | 1                    | 0.14   | 0.42    | 0.30    | 0.50    | 0.30    | 0.67       |
| 35  | 64  | m      | 1                    | 0.15   | 0.30    | 0.29    | 0.31    | 0.27    | 0.67       |
| 36  | 60  | f      | 0                    | 0.20   | 0.39    | 0.27    | 0.90    | 0.23    | 0.70       |
| 37  | 50  | m      | 1                    | 0.13   | 0.41    | 0.40    | 0.44    | 0.19    | 0.71       |
| 38  | 60  | m      | 0                    | 0.13   | 0.31    | 0.31    | 0.35    | 0.20    | 0.96       |
| 39  | 64  | m      | 1                    | 0.18   | 0.31    | 0.38    | 0.28    | 0.38    | 0.62       |
| 40  | 67  | m      | 1                    | 0.16   | 0.42    | 0.38    | 0.42    | 0.38    | 0.69       |
| 41  | 84  | f      | 1                    | 0.27   | 1.04    | 1.45    | 0.91    | 1.01    | 0.51       |
| 42  | 69  | f      | 0                    | 0.16   | 0.51    | 0.52    | 0.50    | 0.43    | 0.67       |
| 43  | 61  | f      | 0                    | 0.30   | 0.46    | 0.47    | 0.46    | 0.38    | 0.85       |
| 44  | 49  | m      | 1                    | 0.17   | 0.23    | 0.21    | 0.27    | 0.19    | 0.93       |
| 45  | 55  | m      | 1                    | 0.29   | 0.52    | 0.53    | 0.50    | 0.52    | 0.69       |
| 46  | 72  | m      | 0                    | 0.19   | 0.50    | 0.25    | 0.60    | 0.18    | 0.85       |
| 47  | 76  | m      | 0                    | 0.23   | 0.40    | 0.40    | 0.40    | 0.40    | 0.67       |
| 48  | 62  | f      | 0                    | 0.20   | 0.63    | 0.44    | 0.71    | 0.38    | 0.42       |
| 49  | 73  | m      | 0                    | 0.20   | 0.34    | 0.35    | 0.33    | 0.33    | 0.66       |
| 50  | 77  | m      | 0                    | 0.33   | 0.56    | 0.56    | 0.67    | 0.53    | 0.40       |
Table S2. Patient and dosimetry data for the second treatment cycle.

| No | Age | Gender | Skeletal metastases | Dosimetry method | Relative platelet counts |
|----|-----|--------|---------------------|------------------|-------------------------|
|    |     |        |                     | Planar  | L4-SPECT  | V-SPECT  | L-SPECT  | T-SPECT  |
| 3  | 59  | f      | 0                   | 0,12    | 0,24      | 0,21     | 0,24     | 0,24     | 0,77     |
| 4  | 46  | m      | 1                   | 0,14    | 0,25      | 0,23     | 0,23     | 0,23     | 0,68     |
| 5  | 52  | m      | 0                   | 0,17    | 0,29      | 0,49     | 0,36     | 0,36     | 0,81     |
| 6  | 35  | m      | 1                   | 0,17    | 0,39      | 0,41     | 0,68     | 0,68     | 0,16     |
| 7  | 55  | m      | 1                   | 0,19    | 0,47      | 0,72     | 0,65     | 0,65     | 0,47     |
| 8  | 59  | m      | 0                   | 0,16    | 0,28      | 0,30     | 0,30     | 0,30     | 0,62     |
| 9  | 54  | f      | 1                   | 0,23    | 0,42      | 0,65     | 0,56     | 0,56     | 0,63     |
| 10 | 68  | m      | 0                   | 0,17    | 0,25      | 0,35     | 0,28     | 0,28     | 0,66     |
| 11 | 77  | f      | 0                   | 0,19    | 0,21      | 0,23     | 0,22     | 0,22     | 0,73     |
| 12 | 64  | m      | 1                   | 0,14    | 0,20      | 0,24     | 0,21     | 0,21     | 0,67     |
| 13 | 66  | m      | 1                   | 0,14    | 0,19      | 0,37     | 0,22     | 0,22     | 0,34     |
| 14 | 43  | m      | 0                   | 0,21    | 0,45      | 0,60     | 0,59     | 0,59     | 0,36     |
| 15 | 77  | f      | 0                   | 0,16    | 0,43      | 0,46     | 0,43     | 0,43     | 0,72     |
| 16 | 79  | f      | 1                   | 0,22    | 0,92      | 0,93     | 0,92     | 0,92     | 0,61     |
| 17 | 68  | f      | 1                   | 0,20    | 0,70      | 0,70     | 0,74     | 0,74     | 0,38     |
| 18 | 57  | f      | 0                   | 0,21    | 0,21      | 0,39     | 0,32     | 0,32     | 0,64     |
| 19 | 54  | f      | 0                   | 0,13    | 0,31      | 0,29     | 0,27     | 0,27     | 0,77     |
| 20 | 61  | f      | 0                   | 0,21    | 0,34      | 0,34     | 0,30     | 0,30     | 0,29     |
| 21 | 71  | m      | 1                   | 0,19    | 0,26      | 0,46     | 0,40     | 0,40     | 0,37     |
| 22 | 67  | f      | 1                   | 0,17    | 0,35      | 0,39     | 0,36     | 0,36     | 0,64     |
| 23 | 68  | f      | 0                   | 0,19    | 0,31      | 0,43     | 0,43     | 0,43     | 0,47     |
| 24 | 69  | f      | 1                   | 0,18    | 0,28      | 0,33     | 0,33     | 0,33     | 0,80     |
| 25 | 61  | f      | 0                   | 0,14    | 0,25      | 0,29     | 0,25     | 0,25     | 0,69     |
| 26 | 65  | f      | 1                   | 0,24    | 0,65      | 0,66     | 0,93     | 0,93     | 0,28     |
| 27 | 78  | m      | 1                   | 0,28    | 0,62      | 1,01     | 0,83     | 0,83     | 0,48     |
| 28 | 44  | f      | 1                   | 0,19    | 0,23      | 0,28     | 0,24     | 0,24     | 0,69     |
| 29 | 70  | m      | 1                   | 0,25    | 0,40      | 0,49     | 0,49     | 0,49     | 0,58     |
| 30 | 47  | m      | 1                   | 0,12    | 0,55      | 1,04     | 1,04     | 1,04     | 0,53     |
| 31 | 70  | m      | 1                   | 0,12    | 0,17      | 0,42     | 0,68     | 0,68     | 0,90     |
| 32 | 50  | f      | 1                   | 0,14    | 0,36      | 0,37     | 0,36     | 0,36     | 0,62     |
| 33 | 64  | m      | 1                   | 0,15    | 0,36      | 0,28     | 0,36     | 0,36     | 0,64     |
| 34 | 60  | f      | 0                   | 0,20    | 0,29      | 0,39     | 0,29     | 0,29     | 0,74     |
| 35 | 50  | m      | 1                   | 0,13    | 0,17      | 0,31     | 0,29     | 0,29     | 0,89     |
| 36 | 60  | m      | 0                   | 0,13    | 0,24      | 0,32     | 0,26     | 0,26     | 0,96     |
| 37 | 64  | m      | 1                   | 0,18    | 0,30      | 0,24     | 0,30     | 0,30     | 0,89     |
| 38 | 67  | m      | 1                   | 0,16    | 0,29      | 0,29     | 0,29     | 0,29     | 0,65     |
| 39 | 84  | f      | 1                   | 0,27    | 0,71      | 0,65     | 0,71     | 0,71     | 0,15     |
| 40 | 69  | f      | 0                   | 0,16    | 0,70      | 0,55     | 0,60     | 0,60     | 0,77     |
| 41 | 61  | f      | 0                   | 0,30    | 0,70      | 0,54     | 0,60     | 0,60     | 0,59     |
| 42 | 49  | m      | 1                   | 0,17    | 0,22      | 0,27     | 0,25     | 0,25     | 0,90     |
| 43 | 55  | m      | 1                   | 0,29    | 0,46      | 0,46     | 0,46     | 0,46     | 0,53     |
| 44 | 72  | m      | 0                   | 0,19    | 0,23      | 0,50     | 0,33     | 0,33     | 0,70     |
| 45 | 76  | m      | 0                   | 0,23    | 0,53      | 0,53     | 0,53     | 0,53     | 0,57     |
| 46 | 62  | f      | 0                   | 0,20    | 0,34      | 0,47     | 0,40     | 0,40     | 0,29     |
| 47 | 73  | m      | 0                   | 0,20    | 0,35      | 0,40     | 0,40     | 0,40     | 0,55     |
| 48 | 77  | m      | 0                   | 0,33    | 0,40      | 0,50     | 0,50     | 0,50     | 0,34     |