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Research paper

Value of somatostatin receptor scintigraphy in patients with appendiceal neuroendocrine neoplasms based on clinical follow-ups

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Abstract

Introduction: Appendiceal neuroendocrine neoplasms (ANEN) constitute a significant proportion of the tumours identified within the appendix.

Aim: This retrospective study assesses the value of somatostatin receptor scintigraphy (SRS) in evaluating tumour extent, as well as in follow-up imaging, for those patients with confirmed well (G1) or moderately (G2) differentiated ANEN before or after surgery, and using intention to treat (ITT) analysis.

Material and methods: Whole body (WB) and SPECT/CT SRS using 99mTc HYNICTOC was performed on 77 patients with confirmed ANEN to assess tumour extent before or after surgery also as follow-up imaging.

Results and discussion: Of 77 patients, 71 (92%) were found to have NENG1 and 6 (8%) were found to have NENG2 ANEN. Post-surgical imaging restaging was performed on 30 patients. SRS detected active disease in 3 subjects (true positive, TP), and true negative (TN) results were found in 27 cases. Follow-up SRS imaging was performed after surgery with ITT on 47 patients, detecting TP result in single patient and TN in 46 patients, with no false positive or negative results. Sensitivity was shown to be 100%.

Conclusions: SRS is a precise screening method for identifying the presence of active disease after non radical or extended surgery. However, as the primary treatment of the disease is highly effective, SRS is not a cost-effective choice for post-surgical follow-up screening.

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1. INTRODUCTION

Neuroendocrine neoplasms (NEN) are tumours which typically arise from the gastro-enteropancreatic and bronchopulmonary tract.[1] Appendiceal NEN (ANEN) comprise approximately 15%–40% of all NEN (depending on the registry), with an annual incidence of 0.15–0.60 cases per 100 000. It has been reported that there is a slightly higher female prevalence of NEN in Europe and North America.[2] The incidence of ANEN appear to have increased over the last 2 decades,[3] the majority of which are diagnosed incidentally during appendectomy and at postoperative histopathological evaluation. ANEN are usually small, rarely symptomatic, and are often benign.[2,3]

NEN constitute the majority of appendiceal tumours, comprising 88% of all lesions within the appendix. ANEN are able to invade neighbouring organs and metastasize to regional lymph nodes and distant sites,[3–5] where they are likely to cause symptoms relating to the localisation of the metastases, such as abdominal pain, a tumour mass effect or signs of bowel obstruction.[2] The latest analysis of the SEER database revealed that 49% of reported ANEN were associated with lymph node invasion, and 9% with distant metastases. Tumour size is strongly related to the risk of metastasis, particularly in tumours larger than 2 cm.[4,5] ANEN are primarily treated surgically, by simple appendectomy or right-hemicolectomy (RH) with lymphadenectomy, according to oncologic principles and recent European Neuroendocrine Tumor Society (ENETS) guidelines.[5]

As ANEN are normally only discovered after surgical removal of the primary tumour, imaging tends to be performed post appendectomy.[3,5,6] Conventional radiological methods such as CT and MRI, and occasionally ultrasound (US), can be used in postoperative staging and follow-up to rule out metastasis. ANEN, like most NEN, have specific tissue characteristics which include expression of receptors, especially somatostatin receptor subtype 2 (SSTR2), and to a lower degree, somatostatin receptor subtype 5 (SSTR5). ANEN can therefore be targeted by molecular imaging using somatostatin receptor imaging (SRI) including somatostatin receptor scintigraphy (SRS).[2,3,5–7]

2. AIM

The aim of this retrospective study was to review the value of somatostatin receptor scintigraphy (SRS) in evaluation of the tumour extent and follow-up functional imaging in those patients with confirmed well (G1) or moderately (G2) differentiated ANEN before and after radical surgery using intention to treat (ITT) analysis.

3. MATERIAL AND METHODS

A total of 90 patients with confirmed ANEN were enrolled, including 52 females and 38 males (ratio 1.37 : 1). Patients with other appendiceal tumours such as goblet cell carcinoma or MINEN were excluded from this analysis. All histology results were reported and verified by a pathologist specializing in NEN. The histology reports including grading and TNM staging were prepared in line with WHO2017/ENETS and AJCC/UICC classifications.[2,6,8] For cases where the classifications systems disagreed, ENETS classification was given precedence. The patients and tumour characteristics are presented in Table 1.

Patient treatment was managed within a multidisciplinary team (MDT), with further analysis and diagnostic/imaging approaches undertaken for patients found to have advanced local disease after initial non radical surgery.

Patients were referred for SRS when there was suspicion of regional nodal involvement, or the presence of metastatic disease, resulting in a highly selective group of patients not comparable to the general population.

In 13 cases, patients without indications for SRS decided by a MDT, or patients who declined to have SRS were excluded from further analysis. Overall SRS being performed on, in 77 subjects, using mean 600 MBq (range 550–650 MBq) of ^{99m}Tc-[HYNIC,Tyr3]-Octreotide [^{99m}Tc-TOC] (Tektrotyd, National Centre For Nuclear Research Radioisotope Centre, POLATOM, Poland). The detailed method of kit labelling with ^{99m}Tc has been described previously.[9,10]

Images were acquired 1–3 h after intravenous (IV) injection of radiotracer using a dual-head GE Discovery 670 Pro SPECT/CT hybrid gamma camera CT system (GE Healthcare, Milwaukee, WI, USA). Head, neck, chest, abdominal and pelvis scans were acquired using whole-body (WB) single photon emission computed tomography (SPECT/CT). A low energy high resolution (LEHR), parallel-hole collimator, with a single photopeak window (140 keV +15%) was used in each case.

SPECT data was acquired in 60 projections using 128 × 128 matrix, 360° rotation, 25 s per projection, with no zoom. Reconstruction algorithms were based on the commercially available iterative reconstruction algorithm Evolution – ordered subset expectation maximization (OSEM; with resolution recovery), including 10 subsets and 4 iterations with a standard Gaussian filter on a Xeleris workstation (GE Healthcare, Milwaukee, WI, USA). CT was performed without IV contrast enhancement. Standard acquisition parameters were used for scout 120 keV, 10 mA and helical 120 keV, mA modulated in the range of 60 – 210 mA with noise index 21, rotation time 0.8 s, pitch 1.375 : 1 and collimation of 20 mm.

For each SRS, any focal or diffuse non-physiological accumulation observed during the examination was reported as pathological. Diffuse, low activity intestinal uptake observed through SRS was disregarded as non-specific, physiologic bowel uptake. Lesions and disease progression was classified by radiotracer uptake intensity using the Krenning scale, as used in standard somatostatin receptor scintigraphy with Octreoscan evaluation. Both methods have been described previously.[11]

SRS was read by two specialists in nuclear medicine and was defined as true positive (TP) when the patient had

Table 1. Patients and tumour characteristics in well (G1) and moderate (G2) differentiated ANEN.

Characteristics	ALL, $n = 77$	NENG1, $n = 83$	NENG2, $n = 7$
Female to male ratio	1.37	1.24	6
Age in initial diagnosis, mean (range)	33.52 (9–73)	33.01 (9–73)	39.57 (19–64)
Size of the tumour (pathology), mean ± SD	11.10 ± 8.28	10.80 ± 8.31	14.71 ± 6.96
Ki-67, mean ± SD	1.43 ± 1.37	1.11 ± 0.41	5.29 ± 2.49
Type of surgery, *n*	90	83	7
Appendectomy, *n*(%)	56(62.2)	53(64)	3(43)
Right hemicolectomy, *n*(%)	31(34.4)	27(32.5)	4(57)
Other surgery, *n*(%)	3(3.3)	3(3.5)	0(0)
Resection margin, *n*	87	81	6
R0, *n*(%)	69(79)	66(81)	3(50)
R1, *n*(%)	18(21)	15(19)	3(50)
pT (initial), *n*	90	83	7
pT1, *n*(%)	40(44)	40(48)	0(0)
pT2, *n*(%)	33(37)	30(36)	3(43)
pT3, *n*(%)	15(17)	11(13)	4(57)
pT4, *n*(%)	2(2)	2(2)	0(0)
Any other surgery, than appendectomy, *n*	34	30	4
N0, *n*(%)	25(73.5)	23(76)	2(50)
N1, *n*(%)	7(20.5)	5(17)	2(50)
Nx, *n*(%)	2(6)	2(7)	0(0)
M base on surgery/follow-up/imaging, *n*	34	30	4
M0, *n*(%)	12(35)	9(30)	3(75)
M1, *n*(%)	3(9)	2(7)	1(25)
Mx, *n*(%)	19(56)	19(63)	0(0)
CS (initial), *n*	90	83	7
I–IIIa – local, *n*(%)	82(91)	77(93)	5(71)
IIIb – regional, *n*(%)	5(6)	4(5)	1(14)
IV – dystal, *n*(%)	3(3)	2(2)	1(14)
Localisation of primary tumour, *n*	83	77	6
Tip, *n*(%)	71(86)	66(86)	5(83)
Middle, *n*(%)	5(6)	4(5)	1(17)
Base, *n*(%)	7(8)	7(9)	0(0)

histologically confirmed NEN and/or the active disease was confirmed at the same site during clinical or follow-up imaging using structural and functional approaches. A true negative (TN) result was recorded when no uptake was detected by SRS in the patient body, and no confirmed NEN after 12 months of follow-up. A false positive (FP) was recorded when there was uptake of radiotracer on SRS but no evidence of NEN found by other imaging methods and during clinical follow-up. A false negative (FN) result was recorded when a NEN tumour was verified but not detected by SRS imaging.

Histological and clinical information including evaluation of resection margins, localisation of primary tumour, and tumour type based on WHO 2017 classification, including Ki-67 and the initial clinical stage (CS) of disease were available for analysis.

4. RESULTS

Eighty-three patients with G1 (92.2%) and 7 with G2 NEN (7.8%) were studied. Tumour grading, type, initial clinical stage and cell differentiation, including Ki-67 (Table 1) clinical data were considered within this study.

In total, 56 patients were initially treated by appendectomy, 31 by right hemicolectomy, and 3 by other types of surgery, including laparotomy. An R0 resection was recorded in 66 patients with G1 and 3 with G2. An R1 resection was recorded in 15 subjects with G1, and in 3 patients with G2. There were 3 patients with no data concerning resections in this analysis, 2 with NENG1 and 1 with NENG2 (Table 1).

Analysis of the localization of tumour found that the majority of patients (71) had tumours localized to the appendi-

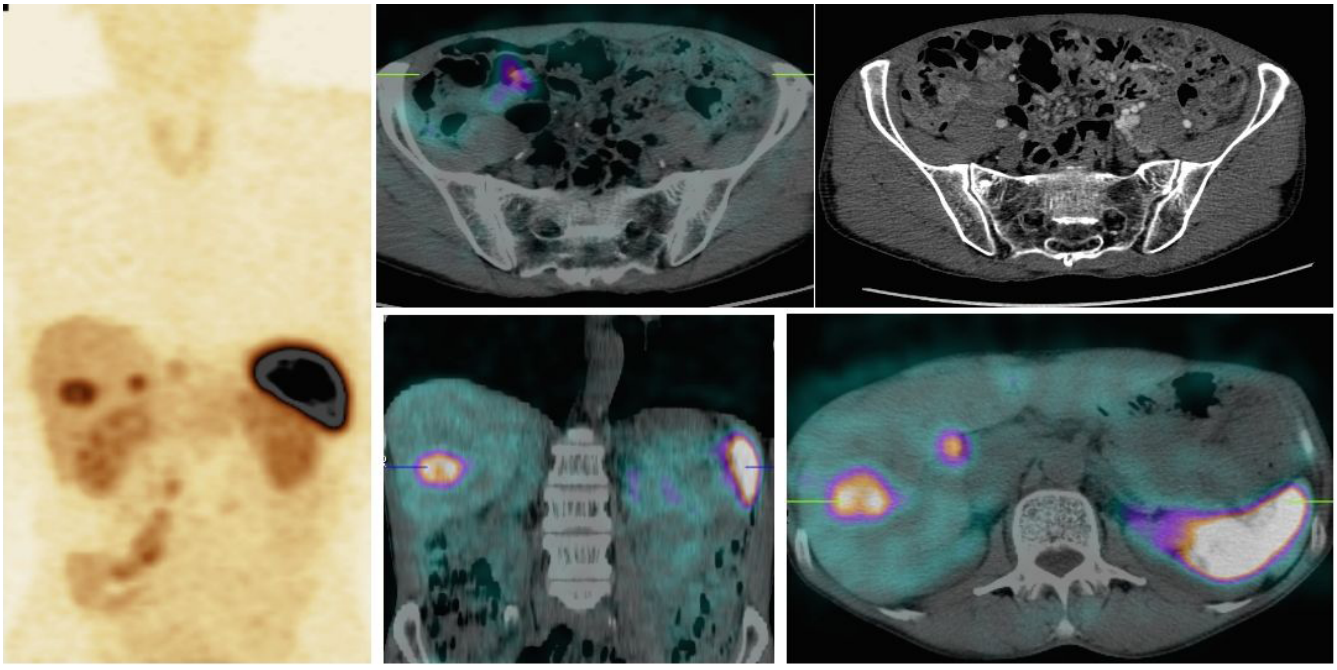

Figure 1. Example images generated by SRS using ^{99m}Tc HYNICTOC (Tektrotyd, PL) and whole-body SPECT/CT on a 64 year old male with NENG2 and after right hemicolectomy (Ki-67 8%; pT3N1M1, CS IV at baseline, size of the tumour – 23 mm).

Table 2. Results of somatostatin receptor scintigraphy examinations in staging group and in follow-up group.

Results of SRS examinations	All patients	Staging group, $n = 30$		Follow-up group, $n = 47$	
		NENG1	NENG2	NENG1	NENG2
TP	4	3	0	1	0
TN	73	25	2	42	4
FN	0	0	0	0	0
FP	0	0	0	0	0
All patients	77	28	2	43	4

Table 3. Results of somatostatin receptor scintigraphy examinations in patients after appendectomy, before or after right hemicolectomy and after other types of surgery.

Group	All patients	After appendectomy $n = 50$		Before or after right hemicolectomy $n = 24$		After other types of surgery $n = 3$	
		NENG1	NENG2	NENG1	NENG2	NENG1	NENG2
Results of SRS examinations							
TP	4	0	0	2	0	2	0
TN	73	47	3	19	3	1	0
FN	0	0	0	0	0	0	0
FP	0	0	0	0	0	0	0
All patients	77	47	3	21	3	3	0

ceal tip, 5 in the middle and the remainder (7) at the base of appendix. The analysis revealed that pT1 tumours were seen in 40 (48.2%) patients with G1. The majority of patients with NENG2 were found to have pT2 and pT3 tumours.

SRS was performed in 77 selected cases to confirm the presence of metastatic disease. Group 1 comprised of 30 patients (39%) where SRS was performed after initial or repeat surgery with ITT analysis (Figure 1). Group 2 comprised 47 patients (61%) where SRS was performed as follow-up functional imaging. Group 1 patients evaluated by SRS yielded 3 TP, 27 TN, 0 FP and 0 FN results. Group 2 patients evaluated by SRS yielded 1 TP, 46 TN, 0 FP and 0 FN. SRS results for both groups are shown in Table 2.

Surgical evaluation identified that after appendectomy, there were 50 TN results. Before or after right hemicolectomy, there were 2 TP and 22 TN results, with 0 FN noted. For the other types of surgery, there were 2 TP and 2 TN cases (Table 3).

Performed as an initial SRS to assess disease progression, the mean time until first SRS examination was 12 months in patients after right hemicolectomy and 49 months for follow-up studies. The mean time after appendectomy was 21 months for staging and a further 23 months for follow-up studies.

5. DISCUSSION

Most patients with ANEN can be treated by appendectomy due to small size and the indolent growth rate of this type of NEN.[2,3,5,6] The few patients who develop lymph node metastases still have a favorable prognosis when compared to other GEP-NEN localizations.[2,5,12] Patients with histopathological features that suggest greater risk of metastatic spread require right hemicolectomy (RH), as per local guidelines for the treatment of ANEN.[2,5,12–18]

Only a few reports have identified residual NEN in patients that have undergone RH, and in cases of further disease, this typically involves few lymph nodes, however most of these studies report on 30 or less subjects and is therefore difficult to come to draw meaningful conclusions.[12–16] A study recently published by Pawa et al. used a significantly larger sample size, analyzing 215 patients with ANEN from the United Kingdom and Poland after appendectomy. RH was performed in a further 49 patients (23%).[5] In our study, which consists of patients included in analysis mentioned above, the rate of RH was even higher and was performed by selected centers which special interests of NEN. This may be unrelated to general trend of such high incidence of RH in our group of patients.[17,18]

In those patients exhibiting potentially malignant NEN, imaging could be used to evaluate any residual disease after simple appendectomy. The problem with this type of approach is the relatively low sensitivity of any structural imaging such as CT and MRI or US in detecting low volume disease, which is a characteristic of most cases of advanced ANEN.[19,20] Therefore, the best form of imaging are more sensitive and specific functional techniques including somatostatin receptor imaging using SPECT/CT or PET/CT.[10,11] It has been our standard practice to perform SRS ^{99m}Tc-Tektrotyd as the main form of follow-up imaging in subjects who had previously undergone appendectomy and/or right hemicolectomy.

The results of SRS in both groups of subjects, based on our results are promising, and identified 3 cases of patients with advanced disease and of a patient who had active disease during the follow-up study. However, the number of patients with residual tumours after appendectomy (or, when appropriate, RH) is low. Therefore, to perform SRS on all patients may not be cost efficient approach.

The clinical follow-up of our patients indicates a high predictive value of a negative SRS result after follow-up in the short-term, although NEN are slow growing and may take years before any missed sub-centimeter tumour becomes evident.

Survival data, shows that vast majority of ANEN, do not need any additional imaging methods after radical surgery such as a simple appendectomy with R0 resection, and/or RH including both NENG1 and NENG2 ANEN.[5,15–18] Distant metastatic disease is seen in less than 1% of NENG1/G2 ANEN.[19,20] In our study, most patients were referred for SRS on suspicion of metastatic disease and as such, this retrospective study includes many patients who had undergone right hemicolectomy, which is not comparable to most practices.

In our analysis 3 patients (3.3%) had liver metastases, 2 patients had RH and we performed SRS in 2 patients, both of which were TP.

As a consequence, our study confirms ENETS and the North America Neuroendocrine Tumor Society (NANETS) recommendation, that after radical surgery, which include appendectomy, or RH, there is little value in additional imaging to capture those patients who will develop metastatic disease. There are however some features which could influence the behavior of a particular ANEN such as the presence of small vessel invasion (SVI), which is correlated with disseminated disease.[21,22]

6. CONCLUSIONS

SRS appears useful in the evaluation of disease status in patients after initial non-radical or extended surgery (RH), accurately identifying a high true negative rate for ANEN disease. However, due to the effectiveness of primary ANEN treatment, this imaging technique appears to have little value for post-surgical follow-up screening in ANEN patients.

Conflict of interest
None declared.

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None declared.

Ethics
The protocol for this retrospective study was approved by the institutional ethics committee.

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