# Pretherapeutic estimation of kidney function in patients treated with peptide receptor radionuclide therapy: can renal scintigraphy be safely omitted?

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## Introduction

Peptide receptor radionuclide therapy (PRRT) is beneficial for treating patients with advanced and/or metastasized neuroendocrine tumors (NETs) [1]. Radiolabeled somatostatin agonists such as [$^{90}$Y-DOTA$^{0}$,Tyr$^{3}$]-octreotide, [$^{177}$Lu-DOTA$^{0}$,Tyr$^{3}$,Thr$^{8}$]-octreotide, or [$^{177}$Lu-DOTA$^{0}$, Tyr$^{3}$]-octreotate are commonly used [1–10]. Although treatment with these compounds is typically well tolerated, related side effects have been described, including myelosuppression and renal toxicity [10–15]. Serious renal impairment has been described in ~1.3% of patients, whereas minor nephrotoxicity has been reported in nearly half of the patients [14]. The coadministration of amino acids significantly reduces the renally absorbed dose of radiopeptides [13,16] and has therefore been implemented into recent practice guidelines [1].

Because of the potential nephrotoxicity of PRRT, pretherapeutic assessment of kidney function is essential. According to 'The joint IAEA, EANM, SNMMI practical guidance on peptide radionuclide therapy in neuroendocrine tumours', pretherapeutic estimation of the kidney function using laboratory tests [creatinine and blood urea nitrogen (BUN)] or renal scintigraphy should be performed [1]. For the latter, $^{99m}$Tc-mercaptoacetyltriglycine (MAG3) or $^{99m}$Tc-diethylene triamine pentaacetic acid (DTPA) scintigraphy is the currently used clinical standard [17–20].

However, the guidelines do not report on the test performance of the available modalities, and an explicit recommendation regarding which test should be performed is missing. Therefore, the decision of the method

of choice varies depending on local experience and preferences [1].

The aim of this study was to investigate the test performance of different kidney function methods (laboratory testing of venous blood samples and $^{99m}$Tc-MAG3 renal scintigraphy).

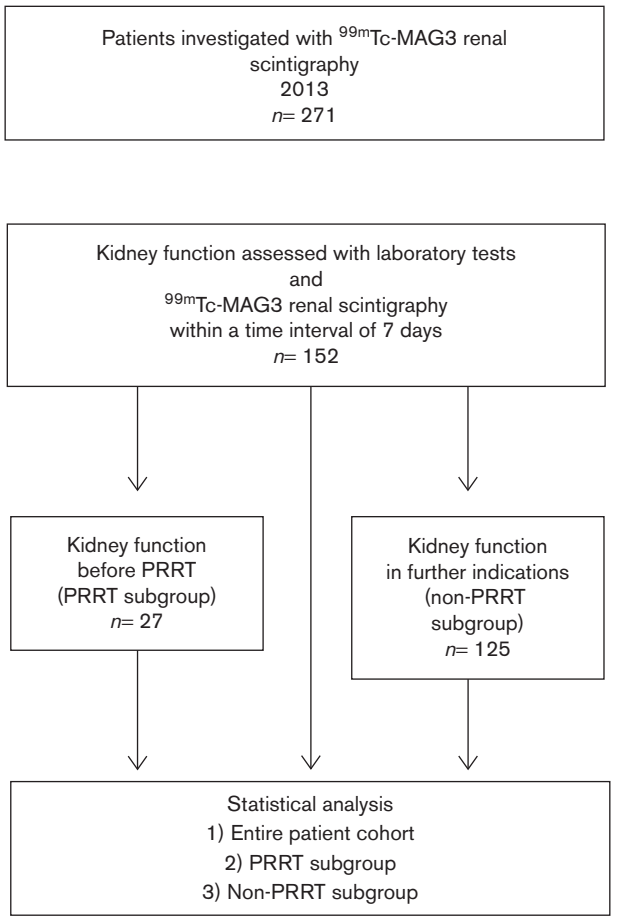
## Materials and methods

### Patients

From January to December 2013, the kidney function of 271 patients was investigated using $^{99m}$Tc-MAG3 renal scintigraphy in our department. In this retrospective study, only patients additionally undergoing venous blood sampling for the prediction of kidney function within 7 days of renal scintigraphy were included (Fig. 1). A total of 152 patients (93 male and 59 female) met this inclusion criterion. A subgroup of 27 patients (18 male and nine female) underwent kidney function assessments before PRRT (the PRRT subgroup). In the remaining 125 patients, clinical reasons for assessing the kidney function (the non-PRRT subgroup; 80 male and 45 female) included status before chemotherapy ($n=64$, 51%), suspicion of urinary tract obstruction ($n=23$, 18%), tumor of the urinary tract ($n=17$, 14%), renal failure ($n=6$, 5%), and other reasons not specified ($n=15$, 12%). The following risk factors for the occurrence of kidney toxicity were systematically assessed in all patients: diabetes mellitus, arterial hypertension, history of nephrotoxic chemotherapies, long-term use of NSAIDs, and angiotensin converting enzyme inhibitors.

Because this retrospective study comprised only additional analysis algorithms of routinely acquired data, additional informed consent of patients was waived. However, all patients gave written consent for renal scintigraphy and PRRT.

**Fig. 1**




Flow chart of patient selection. MAG3, mercaptoacetyltriglycine; PRRT, peptide receptor radionuclide therapy.

### Renal scintigraphy

All patients underwent kidney function scintigraphy with $^{99m}$Tc-MAG3 on a single-head gamma camera (Siemens Signature, Erlangen, Germany) equipped with low-energy, high-resolution collimators. In the PRRT subgroup, renal scintigraphy was performed within 2 weeks before therapy. The radiopharmaceutical was prepared using a commercially available kit (MAG3; Mallinckrodt Pharmaceuticals, Dublin, Ireland) and renal scintigraphy was performed according to national guidelines [21]. Imaging began immediately after an injection of $99.1 \pm 5.5$ MBq $^{99m}$Tc-MAG3 in the PRRT subgroup and $100.0 \pm 7.0$ MBq $^{99m}$Tc-MAG3 in the non-PRRT subgroup ($99.8 \pm 6.8$ MBq in the entire patient group).

### Venous blood sampling

In the PRRT subgroup, blood samples were drawn to assess standard biochemical values [creatinine, BUN, and glomerular filtration rate (GFR)] on the day before treatment. The kidney function in the non-PRRT subgroup was equally evaluated. The mean time interval between renal scintigraphy and blood collection was $3 \pm 4$ days.

### Statistical analysis

Student's *t*-test was used to compare the results between $^{99m}$Tc-MAG3 clearance and venous blood sample (normal vs. abnormal kidney function). Student's *t*-test was also used to compare the $^{99m}$Tc-MAG3 clearance with other risk factors for kidney toxicity. A *P*-value of 0.05 or less was considered significant. To detect a linear association, Pearson's correlation was utilized.

To calculate the cutoff values of the parameters of venous blood samples to predict an abnormal kidney function considering $^{99m}$Tc-MAG3 clearance as the reference standard, a discriminant analysis was performed. Using discriminant analysis, a formula including all of the serum parameters (creatinine, BUN, and GFR) could be derived. The cutoff values for the prediction of normal kidney function were determined by means of receiver operating characteristic (ROC) analysis.

The linear relationship between $^{99m}$Tc-MAG3 clearance and laboratory tests was determined using linear regression analysis ($^{99m}$Tc-MAG3 clearance as the independent variable and parameters of the laboratory test as the dependent variables).

## Results

### Patient characteristics

In total, 152 patients met the inclusion criteria. The mean age of the entire patient cohort was 60 ± 16 years (range: 19–84 years). The mean age of the PRRT subgroup ($n = 27$) was 61 ± 14 years (range: 24–82 years). In the PRRT subgroup, 67% (18/27) of patients had gastroenteropancreatic NET, 7% (2/27) had NET of unknown origin, 11% (3/27) had meningioma, and one patient each (4%) had small-cell lung cancer, medullary thyroid carcinoma, thymus NET, and paraganglioma (Table 1). The patients were scheduled to undergo PRRT for their first ($n = 6$, 22%), second ($n = 11$, 41%), third ($n = 6$, 22%), fourth ($n = 2$, 7%), seventh ($n = 1$, 4%), or eighth ($n = 1$, 4%) cycles (mean, 2.6 ± 1.6 cycles). The mean cumulative dose for the patients with previous PRRT was 18.0 ± 13.0 GBq (range: 7.0–62.5 GBq). The mean age of the non-PRRT subgroups was 60 ± 16 years (range: 19–84 years). In both subgroups, risk factors for kidney toxicity were present; 29% (8/27) of patients in the PRRT subgroup and 38% (48/125) of patients in the non-PRRT subgroup had such risk factors.

### Correlation of venous blood sample-derived kidney function and $^{99m}$Tc-MAG3 renal scintigraphy

In the entire patient group ($n = 152$), 77% (117/152) had a normal kidney function (≥100% of lower limit) according to the $^{99m}$Tc-MAG3 renal scintigraphy (mean, 220.1 ± 71.0 ml/min/1.73 m$^2$). The venous blood sample-derived mean creatinine (1.1 ± 0.6 mg/dl) correlated significantly with the $^{99m}$Tc-MAG3 clearance ($r = -0.60$, $P < 0.001$). Furthermore, the mean BUN (33.0 ± 19.2 mg/dl) and the mean GFR (76.5 ± 26.7 ml/min) correlated significantly with the $^{99m}$Tc-MAG3 clearance ($r = -0.53$, $P < 0.001$, and $r = 0.67$, $P < 0.001$, respectively).

In the PRRT subgroup ($n = 27$), before PRRT, 85% of patients had a normal kidney function on assessment with $^{99m}$Tc-MAG3 renal scintigraphy (mean, 221.4 ± 53.4 ml/min/1.73 m$^2$). The mean creatinine (0.9 ± 0.2 mg/dl) correlated significantly with the $^{99m}$Tc-MAG3 clearance ($r = -0.43$, $P = 0.037$). The venous blood sample-derived mean BUN (26.5 ± 10.8 mg/dl) and mean GFR (81.0 ± 27.6 ml/min) also correlated significantly with $^{99m}$Tc-MAG3 clearance ($r = -0.45$, $P = 0.027$, and $r = 0.44$, $P = 0.022$, respectively).

In the non-PRRT subgroup ($n = 125$), 75% (94/125) of the patients had a normal kidney function on assessment with $^{99m}$Tc-MAG3 renal scintigraphy (mean, 219.8 ± 74.3 ml/min/1.73 m$^2$). The mean creatinine level (1.1 ± 0.7 mg/dl) correlated significantly with the $^{99m}$Tc-MAG3 clearance ($r = -0.62$, $P < 0.001$). The venous blood sample-derived mean BUN (34.3 ± 20.2 mg/dl) and mean GFR (75.4 ± 26.4 ml/min) also correlated significantly with the $^{99m}$Tc-MAG3 clearance ($r = -0.55$, $P < 0.001$, and $r = 0.71$, $P < 0.001$, respectively).

### Correlation of kidney function and risk factors for kidney toxicity

With respect to risk factors for the occurrence of renal toxicity (diabetes mellitus, arterial hypertension, history of nephrotoxic chemotherapies, long-term use of NSAIDs, angiotensin converting enzyme inhibitors), no significant correlation with $^{99m}$Tc-MAG3 clearance was found in the entire study population or in the PRRT and non-PRRT subgroups ($P > 0.05$).

### Prediction of kidney function using laboratory tests

The ROC analysis helped determine the optimal cutoff value for predicting abnormal kidney function according to $^{99m}$Tc-MAG3 renal scintigraphy in the entire population of 152 patients; the optimal cutoff value was a creatinine level of 0.995 mg/dl or more, which resulted in a sensitivity of 74.3%, a specificity of 71.1%, and an accuracy of 71.8% [area under the curve (AUC) = 0.779]. The corresponding cutoff values were 31.8 mg/dl or more for BUN (sensitivity 68.6%, specificity 71.9%, AUC = 0.722) and 69.5 ml/min or less for the GFR (sensitivity 71.4%, specificity 73.7%, AUC = 0.719).

Expecting an increase in the predictive value by combining all of the renal blood parameters, a formula including creatinine, BUN, and GFR was derived to predict abnormal kidney function:

$$\begin{aligned}&\mathrm{GFR}\times 0.001316+\mathrm{creatinine}\times 1.988\\&\quad+\mathrm{BUN}\times -0.004195-2.112=X.\end{aligned}$$

Defining the cutoff as $X$ of at least −0.1669 resulted in a sensitivity of 74.3% and a specificity of 69.3% (AUC = 0.779) (Table 2). The respective ROC curves are shown in Fig. 2.

### Linear regression of venous blood parameters

Because of its predictive value, a linear regression of creatinine, BUN, and GFR was performed to illustrate the linear relationship of $^{99m}$Tc-MAG3 clearance and various renal parameters.

The following equations were derived using a linear regression for creatinine, BUN, and GFR:

$$\begin{aligned}&\mathrm{Creatinine(mg/dl)}\\&\quad=2.20+-0.005\times(\mathrm{MAG3\,clearance}),\end{aligned}$$

**Table 1** Main baseline features of the patients undergoing treatment with peptide receptor radionuclide therapy enrolled in the study

| Patient number | Age | Sex | Primary tumor | Metastases | Previous therapy | Number of cycles | Cumulative dose (GBq) | Drugs influencing kidney function[a] | Diabetes mellitus |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 70 | F | Small bowel NET | Liver, bone, pancreas | Surg., TACE | 7 | 55.7 | Spironolactone, ACE inhibitor | None |
| 2 | 66 | F | Small bowel NET | PC | Surg. | 3 | 23 | None | None |
| 3 | 53 | M | Meningioma | None | Surg., RTx | 4 | 23.1 | None | None |
| 4 | 79 | M | Pancreatic NET | Liver | Octreotide | 2 | 14.5 | None | None |
| 5 | 62 | M | Meningioma | None | None | 1 | 7.7 | None | None |
| 6 | 76 | M | Ileum NET | Liver | Octreotide, interferon-α 2B | 2 | 15.5 | ACE inhibitor | None |
| 7 | 61 | M | Pancreatic NET | Infiltration of vessels | Surg. | 1 | 7.7 | None | None |
| 8 | 82 | F | Gastric NET | Liver, LN | TACE | 2 | 15.6 | None | None |
| 9 | 69 | M | Small bowel NET | Lung, liver, LN | Octreotide | 3 | 22.8 | ACE inhibitor | |
| 10 | 50 | F | Pancreatic NET | Liver, LN | Octreotide, everolimus | 2 | 15 | None | |
| 11 | 49 | M | Small-cell lung cancer | LN, pericardial, mediastinal | Cisplatin/etoposide, topotecan | 1 | 7.5 | None | None |
| 12 | 73 | F | Pancreatic NET | Bone, liver | Surg. | 2 | 14.6 | None | None |
| 13 | 58 | F | Ileum NET | Liver, LN | Surg., octreotide, thermoablation | 8 | 62.5 | ASS | Type 2 diabetes |
| 14 | 57 | F | Small bowel NET | Lung, skull base | Surg., RTx, CTx | 1 | 7.1 | None | None |
| 15 | 31 | F | MTC | Lung, LN, trachea | Surg., CTx | 1 | 7 | NSAIDs | None |
| 16 | 24 | M | Ileum NET | Liver | Surg., TACE, octreotide | 2 | 15.05 | None | None |
| 17 | 66 | M | Thymus NET | Bone, lung, LN | None | 2 | 15.1 | ASS, NSAIDs | Type 2 diabetes |
| 18 | 60 | M | Ileum NET | Liver | Octreotide, Surg. | 4 | 24.1 | None | None |
| 19 | 60 | M | Meningioma | None | Surg. | 2 | 13 | None | None |
| 20 | 34 | M | Paraganglioma | Bone | Surg., RTx | 2 | 13.8 | None | Type 2 diabetes |
| 21 | 61 | M | Small bowel NET | PC, LN, liver | Surg., octreotide | 1 | 6.9 | None | None |
| 22 | 79 | M | Pancreatic NET | Liver | Octreotide | 2 | 14.4 | None | None |
| 23 | 76 | M | NET of unknown origin | Lung, bone, LN | Surg. | 2 | 15 | None | None |
| 24 | 55 | M | Pancreatic NET | Liver | 5-FU, streptozotocin | 3 | 22.6 | None | None |
| 25 | 63 | M | Pancreatic NET | Liver, bone | Surg. | 3 | 21.9 | ASS | None |
| 26 | 63 | M | NET of unknown origin | Bone | Carboplatin/etoposide | 3 | 23 | None | None |
| 27 | 82 | F | Gastric NET | Liver, LN | TACE | 3 | 23.5 | None | None |

ACE, angiotensin converting enzyme; ASS, acetylsalicylic acid; AT, angiotensin; CTx, chemotherapy; F, female; 5-FU, 5-fluorouracil; LN, lymph node; M, male; MTC, medullary thyroid cancer; NET, neuroendocrine tumors; PC, peritoneal carcinomatosis; RTx, radiotherapy; Surg., surgery; TACE, transarterial chemoembolization.
[a]Drugs influencing kidney function: ACE inhibitor, spironolactone, ASS, NSAIDs, AT blocker.

**Table 2** Optimal cutoff value of renal blood for predicting abnormal kidney function according to $^{99m}$Tc-mercaptoacetyltriglycine renal scintigraphy

| | Cutoff value | Sensitivity (%) | Specificity (%) | FPR (%) | FNR (%) | ACC (%) | AUC |
|---|---|---|---|---|---|---|---|
| Creatinine (mg/dl) | ≥0.995 | 74.3 | 71.1 | 28.9 | 25.7 | 71.8 | 0.779 |
| BUN (mg/dl) | ≥31.8 | 68.6 | 71.9 | 28.1 | 31.4 | 71.1 | 0.722 |
| GFR (ml/min) | ≤69.5 | 71.4 | 74.4 | 25.6 | 28.6 | 73.6 | 0.719 |
| Formula including creatinine, BUN, GFR[a] | ≥−0.1669 | 74.3 | 69.3 | 30.7 | 25.7 | 70.5 | 0.779 |

ACC, accuracy; AUC, area under the curve; BUN, blood urea nitrogen; FNR, false-negative rate; FPR, false-positive rate; GFR, glomerular filtration rate.
[a]Formula assessing all serum parameters: $\mathrm{GFR}\times 0.001316+\mathrm{creatinine}\times 1.988+\mathrm{BUN}\times -0.004195-2.112=X$.

$$\mathrm{BUN(mg/dl)} = 64.31+-0.142\times(\mathrm{MAG3\,clearance}),$$

$$\mathrm{GFR(ml/min)} = 21.43+0.25\times(\mathrm{MAG3\,clearance}),$$

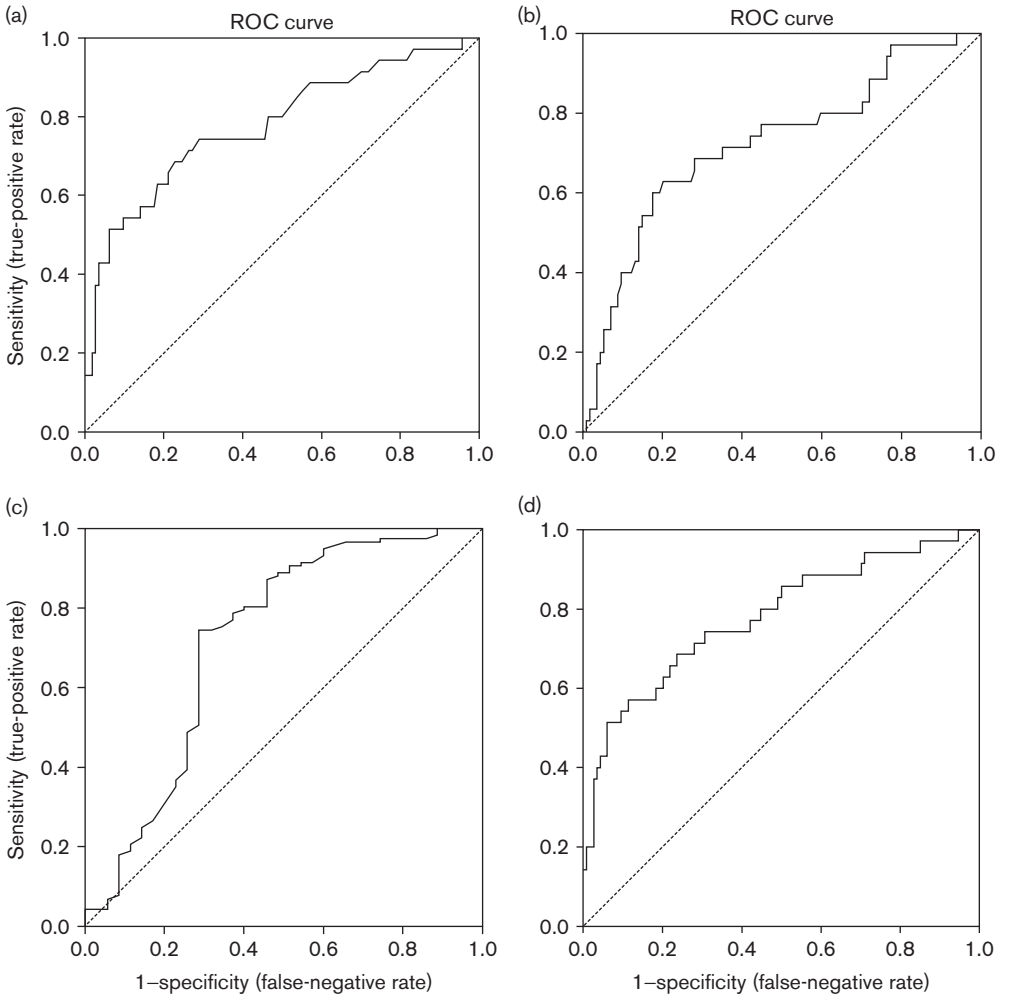
where MAG3 clearance is in ml/min/1.73 $m^2$ in each of these three equations.

The respective linear regression graphs are shown in Fig. 3.

## Discussion

The results of the present study demonstrate a significant correlation of laboratory test-derived kidney function parameters (creatinine, BUN, GFR) and $^{99m}$Tc-MAG3 renal scintigraphy for all of the investigated patients and for the PRRT subgroup and non-PRRT subgroup. An abnormal $^{99m}$Tc-MAG3 clearance could be best predicted by creatinine using a cutoff of 0.995 mg/dl or higher. However, the corresponding accuracy is moderate, resulting in a false-negative rate of 25.7% and a false-

**Fig. 2**




Prediction of kidney function in the entire patient cohort ($n = 152$) using venous blood parameters (ROC curves, $^{99m}$Tc-MAG3 clearance considered as the standard reference). (a) Creatinine, AUC = 0.779. (b) BUN, AUC = 0.722. (c) GFR, AUC = 0.719. (d) Formula assessing all of the serum parameters: $\mathrm{GFR}\times 0.001316+\mathrm{creatinine}\times 1.988+\mathrm{BUN}\times -0.004195-2.112 = X$, AUC = 0.779. Diagonal segments are produced by ties. AUC, area under the curve; BUN, blood urea nitrogen; GFR, glomerular filtration rate; MAG3, mercaptoacetyltriglycine; ROC, receiver operating characteristic.

positive rate of 28.9%. The combination of multiple blood parameters (creatinine, BUN, and GFR) does not improve the predictive value of $^{99m}$Tc-MAG3 clearance.

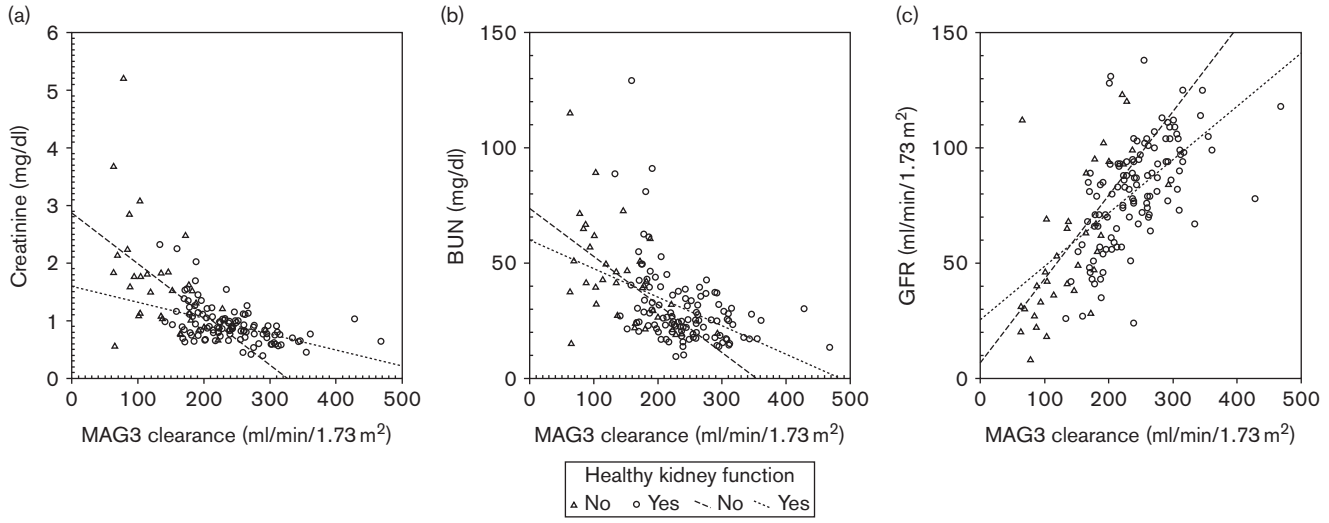
To the best of our knowledge, this is the first study to compare several blood parameters and $^{99m}$Tc-MAG3 renal scintigraphy for the pretherapeutic assessment of kidney function.

However, Sabet *et al.* [14] also reported an underestimation of the maximum observed renal toxicity grade in 12% of patients if the creatinine serum level alone, without the $^{99m}$Tc-DTPA clearance assessment, was used to evaluate long-term nephrotoxicity. In a cohort of 113 patients, Esteves *et al.* [22] demonstrated that $^{99m}$Tc-MAG3 renal scintigraphy correlates with 24-h urine collection. However, the authors did not report on the correlation between renal scintigraphy and laboratory tests.

The kidney represents one of the most important dose-limiting organs for PRRT. According to recent practice guidelines, a pretherapeutic estimation of kidney function using laboratory tests (creatinine and BUN) or renal scintigraphy methods should be performed; however, these guidelines do not state which examination is preferable [1].

In daily routine practice, many institutions rely on $^{99m}$Tc-MAG3 renal scintigraphy for the assessment of kidney function. $^{99m}$Tc-MAG3 is eliminated by tubular secretion, and therefore estimates the excretion of renal tubular cells [23]. In contrast, the creatinine from venous blood samples used for the calculation of GFR is excreted by glomerular filtration and additional tubular

**Fig. 3**




Linear regression of venous blood parameters ($n = 152$ patients). (a) Linear regression of creatinine (venous blood sample) and $^{99m}$Tc-MAG3 clearance ($r = -0.596$). (b) Linear regression of BUN and $^{99m}$Tc-MAG3 clearance ($r = -0.531$). (c) Linear regression of GFR and $^{99m}$Tc-MAG3 clearance ($r = 0.665$). BUN, blood urea nitrogen; GFR, glomerular filtration rate; MAG3, mercaptoacetyltriglycine.

secretion. Nevertheless, the methods are considered equivalent for estimating the overall kidney function. The advantages of renal scintigraphy comprise the separate evaluation of both kidneys as well as the evaluation of potential urinary flow obstruction in a single examination. Renal scintigraphy-derived clearance could also be affected by drugs (e.g. sulfonamides used for urinary tract infections) [24]; however, this method has also been shown to be reliable and highly reproducible [18,25]. However, the downsides of renal scintigraphy comprise higher patient discomfort, higher costs, longer duration, and radiation exposure (0.007 mSv/MBq in adults) compared with blood tests [26]. However, radiation exposure appears to be negligible in the PRRT subgroup.

Creatinine is the most frequently used parameter for the assessment of kidney function in daily routine. GFR estimations with venous blood samples are possible by means of the 'Modification of Diet in Renal Disease' (MDRD) prediction equation [27], which appears to be more accurate than the former 'Cockcroft–Gault' formula [28]. Nevertheless, creatinine ingestion (e.g. from meat) could affect the creatinine level, which accounts for 30% of the total creatinine excretion [29]. In addition, the decline of GFR is dependent on patient age, and estimation equations might fail in patients with comorbidities (e.g. hepatic insufficiency) [22,30]. Furthermore, the creatinine-clearance and creatinine-based estimations of GFR do not change unless the actual GFR declines by at least 50% [31]. Especially for cases of glomerulopathy, creatinine is not suitable as a single marker for evaluating and monitoring the GFR [32].

### Recommendations for daily routine

For renal scintigraphy, $^{99m}$Tc-MAG3 and $^{99m}$Tc-DTPA are commonly used for the assessment of kidney function. As discussed by Sabet *et al.* [14], $^{99m}$Tc-MAG3 renal scintigraphy, which measures the tubular extraction rate, might be preferred because the proximal tubules are the primary targets of irradiation during PRRT. Because $^{99m}$Tc-MAG3 clearance could be predicted only with moderate accuracy using blood test parameters (creatinine, AUC = 0.779; BUN, AUC = 0.722; GFR, AUC = 0.719; combination of creatinine, BUN, and GFR, AUC = 0.779), scintigraphy remains the most reliable method for kidney function assessment, especially in patients scheduled to undergo PRRT. In addition, renal scintigraphy allows for the distinctive evaluation of each individual kidney and could rule out potential urinary flow obstructions.

$^{99m}$Tc-MAG3 renal scintigraphy constitutes the gold standard and should remain the method of choice in patients undergoing PRRT and in patients with suspicion of renal failure. For rough estimation, laboratory tests with biochemical standard values including renal parameters might be sufficient to detect a loss of kidney function. However, factors influencing the calculation of GFR (e.g. glomerulopathy) should be excluded and no clinical suspicion for the loss of kidney function should be present (e.g. metastasis next to kidney potentially infiltrating them).

Limitations of this study include the retrospective design, the limited patient number, and the heterogeneity of the included patients (different primary tumors and different accumulated doses). However, this

is the first study to report on the comparability of laboratory tests and renal scintigraphy for the assessment of kidney function, especially in patients before PRRT.

Despite a highly significant correlation between $^{99m}$Tc-MAG3 clearance and blood sample-derived parameters, the predictive value of any of the investigated blood parameters (single and combined) is only moderately accurate. Therefore, we conclude that $^{99m}$Tc-MAG3-based clearance should be the method of choice in patients undergoing their first PRRT cycle and in patients with a strong clinical suspicion for impaired kidney function.

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### Conflicts of interest

There are no conflicts of interest.

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