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Original

The Value of Somatostatin Receptor Scintigraphy (SRS) in Patients with NETG1/G2 Pancreatic Neuroendocrine Neoplasms (p-NENs)

Agnieszka D. Kolasińska-Ćwikła[1], Sonia J. Konsek[2], John R. Buscombe[3], Katarzyna Maciejkiewicz[1], Andrzej Cichocki[1], Katarzyna Roszkowska-Purska[1], Łukasz Sawicki[1], Michał Tenderenda[1], Jarosław B. Ćwikła[2]

[1]MSC Memorial Cancer Centre and Institute Maria Sklodowska-Curie, Warsaw, Poland
[2]School of Medicine, University of Warmia and Mazury, Olsztyn, Poland
[3]Addenbrookes Hospital; Cambridge, UK

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Abstract

BACKGROUND: Neuroendocrine neoplasms of the pancreas (p-NEN) are common gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). The aim of this retrospective study was to review the value of Somatostatin Receptor Scintigraphy (SRS) in initial detection of p-NEN, evaluation of tumour extent and as imaging follow-up after radical surgery in patients with confirmed well (NETG1) or moderately (NETG2) differentiated p-NEN based on pathological WHO 2017 classification.

MATERIAL AND METHODS: Overall 281 patients with confirmed p-NEN were enrolled. The SRS was performed to evaluate primary p-NEN, to assess clinical stage of disease, based on current World Health Organization (WHO) classification and during clinical follow-up. A total of 829 examinations were performed over time in these 281 patients using ^{99m}Tc HYNICTOC. Images were acquired between 1–3 h after i.v. injection of radiotracer. Initially whole body WB-SPECT and then WB-SPECT/CT with standard iterative reconstruction were used.

RESULTS: There were 159 patients with NETG1 (57%) and 122 subjects with NETG2 (43%). The female to male ratio was 1.1:1. In 68 patients (22%) with NETG1/G2 eighty-seven SRSs (10%) were performed to confirm initial diagnosis. SRS results were as follow: true positive (TP) = 84 (97%), false negative (FN) = 3 (3%), no true negative (TN) or false positive (FP) results of SRS examination (sensitivity of SRS per patient was 96%). In 198 subjects (66%) SRS was used in evaluation and re-evaluation of the clinical stage. A total of 661 (80%) examinations were carried out in these patients. There were TP = 514 (77%), TN = 136 (21%), FN = 7 (1%) and FP = 4 (1%) results. The sensitivity and specificity per patient were: 96% and 95%. The sensitivity and specificity per study were: 98% and 97%. In 35 patients (12%) SRS was used as imaging follow-up after radical surgery; there were overall 81 examinations (10%) performed. There were 76 (91%) TN results of SRS examinations and in 4 patients we identified recurrence (TP). In total, which consists of initial diagnosis/staging and patient follow-up, the sensitivity of SRS was 96% and specificity 97% per patient and per study sensitivity and specificity was 98%.

CONCLUSIONS: SRS using ^{99m}Tc HYNICTOC acquired in WB-SPECT or WB-SPECT/CT techniques is an excellent imaging modality in detection of primary NETG1/G2 p-NEN. Our study confirms that SRS has high sensitivity and specificity, as a result has tremendous value as an examination method to assess clinical stage of disease and as an imaging follow-up after radical treatment.

KEY words: neuroendocrine neoplasms of the pancreas, p-NENs, gastro-entero-pancreatic neuroendocrine neoplasms, GEP-NENs, Somatostatin Receptor Scintigraphy, SRS

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Correspondence to: Agnieszka D. Kolasińska-Ćwikła, Klinika Onkologii, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie; ul. Wawelska 15, Warszawa, tel.: 601359657, e-mail: adkolasinska@yahoo.com

Introduction

Neuroendocrine neoplasms (NENs) are a relatively rare, heterogeneous group of various neoplasms which develop from highly specialized neuroendocrine cells located in the entire body. Gastro-entero-pancreatic neuroendocrine neoplasms/tumours (GEP-NENs/NETs) comprise about 70% of all NENs, and about 2% of all neoplasms of the digestive system [1–3].

Neuroendocrine neoplasms of the pancreas (p-NEN) are common gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs), which are clinically and functionally heterogeneous [4, 5]. Those tumours derive from the diffuse endocrine system (DES) cells which exist in the gastro-intestinal tract and in the pancreas [3]. According to the latest analysis of the Surveillance, Epidemiology, and End Results (SEER) database an annual incidence of p-NEN is 0.48 per 100,000 population and appears to be increasing in the new millennium, probably as a consequence of using high quality imaging techniques which lead to better and earlier detection of p-NEN [6, 7].

Pancreatic NENs can be functional and non-functional tumours. This classification of p-NENs is based on the presence or absence of clinical symptoms caused by hormonal over-secretion. It has been reported that 60–90% of p-NENs are non-functional (depending on which database is used) and as a result of their clinical silence they are usually diagnosed at more advanced clinical stages (CS) than those which present with a hormonal syndrome. In the case of metastatic disease at the time of initial diagnosis the possibility of a curative resection is limited, but still be considered even advanced disease [4, 5, 8].

The majority of p-NENs occur sporadically, as non-inherited tumours. However, a significant minority are associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1), von Hippel Lindau disease (VHL), von Recklinghausen's syndrome (neurofibromatosis 1), and tuberous sclerosis. Of those tumours which produce detectable hormones multiple insulinomas are less than 5%, gastrinomas from 20% up to 30% are associated with MEN1. In comparison to gastrinomas, glucagonomas and somatostatinomas, well-differentiated insulinomas show benign clinical behaviour and have a notably good prognosis in most of cases. More malignant insulinoma is seen in approximately 10% of cases [4, 5, 9, 10].

The majority of NENs have specific tissue characteristics which include expression of somatostatin receptors (SSTR). Numerous pNENs, including non-functional tumours except insulinomas, have high-level expression of SSTR among which SSTR subtype 2 is mainly expressed by β-cells with a slightly lower expression of SSTR5 mostly by β-cells [4, 7].

This means that p-NENs can be targeted by molecular imaging using somatostatin receptor imagining (SRI) and, as a result, SRS using ^{99m}Tc HYNICTOC has positive uptake for visualizing p-NENs [4, 5, 11–13].

When looking at the prognosis of any p-NEN, the histopathological grade (G) is vital. This grading divides NENs into three groups: tumours of low (G1), moderate (G2), and high (G3) malignancy. The criteria for the assessment of the "G" grading were firstly specified by European Neuroendocrine Tumour Society (ENETS) in 2006 [14] and then were supported by the World Health Organization (WHO). Currently the new pathological classification of NETG1 and NETG2 is used based on UICC/AJCC, which is a new version of previous one based on ENETS/WHO classification from 2010 [15]. The new classification of NENs, including p-NENs is presented in Table 1. Histological malignancy grading was based on two criteria, the first was number of mitotic figures and the second was Ki-67 proliferation index determined by immunohistochemical analysis of expression of MIB1 antibody provided in percentages. If there were differences using both criteria, Ki-67 was used as a preferential one [16]. According to the above classification, two main categories of GEP-NENs were distinguished. The first group includes well-differentiated neoplasms NETG1 and NETG2 with Ki-67 below 20%; the second group consists of poorly-differentiated NET G3 or neuroendocrine carcinomas (NEC) with Ki-67 above 20%.

Various imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), endoscopic ultrasonography (EUS), positron emission tomography (PET) and somatostatin receptor scintigraphy (SRS) are performed to localize primary pNENs, assess clinical stage (CS) of disease and also as imaging follow-up.

The following factors including: initial histological grade of p-NEN cells, secretion and presence of local and distant metastases are important in evaluation of clinical stage of disease and help multidisciplinary team (MDT) to plan further treatment of p-NEN [4].

Aim of the study

The aim of this retrospective study was to evaluate whether Somatostatin Receptor Scintigraphy (SRS) using whole body (WB) SPECT or WB-SPECT/CT techniques are effective tools in initial detection of p-NEN, evaluation of tumour extent and alters clinical management during clinical follow-up after radical surgery in

Table 1. Proposed NEN classification according to AJCC/UICC and WHO 2017

NEUROENDOCRINE NEOPLASMS, NEN			
Ki-67 < 20%		Ki-67 > 20%	
NET G1	NET G2	NET G3	NEC
	Well-differentiated tumours		Neuroendocrine cancers
Ki-67 < 3%	Ki-67 from 3% to 20%	Ki-67 > 20%, usually between 21% a 55%	Ki-67 > 21%, usually > 55% — large-cell cancers — small-cell cancers

patients with well (NETG1) or moderate (NETG2) differentiated p-NEN confirmed by pathology.

Material and methods

The protocol for this retrospective study was accepted by the institutional ethics committee. A total of 281 patients with confirmed neuroendocrine neoplasms of the pancreas were included. There were 148 females and 133 males (ratio 1.11:1). In all cases a pathologist specialized in NEN reported and verified the histology results, in each case. The histopathology reports comprised histological grade and the stage of the neuroendocrine neoplasm (TNM) according to AJCC/UICC 2017 classification. Patients and tumour characteristics are presented in Table 2.

In all subjects, diagnosis, treatment and further diagnostic/imaging approaches were discussed within a multidisciplinary team (MDT).

Somatostatin receptor scintigraphy (SRS) was performed to evaluate primary p-NEN, to assess clinical stage of disease, based on current AJCC/UICC classification, and during clinical follow-up. Overall 829 SRS examinations were performed.

In each case 550-740MBq of ^{99m}Tc HYNICTOC (Tektrotyd®; National Centre for Nuclear Research — Polatom, PL) was used. The detailed method of kit labelling with ^{99m}Tc has been described previously [17, 18]. Briefly, the peptide conjugates [HYNIC, Tyr^3] octreotide was synthesized by standard F-moc solid-phase synthesis [19] and used for kits manufacturing under aseptic conditions. The labelling yield exceeded 90% in all cases with the free pertechnetate content in the range of 3.63 ± 1.67% (TLC).

SRS images were acquired between 1 and 3 h after i.v. injection of radiotracer. Initially SRS was performed using a whole-body (WB) SPECT (Single Photon Emission Computed Tomography) method using Symbia-E gamma camera (Siemens Healthcare, IL; USA). Reconstruction algorithms were based on the ordered subset expectation maximization (OSEM), iterative reconstruction software (3D flash) on e-soft workstation. In each case using 30 iteration and 16 subsets, with standard Gaussian filter 9.0, recommended by manufacturer. In each case 128 x 128 matrix with approximately 64 projections (20 seconds per projection) over an 360° rotation were utilized, there was no attenuation correction (non AC).

Then SRS was performed using Discovery 670 Pro SPECT/CT system (GE Healthcare, WI, USA), based on WB-SPECT/CT method of examination. SPECT data was acquired using 128 x 128 matrix with approximately 60 projections (25 seconds per projection) over an 360° rotation. Computed tomography (CT) was performed without i.v. contrast enhancement. Reconstruction algorithms were based on iterative reconstruction algorithm: Evolution — OSEM

Table 2. Patients and tumour characteristics in well (G1) and moderate (G2) differentiated pNENs

	ALL, n = 281	NETG1, n = 159	NETG2, n = 122
Female to male ratio	1.11	1.01	1.26
Mean age (range) in initial diagnosis	54.86 (17-87)	55.23 (17-86)	54.29 (20-87)
Size of the tumour (pathology) mean (SD), mm	33.88 (± 26.22)	27.34 ± 23.62	43.21 ± 28.84
Ki-67 (mean, standard deviation)	4.17 ± 4.60	1.39 ± 1.28	7.89 ± 5.33
pT (initial), n = 281	n = 281	n = 159	n = 122
pT1 (%)	73 (26)	65 (41)	8 (7)
pT2 (%)	71 (25)	48 (30)	23 (19)
pT3 (%)	61 (22)	16 (10)	45 (37)
pT4 (%)	40 (14)	9 (6)	31 (25)
pTx or no data (%)	36 (13)	21 (13)	15 (12)
N base on surgery, n = 281	n = 281	n = 159	n = 122
N0 (%)	126 (45)	95 (60)	31 (25)
N1 (%)	122 (43)	37 (23)	85 (70)
Nx or no data (%)	33 (12)	27 (17)	6 (5)
M base on surgery/follow-up/imaging, n = 281	n = 281	n = 159	n = 122
M0 (%)	139 (49)	97 (61)	42 (34)
M1 (%)	102 (36)	32 (20)	70 (57)
Mx or no data (%)	40 (14)	30 (19)	10 (8)
CS (initial), n = 281	n = 281	n = 159	n = 122
I — IIIa — local (%)	145 (52)	115 (72)	30 (25)
IIIb — regional (%)	33 (12)	13 (8)	20 (16)
IV — distal (%)	103 (37)	31 (19)	72 (59)
Metastases			
Liver (%)	97 (35)	26 (16)	71 (58)
Bones (%)	13 (5)	4 (3)	9 (7)
Lungs (%)	5 (2)	2 (1)	3 (2)

(with resolution recovery) including 4 iterations and 10 subsets with standard Gaussian filter using in each case a Xeleris workstation.

Each SRS was defined as pathological if any focal or diffuse non-physiological accumulation was recognized during examination. Diffuse low-activity intestinal uptake on SRS was defined as non-specific, physiologic bowel uptake. Lesions were assessed due to their intensity of accumulation using the Krenning scale, similar to the standard SRS using Octreoscan™ evaluation. In each case, the Krenning extension of disease was used to classify the extension of the tumour, both methods have been described previously [18–20].

SRS was read by two specialists in nuclear medicine and was interpreted as true positive (TP) when the patient had histologically confirmed p-NEN and there were at least Krenning 2 focal pathologically high uptake of radiotracer. True negative (TN) result was associated with no focal uptake of radiotracer on SRS and no evidence of the presence of disease during at least 12-month follow-up, clinically and on other imaging techniques, including endoscopic ultrasound (EUS), CT and magnetic resonance imaging (MRI) before and after i.v. contrast administration. A false positive (FP) was reported when there was focal high uptake on SRS (at least Krenning 2), but there was no evidence of p-NEN on other imaging techniques, clinically and during clinical and imaging follow-up. A false negative (FN) study was defined when there was confirmable tumour (p-NEN) which was not seen in SRS.

Histological and clinical information including assessment of tumour type based on ACJJ/UICC 2017 classification, including Ki-67 and the initial clinical stage (CS) of disease were available for analysis.

Statistical analysis

The standard statistics using sensitivity, specificity PPV and NPV were used based on pathology reports as gold standard. If no specimen of tumour was available, clinical, biochemical and structural imaging were used to assess final results of examination. In case of negative SRS study and presence of any suspected lesions, patients were evaluated based on clinical follow-up. Differences between groups were assessed using non-parametric Mann-Whitney U test. In each case $P < 0.05$ was defined as significant.

Results

There were 159 subjects with NETG1 (57%) and 122 subjects with NETG2 (43%). In patients with NETG1 the mean age was 55.23 years (range 17–86) and in subjects with NETG2 the mean age was 54.29 (range 20–87). The mean size of the tumour (based on histopathology) were as follows: in NETG1 — 27.34 mm (SD ± 23.62), in NETG2 — 43.21 mm (SD ± 28.84). The mean Ki-67 proliferation index was 1.39 % (SD ± 1.28) in patients with NETG1 and 7.89 % (SD ± 5.33) in those with NETG2. In 54 cases there were no data regarding Ki-67 index and in 103 subjects no information about size of the tumours was available in histopathology reports; in those patients tumour size evaluation was based on structural imaging CT/MRI or EUS.

The image quality of SRS using ^{99m}Tc HYNICTOC was determined by both readers (JRB & JBC) to be excellent or very good; in the cases with small tumours the visualization was difficult but still clear enough to make a diagnosis of p-NET.

The analysis shows that tumours of pT1 and pT2 were usually identified in subjects with NETG1. We detected pT1 tumours in 65 cases with NETG1 (41%) and only 8 with NETG2 (7%) ($P < 0.05$), pT2 in 48 subjects with NETG1 (30%) and in 23 with NETG2 (19%) ($P > 0.05$). In comparison, pT3 and pT4 tumours most frequently occurred in patients with NETG2. We noted pT3 tumours in 45 cases with NETG2 (37%) and in 16 with NETG1 (10%), pT4 in 31 subjects with NETG2 (25%) and in 9 with NETG1 (6%) (Table 2).

The analysis of regional lymph nodes metastasis in patients after surgical treatment revealed no lymph nodes involvement in 126 cases, including 95 with NETG1 (60%) and 31 with NETG2 (25%). There were 122 subjects with metastasis in a single regional lymph (N1), in 37 patients with NETG1 (23%) and in 85 with NETG2 (70%). There were 33 (12%) patients in whom regional lymph nodes could not be assessed (Table 2).

Distant metastasis (M) were noted in 102 patients, in 32 with NETG1 (20%) and in 70 with NETG2 (57%). There were 139 cases with no evidence for metastases. In 40 subjects metastases could not be assessed. There were 97 (35%) patients with metastasis to the liver, including 71 with NETG2 (58%) and 26 with NETG1 (16%). Thirteen subjects (5%) had bone metastases and in 5 (2%) patients we detected lung metastasis (Table 2).

The assessment of clinical stage (CS) revealed that there were 145 patients (52%) with I-IIIa CS, 115 with NETG1 (72%) and 30 with NETG2 (25%). In 33 cases (12%) we noted IIIb CS, in 13 with NETG1 (8%) and in 20 with NETG2 (16%). There were 103 subjects (37%) with IV CS, which included 72 (59%) patients with NETG2 and rest with NETG1 (19%) (Table 2).

In 68 patients (22%) SRS was used to confirm the initial diagnosis and 87 (10%) SRS were carried out. In this group of patients, the results were as follows: true positive (TP) = 84 (97%), false negative (FN) = 3 (3%), no true negative (TN) or false positive (FP) results of SRS examination (sensitivity of SRS per patient was 96%). In 198 subjects (66%) SRS was used in evaluation of the clinical stage and overall 661 (80%) examination were performed. The following results were obtained: TP = 514 (77%), TN = 136 (21%), FN = 7 (1%) and FP = 4 (1%).

The sensitivity and specificity per patient were: 96% and 95%. The sensitivity and specificity per study were 98% and 97%. In 35 patients (12%) SRS was used as imaging follow-up after radical surgery; a total of 81 examinations (10%) were carried out. There were 76 (91%) TN results of SRS and in 4 patients we identified recurrence (TP). In total, which consists of initial diagnosis/staging and follow-up, the sensitivity was 96% and specificity 97% per patient and per study sensitivity and specificity was 98%. Summarized SRS results in all groups of patients are presented in Table 3.

Discussion

As a consequence of recent advances in imaging technology and having better knowledge of p-NENs, the diagnosis and treatment approaches of asymptomatic and symptomatic pNENs have improved. Various structural imaging such as CT, MRI and endoscopic ultrasound (EUS), as well as functional techniques such as somatostatin receptor imaging are currently utilized to localize

Table 3. Results of Somatostatin Receptor Scintigraphy examinations in diagnosis group, staging group and follow-up group

Results of SRS	SRS studies	Diagnosis group, n = 68		Staging group, n = 198		Follow-up group, n = 35	
		NET G1	NET G2	NET G1	NET G2	NET G1	NET G2
TP	602 (73%)	69 (80%)	15 (17%)	216 (33%)	298 (45%)	0	4 (5%)
TN	212 (26%)	0	0	102 (15%)	34 (5%)	51 (63%)	25 (31%)
FN	11 (1%)	2 (2%)	1 (1%)	6 (1%)	1 (< 1%)	0	1 (1%)
FP	4 (< 1%)	0	0	3 (< 1%)	1 (< 1%)	0	0
All	829 (100%)	71 (82%)	16 (18%)	327 (49%)	334 (51%)	51 (63%)	30 (37%)
		87 (10%)		661 (80%)		81 (10%)	

	Diagnosis (n)	Staging (n)	Follow-up (n)	All (%)
NETG1	54	92	13	159 (56.6)
NETG2	15	102	5	122 (43.4)
NETG3	0	0	0	0
SUMA	69	194	18	281

the primary tumour, assess clinical stage (CS) of disease and also as follow-up imaging after radical surgery [2–5].

CT and MRI have a relatively low sensitivity in detecting of low volume disease or multifocality of disease, both of which are common in patients with MEN1 syndrome associated with pNENs. Whilst EUS, which is currently the best method for detection of any focal pancreatic lesions, has a better resolution and sensitivity, it has a limited field of view. It provides very good visualization of the head and body of the pancreas, but the distal part of the pancreatic tail could be problematic in detection of small tumours. Local clinical staging only can be achieved using EUS; therefore, it should be combined with other tests.

In the last 2 decades it has been found that functional imaging of p-NEN plays a key role in evaluation of patients with suspected or confirmed NEN. Numerous studies have demonstrated that the current significance of somatostatin receptor imaging, including SRS, especially using SPECT/CT or PET/CT [4, 17–24]. In our data sets we indicated high accuracy of both the WB-SPECT or WB-SPECT/CT techniques in detection of active disease in patients with p-NEN. To our knowledge, it is the largest series of patients with confirmed NETG1 and NETG2 p-NENs, based on new classification ACJJ/UICC. It has been our standard clinical practice to perform SRS (WB-SPECT/CT) using ^{99m}Tc HYNICTOC as the main imaging technique used for detection of primary p-NENs, staging of disease and in subjects who had previously undergone radical surgery. This approach has been explored by our team for at least previous 14 years [25–27].

Various studies indicated that PET/CT with ^{68}Ga labelled somatostatin analogues is immensely sensitive and has a high specificity for localizing p-NENs [4, 28–29]. Generally, when performing PET/CT using ^{68}Ga SST analogues in greater number of studies for p-NENs, the sensitivity varies from 86% up to 100% and the specificity from 79% up to 100% and is superior to MRI with DWI [30]. But this technique has a limitation which is the detection of insulinomas — the sensitivity decreases to 25% [31]. In addition, access to PET/CT and the ^{68}Ga analogues may be limited.

Most comparative studies used planar ^{111}In pentetreotide and compare to tomographic ^{68}Ga PET/CT, which is methodologically incorrect, because these studies do not compare like with like. Only a few reports compare SRS using ^{99}Tc HYNICTOC vs. ^{68}Ga DOTA-TOC/TATE/NOC. In all these studies SPECT was compared to PET, but SPECT was not performed using current state-of-the-art imaging techniques such as iterative reconstruction and WB-SPECT/CT attenuation correction reconstruction technique, except single recent study which indicated clinical decision change in the one third of cases [32]. However, the authors did not use optimized reconstruction methods with the SPECT/CT.

Compared to previously published studies using ^{68}Ga DOTA-TOC/TATE PET/CT the results of our study, showing a sensitivity and specificity which was always equal or greater than 95% in all group of patients with confirmed p-NETs, shows that, if optimized, the SPECT/CT-based agents compare well with PET. This is particularly true in our study because we have the results of a large number of studies performed in in a large cohort of pNET patients. This clearly indicated the high level of accuracy of SRS using ^{99m}Tc HYNICTOC in this patient group. However, the high prevalence of disease means we can be more certain of the sensitivity than the specificity.

The approach described in our study using ^{99m}Tc HYNICTOC is also cheaper than using PET/CT and can be performed on any working day in most Nuclear Medicine departments. Thus, this technology seems to have a practical advantage compared to quite complicated and expensive PET/CT using ^{68}Ga SST analogues The authors acknowledge that although ^{68}Ga DOTA-TOC/TATE PET/CT is currently is the best functional methods in detection p-NEN, its utility is restricted not just by cost but the need to access a PET/CT scanner and the current shortage of the required gallium/germanium generators.

The results of our study show that SRS with ^{99m}Tc HYNICTOC using the best in SPECT/CT is a highly sensitive and specific imaging technique. According to our results, the high sensitivity of the test per patient was noted in the group of subjects in whom SRS

was performed to assess initial diagnosis. As a consequence, ^{99m}Tc HYNICTOC SRS helped correctly identify those patients without the disease. Therefore, this method can be used to assess the localization and extension of tumour when functional p-NENs are suspected but tumours cannot be detected on cross-sectional images such as CT or MRI. Our data also confirm that ^{99m}Tc HYNICTOC SRS is an appropriate tool in evaluation of clinical stage of disease and in follow-up of pNENs.

A further advantage in using ^{99m}Tc HYNICTOC is the lower radiation exposure compared to standard 111In-pentetreotide (Octreoscam®). The agent is cleared rapidly from the blood; most of the activity is eliminated entirely through the kidneys (64% of the injected dose within 12 h). The effective dose is 0.005 mSv/MBq, which for a patient receiving the recommended maximum administered activity of 740 MBq is only 3.8 mSv [33].

This compares favourably to ^{111}In-pentetreotide which is also cleared rapidly from the blood, with excretion almost entirely through the kidneys giving an effective dose is 0.054 mSv/MBq. For a patient recommended maximum administered activity of 222 MBq is 12 mSv, which is over 3 times higher than with ^{99m}Tc HYNICTOC [34]. The radiation dose in 70 kg patient from ^{68}Ga-DOTATOC/TATE is approximately 2.9–3.2 mSv, which is similar to radiation dose of ^{99m}Tc HYNICTOC [35, 36]. A modern CT used as part of the PET/CT or SPECT/CT will contribute an additional 2mSv to the total effective dose. [34].

Conclusions

The results from this study show the SRS using ^{99m}Tc HYNICTOC acquired in WB-SPECT or WB-SPECT/CT techniques delivers high-accuracy results in the detection of primary well (NETG1) and moderate (NETG2) differentiated p-NEN. It is more widely available than ^{68}Ga-DOTATOC/TATE PET but yields similar results at a lower cost. Furthermore, it is excellent method for the assessment of clinical stage of pNEN and in imaging follow-up in patients after radical surgery.

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