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Feasibility of a streamlined imaging protocol in Technetium-99m-Tektrotyd Somatostatin Receptor SPECT/CT

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Abstract

Aim

Somatostatin receptor scintigraphy (SRS) incorporates dual time-point imaging to differentiate pathological uptake by neuroendocrine tumours (NETs) from physiological activity. SPECT/CT improves accuracy allowing reliable distinction. Technetium-99m SRS (Tektrotyd) permits single-day imaging although dual time-point protocols are still recommended. The purpose of this study was to assess the feasibility and efficacy of a streamlined single time-point Tektrotyd SRS protocol.

Methods and Materials

Tektrotyd imaging in 50 consecutive patients with NETs was retrospectively reviewed. Imaging was independently assessed by two experienced reporters with dual-certification in Radiology & Nuclear Medicine and agreed in consensus. The presence of physiological bowel activity and/or further sites of equivocal uptake on 4-hour planar imaging and whether SPECT/CT assessment allowed accurate diagnosis was tabulated. A judgement was also made in each case on whether 2-hour planar imaging was necessary for accurate diagnostic interpretation.

Results

36 patients (72%) had positive findings on Tektrotyd SPECT/CT. 8 patients (16%) had bowel activity on 4-hour planar imaging which could be considered to have hampered interpretation without access to SPECT/CT. 11 studies in 10 patients (20%) demonstrated areas of indeterminate uptake on planar imaging; 5 in the uncinate process of the pancreas, 3 in the nasal cavity or paranasal sinuses, 1 in the adrenal glands, 1 in a focus of inflammation on the posterior abdominal wall and 1 at the tip of a central venous line. In all cases, accurate interpretation of findings was possible with SPECT/CT, without the 2-hour planar image.

Conclusion

2-hour planar imaging could be safely omitted from Tektrotyd SRS incorporating SPECT/CT imaging without reducing accuracy of diagnostic interpretation. Streamlined imaging has the potential to reduce patient inconvenience and improve scanner and staff efficiency.

Keywords

Somatostatin receptor scintigraphy; neuroendocrine tumour; SPECT/CT; Technetium99m-HYNIC-Tyr3-Octreotide (Tektrotyd)

Introduction

Neuroendocrine tumours (NET) comprise a diverse group of malignancies that derive from embryonic neural crest cells of various organs such as the lungs, gastrointestinal tract, adrenal medulla, thyroid and pituitary gland [1,2]. They are known to over express somatostatin receptors, the presence of which, particularly subtypes 2 & 5, allows detection with radiolabelled peptide somatostatin analogues [3]. Since the introduction of these radionuclides, Somatostatin Receptor Scintigraphy (SRS) has been in widespread clinical use for assessment and staging of NETs [4]. More recently, development of highly specific positron emitting radiopharmaceuticals have allowed progress in detection of lesions using somatostatin receptor (SSR) PET-CT which is now considered the gold standard for initial staging, pre-curative surgery and investigation of unknown primaries [5]. However, despite the obvious strengths of SSR PET-CT, adoption into routine clinical practice in the UK has been slow due to a combination of financial and regulatory issues [6]. Consequently, SRS using Indium-111 (In-111) labelled radiopharmaceuticals has continued to be widely utilised for staging of neuroendocrine malignancies, with single photon emission computed tomography / computed tomography (SPECT/CT) fusion improving diagnostic assessment beyond that of traditional planar imaging.

There are some limitations with In-111 SRS including the logistical constraints of supply of cyclotron-produced radio-isotope and a 2-day imaging protocol. Recently a Technetium-99m (Tc99m) labelled Somatostatin analogue has become more widely available and this radiopharmaceutical overcomes some of the issues. Tc99m-HYNIC-Tyr3-Octreotide (Tektrotyd) has the advantage of ready availability of radio-isotope from departmental Technetium-99m generators, a single day imaging protocol and superior image resolution [7]. In addition the mean effective dose from Tc99m-Tektrotyd, reported to be 4.6 +/- 1.1mSv [8], is significantly less than that for In-111-Octreotide at 8-16 mSv [9]

Prior studies of In-111 SRS have shown that integration of SPECT/CT facilitates streamlining of imaging protocols with reduction in imaging time-points needed as it permits more reliable

differentiation of pathological uptake from physiological activity [5,10]. Widely adopted In-111 SRS protocols recommend image acquisition at 24 (+/- 48) hours' post-injection allowing 'wash-out' of accumulated bowel uptake of excreted tracer. 4-hour imaging is conducted in some centres, aimed to image prior to bowel accumulation but this advantage is often offset by higher background activity levels [11,12].

Standard imaging protocols for Tc99m-Tektrotyd include a 2-hour whole body planar acquisition with the aim to obtain images prior to uptake in the bowel and biliary tree, followed by 4-hour whole body planar imaging and SPECT/CT through the abdomen +/- thorax [13–15].

The aim of this study was to review initial experience with Tc99m-Tektrotyd in a large tertiary referral centre and to determine the feasibility of single-time-point SRS with SPECT/CT as a replacement for dual time-point imaging. The hypothesis was that SPECT/CT should distinguish between pathological and physiological uptake at 4 hours' post injection rendering the 2-hour acquisition unnecessary. A single-time point acquisition would allow streamlining of services and be even more patient friendly.

Materials and methods

Patient selection

Following adoption of a new SRS protocol using Tc99m-Tektrotyd in place of In-111 DTPA-Octreotide at a large tertiary referral centre in December 2016, data from 50 consecutive patients with suspected / confirmed NET, or undergoing post-surgical surveillance of a resected NET was collated prospectively. Our institution does not require formal ethics committee approval or written patient consent for retrospective service evaluation studies such as this. The study was registered, received approval and was added to the Institutional Clinical Audit database.

Imaging protocol

After IV administration of 600 – 740 MBq of Tc99m-Tektrotyd, planar whole body images were acquired at 2 and 4 hours post injection, supplemented with abdominal +/- thoracic SPECT/CT imaging at 4 hours. The decision for inclusion of a head and neck or thoracic SPECT/CT acquisition was based on provided clinical information and appearances of the 2-hour planar imaging.

Whole body planar images, from skull vertex to mid-thigh, were acquired in anterior and posterior projections on a dual-head gamma camera with low-energy, high resolution collimators (Discovery 670, GE Healthcare, Amersham, UK); using a 20% energy window centred at 140.5 keV and a table speed of 6 cm per minute. SPECT/CT images were obtained on the same hybrid gamma camera. The SPECT portion of the acquisition was acquired in a 360-degree orbit with 30 steps per head (20 s/stop) resulting in a total of 60 projections, and processed using ordered subset expectation maximization (OSEM) iterative reconstruction (2 sets, 10 subsets) into a 128 x 128 matrix. At our institution a total of 60 projections is obtained as a compromise between the highest SPECT image resolution achievable and acquisition duration aimed at minimising patient motion which would otherwise necessitate movement correction and associated artefact. CT-based attenuation correction was applied to the SPECT data.

As per departmental protocol, a non-contrast enhanced CT acquisition was obtained using a low-dose technique (helical acquisition, 120kVp, Smart mA from 30 – 150mAs) with images reconstructed at a slice thickness of 2.5 mm in a 512 x 512 matrix. CT data was reconstructed using proprietary Adaptive Statistical Iterative Reconstruction [ASiR] (GE Healthcare) using an ASiR processing level of 40%. Median dose-length product (DLP) for all studies was 116.3 mGy/cm (range 39.4 – 833). **Table 1** illustrates the minimum, maximum, median and mean DLP values for head and neck, thorax, abdomen and total study acquisitions.

Image interpretation

Tc99m-Tektrotyd planar, SPECT and SPECT/CT images were viewed on a diagnostic workstation [Xeleris Version 3.0, GE Healthcare, Amersham, UK]. This allows viewing of planar images as well as SPECT and CT data individually and fusion of modalities. CT components of each SPECT/CT study were also viewed on a diagnostic PACS workstation [Agfa IMPAX, Version 5.6, Agfa Healthcare, Belgium].

Two dual-qualified consultants in radiology and nuclear medicine with a minimum of 8 years' experience of reporting SRS studies, independently reviewed images whilst unaware of clinical findings, other diagnostic imaging results or the final histological diagnosis. Each reader assessed the presence or absence of physiological bowel activity and/or further sites of equivocal uptake on 4-hour planar imaging and whether SPECT/CT assessment allowed accurate diagnosis, results were tabulated. True positive findings were considered to be those with uptake secondary to disease and not inflammatory or physiological activity. A judgement was also made in each case on whether 2-hour planar imaging was necessary for accurate diagnostic interpretation. Any disagreements were discussed and agreed in consensus.

Results

Between December 2016 and June 2017, 50 consecutive patients (19 male, 31 female; mean age: 61 years; range 30-84 years) underwent Tc99m-Tektrotyd SRS: 26 patients had a gastroenteropancreatic NET, 3 had a thoracic NET, 2 had a suspected head & neck NET, 7 patients had an unknown primary (5 with hepatic NET metastases, 2 with carcinoid syndrome) and 12 underwent SRS for re-assessment following previously resected NETs.

Prior to consensus review both observers identified identical cases demonstrating true positive findings and cases showing physiological bowel uptake that could hamper planar imaging interpretation. There were six cases identified by both observers with areas of extra-intestinal indeterminate activity on planar imaging and four further cases noted by Observer 1 (**Figure 1**). The four discordant cases were reviewed in consensus by both observers and following discussion all were felt to show additional activity that could be considered indeterminate on 4-hour planar imaging.

36/50 (72%) patients had true positive findings on SRS. 8/50 (16%) had bowel activity on the 4-hour planar image that could be considered to have hampered interpretation in the absence of SPECT/CT (**Table 2**).

As an example; in patient 4, pathological uptake in the pelvis could potentially have been misinterpreted as physiological bowel activity however the SPECT/CT acquisition clearly localised activity to peritoneal disease (**Figure 2**). Utilisation of a dual-phase planar only imaging protocol in this case may have missed this pathology as activity was slightly reduced on the 2-hour image. The lack of a 2-hour image in this study would not have adversely affected imaging interpretation.

10/50 studies (20%) demonstrated areas of indeterminate uptake on planar imaging in addition to that in the bowel; in four cases this was attributable to prominent uptake in the uncinate process of the pancreas. In one example with no tracer-avid pathology (patient 8), there was a relative increase

in activity in the uncinate process of the pancreas on the 4-hour image when compared with the 2-hour planar study (**Figure 3A & 3B**); this potential abnormality was more reliably convincing of physiological uptake on the SPECT/CT acquisition given a lack of an abnormality on the CT component (**Figure 3C**) or prior contrast-enhanced CT (not shown). In this case, planar imaging also demonstrated diffuse bowel-related tracer uptake for which the 2-hour image was helpful in adding confidence for the bowel activity being physiological. The SPECT/CT acquisition however allowed greater confidence in accurate image interpretation than the 2-hour planar image.

Patients 25 and 28 also had prominent uptake in the region of the uncinate process potentially hampering interpretation. In the former, the 2-hour image was not helpful and in the latter, the SPECT/CT provided more convincing evidence of a physiological aetiology.

In all cases, the combination of 4-hour planar imaging and SPECT/CT permitted confident image interpretation without 2-hour imaging. In two cases the 2-hour planar views would have potentially been helpful but in both instances SPECT/CT was more definitive. As an example, Patient 49, a 59-year-old male with a history of previously resected midgut carcinoid tumour underwent Tc99m-Tektrotyd SRS for characterisation of equivocal mesenteric nodes demonstrated on contrast enhanced CT. With the benefit of 2-hour planar imaging, a lesion blending with physiological bowel activity on the 4-hour image becomes appreciable. However, the subsequent SPECT/CT guided confident diagnosis of a distal ileal NET (**Figure 4**).

Discussion

This study aimed to determine the feasibility of a streamlined imaging protocol in Tc99m-Tektrotyd SRS SPECT/CT with omission of 2-hour planar imaging, which, to the best of our knowledge has not been previously reported. Two prior studies have reported that use of SPECT/CT in In-111-labelled SRS allows rationalisation of dual time-point imaging to a single time-point protocol without impairment of diagnostic ability [5,10]. Our rationale for switching from In-111 SRS to Tc99m-Tektrotyd imaging of NETs included the superior image resolution afforded by the physical characteristics of Tc99m which make it better suited to gamma camera imaging, lower patient radiation exposure and increased availability of tracer from departmental generators permitting more flexibility in departmental workflow [7]. A national survey of CT doses in hybrid imaging which obtained data from 43 SPECT/CT systems across the UK reported a median DLP from Octreotide studies of 152 mGy/cm (range 43-907) and suggested a national diagnostic reference level for Octreotide SPECT-/CT of 240 mGy/cm, the median DRL in this series was well within that recommended limit (116 mGy/cm) [16]. Tc99m-Tektrotyd has been in clinical use in Eastern European countries for over a decade but has only become commercially available in the UK more recently.

The implementation of a new Tc99m-Tektrotyd based SRS + SPECT/CT protocol in our department from December 2016 allowed patients to undertake their examination during a single day rather than having to return the next day for additional imaging at 24 hours after injection with In-111 SRS. Gabriel et al reported a higher sensitivity for Tc99m-Tektrotyd in an early intra-patient comparison study with In-111 SRS in a cohort of 41 patients with NETs before the widespread introduction of SPECT/CT [17]. In their series 2 patients (5%) had false positive findings on Tc-99m Tektrotyd SRS due to non-specific tracer accumulation and for this reason additional early scanning at 1-2 hours was advocated [17]. Co-registration of SPECT and separate diagnostic CT was subsequently reported to reduce false positive results [18]. In our patient cohort, ten patients (20%) demonstrated areas of

indeterminate uptake on planar imaging; in five cases this was attributable to prominent uptake in the uncinata process of the pancreas. Findings at integrated SPECT/CT and/or prior contrast enhanced imaging, specifically the absence of a focal lesion on anatomical imaging, surpassed the ability of the 2-hour study in aiding interpretation. Uncinate process activity is a well-known physiological appearance in SRS, occurring as a result of physiological peptide uptake [18-20] and awareness of this normal variant should allow confident interpretation with the benefit of a 4-hour planar image and SPECT/CT acquisition.

There were eight cases (16%) in which bowel activity could potentially have hampered interpretation on planar imaging analysis alone. In one example, pathology which could feasibly have been mistaken for physiological bowel activity on the 4-hour planar image was clearly identified as peritoneal disease on SPECT/CT. SPECT/CT permitted a confident diagnosis of physiological bowel uptake in instances of equivocal upper abdominal activity, as in the case described. In cases where there is clinical concern for head & neck or thoracic disease or whole body planar imaging reveals indeterminate head & neck or thoracic uptake, SPECT/CT of the corresponding region is included as per departmental protocol.

Pooled sensitivity (93%) and specificity (96%) for Gallium-68 labelled SSR PET-CT exceeds SRS SPECT/CT detection rates for NETs [22]. For this reason, SSR PET-CT has been widely adopted into routine clinical practice in many countries. Unfortunately, despite SSR PET-CT being on the list of indications funded by NHS England there is limited availability in the UK at present with only a few highly-specialised centres able to provide this imaging technique. It is hoped that this technology will become more widely available in the next few years.

There are limitations to this study including the relatively small cohort size, retrospective nature and lack of definitive histological confirmation of findings. Despite these shortcomings, the study suggests that 2-hour planar imaging could be safely omitted from Tc99m-Tektrotyd SPECT/CT imaging protocols without reducing confidence in diagnostic interpretation. This not only allows

streamlining of camera and staff time but also reduces patient discomfort and potentially improves their experience during their time in the nuclear medicine department.

Conclusion

2-hour planar imaging could be safely omitted from Tekrotyd SRS incorporating SPECT/CT imaging without reducing accuracy of diagnostic interpretation. Streamlined imaging has the potential to reduce patient inconvenience and improve scanner and staff efficiency.

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Figures & Tables

FIGURE 1 Observer variability prior to consensus discussion for (A) true positive activity (B) 4-hour planar bowel activity potentially hampering planar interpretation and (C) sites of indeterminate uptake on 4-hour planar imaging.

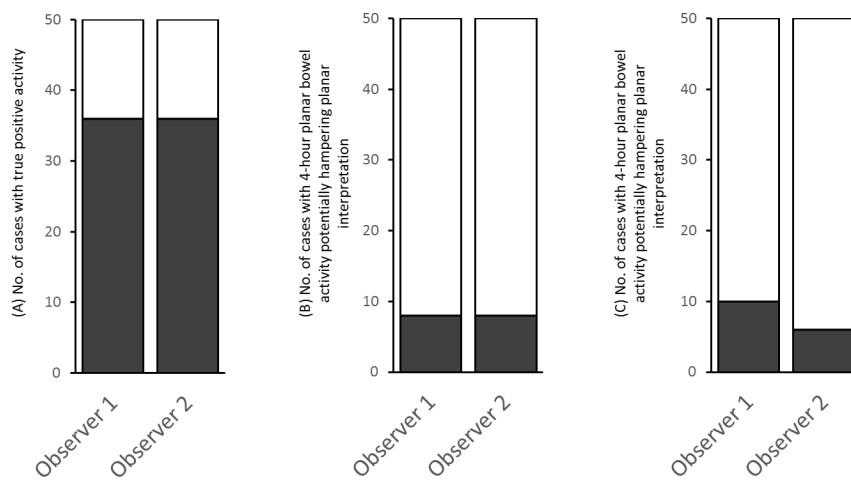


FIGURE 2 Tc99m-Tektrotyd (A) 2-hour and (B) 4-hour planar imaging (C) non-contrast CT and (D) fused images from a subsequent SPECT/CT acquisition through the pelvis. Tracer uptake within a focus of peritoneal recurrence (white and yellow arrows) which could be mistaken for physiological bowel uptake on planar whole-body imaging (arrow heads).

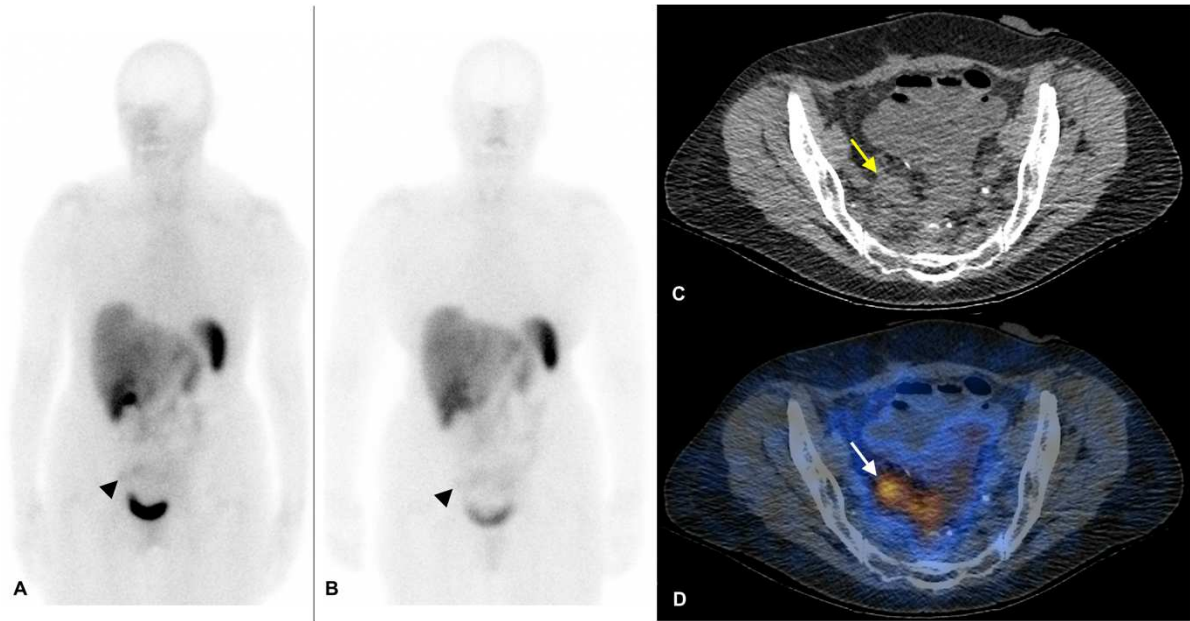


FIGURE 3 Tc99m-Tektrotyd planar whole-body anterior (A) 2-hour and (B) 4-hour images demonstrate focal uptake in the region of the central upper abdomen of increased prominence on the delayed study (black arrow and arrow-head). Axial (C) SPECT/CT fusion images at 4 hours clearly showing the central upper abdominal activity localising to a morphologically normal pancreatic uncinuate process (white arrow) in keeping with physiological polypeptide tracer uptake.

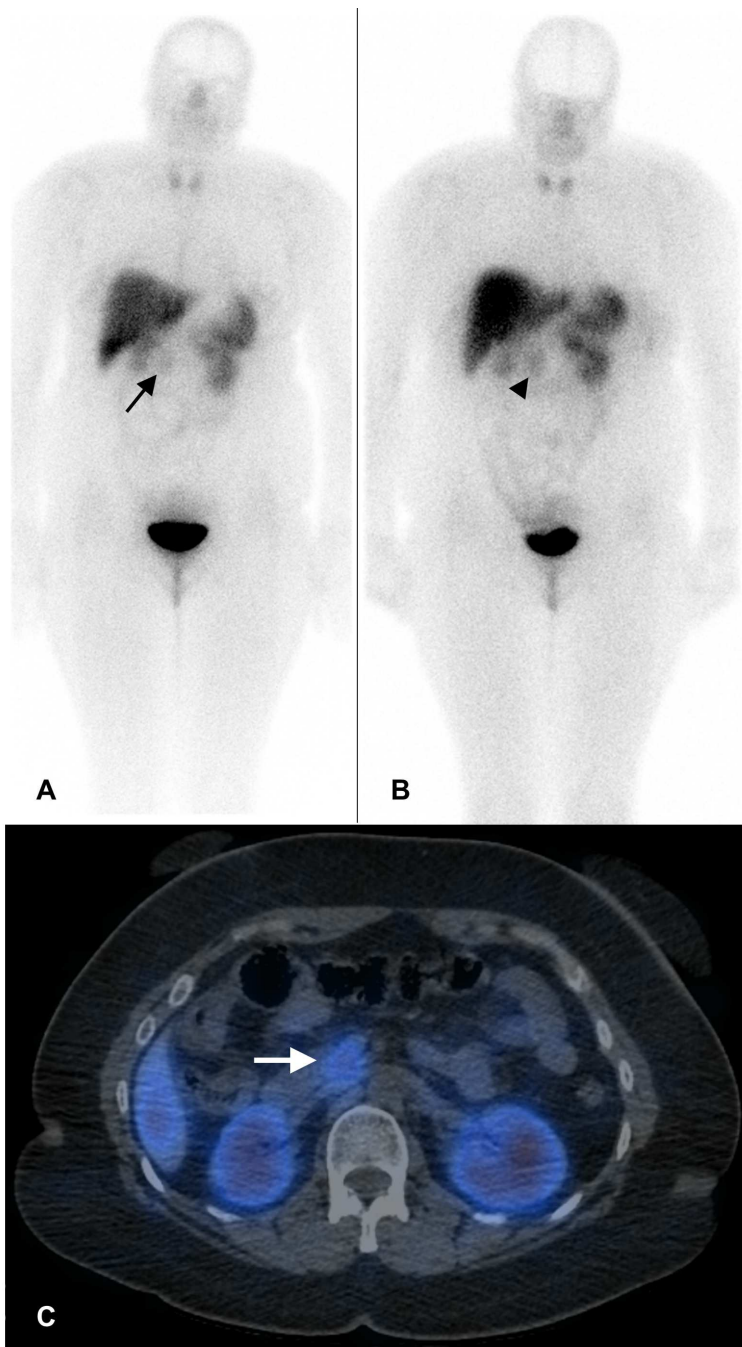


FIGURE 4 Tc99m-Tektrotyd (A) 2-hour and (B) 4-hour planar imaging, (C) coronal fused SPECT/CT image and (D) fused 3D reconstruction. A focus of equivocal tracer activity on 4-hour planar imaging (black arrow head) which should be interpreted as pathological with appreciation of its persistence from the 2-hour image (black arrow). The subsequent SPECT/CT clearly demonstrates pathological uptake in a primary distal ileum NET (red cross hairs).

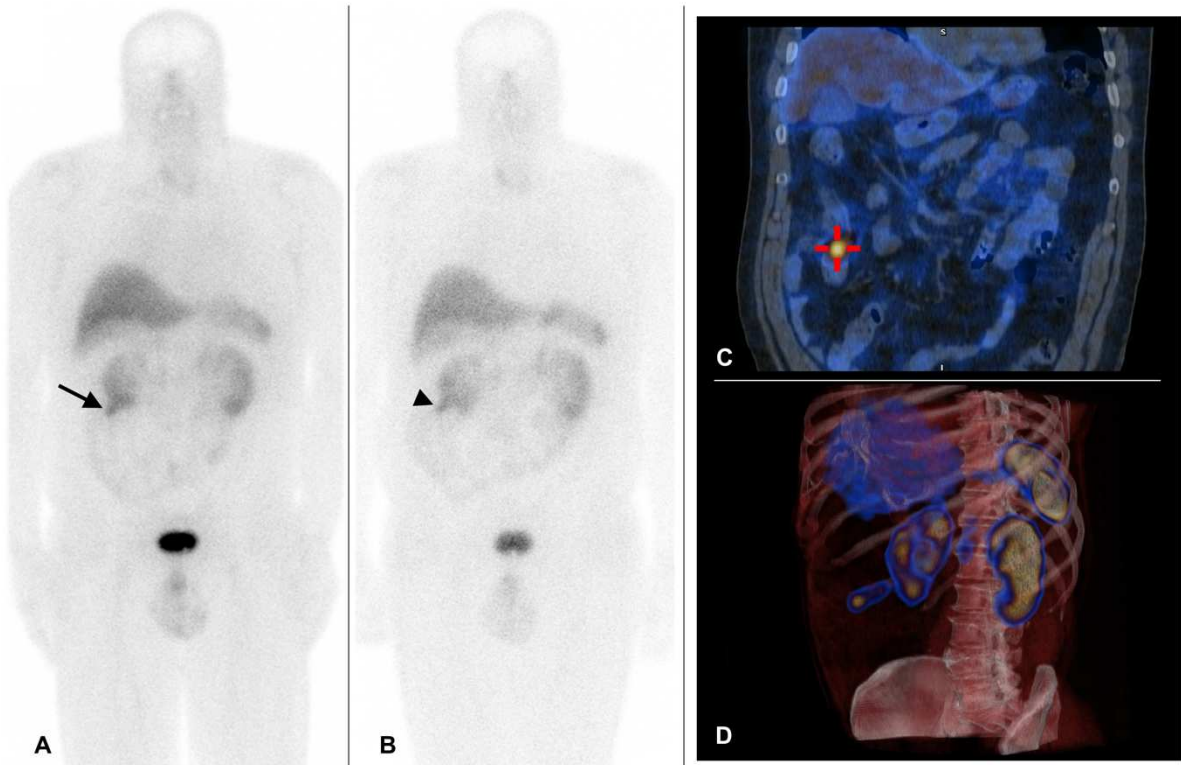


TABLE 1 Dose Length Product (DLP) minimum, maximum, median and mean values for abdominal, thoracic, head/neck and total study CT acquisitions.

	Abdomen	Thorax	Head & Neck	Total study
Number of studies	50	7	2	50
Minimum DLP (mGy-cm)	39.4	22.3	21.0	39.4
Maximum DLP (mGy-cm)	607.1	169.9	356.0	833.0
Median DLP (mGy-cm)	115.5	70.8	188.5	116.3
Mean DLP (mGy-cm)	161.1	77.5	188.5	180.1

TABLE 2 Assessment of Tc99m-Tektrotyd studies for presence of bowel activity on 4-hour imaging

hampering interpretation, sites of indeterminate uptake and the ability to confidently diagnose

without 2-hour imaging. + present; - absent.

Patient No.	Positive study	Bowel activity hampering interpretation on 4-hour planar imaging	Sites of Indeterminate uptake on 4-hour planar imaging	2-hour images necessary for correct interpretation?
1	+	-	-	-
2	-	-	Paranasal sinuses	-
3	+	-	-	-
4	+	+	-	-
5	+	-	-	-
6	+	-	-	-
7	+	-	-	-
8	-	-	Uncinate process	-
9	+	-	-	-
10	+	-	-	-
11	-	-	Hickman Line	-
12	-	-	-	-
13	+	-	-	-
14	+	-	-	-
15	+	+	-	-
16	-	-	-	-
17	+	+	-	-
18	+	-	Adrenal glands and uncinat process	-
19	+	-	-	-
20	+	-	-	-
21	-	-	-	-
22	+	-	-	-
23	-	-	-	-
24	+	-	Inflammatory uptake posterior abdominal wall	-
25	+	-	Uncinate process	-
26	+	+	-	-
27	+	-	-	-
28	+	-	Uncinate process	-
29	-	-	-	-
30	-	-	-	-
31	-	-	-	-
32	+	-	-	-

33	+	-	-	-
34	+	-	-	-
35	+	-	-	-
36	+	-	-	-
37	+	-	-	-
38	+	+	-	-
39	+	+	-	-
40	+	-	-	-
41	-	-	-	-
42	-	-	Nasal mucosa	-
43	+	-	-	-
44	+	-	-	-
45	+	-	-	-
46	-	-	Nasal mucosa	-
47	-	-	-	-
48	+	+	Uncinate process	-
49	+	+	-	-
50	+	-	-	-