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가스트린종 환자에서 In-111 Pentetreotide 스캔: 영상법의 비교

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In-111 Pentetreotide Scanning in Gastrinoma Patients: Comparison of Imaging Methods

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Abstract

Background Because multiple imaging sessions increase the cost and time of In-111 pentetreotide studies, we evaluated various imaging methods and times to see whether we could simplify the overall process while maintaining our ability to detect lesions in diagnosis of gastrinoma. ***Methods*** Seventy nine studies from 77 gastrinoma patients were reviewed, including twenty six studies in previously cured patients with normal basal and negative secretin stimulated serum gastrin levels. Fifty one patients with elevated serum gastrin levels were considered to have active disease. Whole body, planar spot and SPECT (orthogonal, reprojected) images were obtained 4 and 24 hours after administration of 222 MBq of In-111 pentetreotide and reviewed separately. Three Nuclear Medicine physicians reviewed 541 image sets in random order, blinded to patient identifiers and time of imaging (4 vs 24 hours). Lesions were graded using 5 categories: 0 - negative; 1 - unlikely; 2 - possible lesion; 3 - probable lesion; 4 - definite lesion. ROC analysis and comparison of sensitivity and specificity were performed. Biopsy and radiological imaging provided final diagnoses for 112 lesion sites: 51 with gastrinoma, 61 sites were negative. ***Results*** The area under the curve (AUC) for 4 hour imaging was always greater than for 24 hours, but the differences were not statistically significant. At both 4 and 24 hours, the AUC was greater with SPECT orthogonal imaging than planar imaging (4 hour, 0.94 vs 0.82, $p<0.05$; 24 hour, 0.89 vs 0.81, $p=0.09$). Using a cutoff of grade 3 or 4 as positive, the sensitivity was always greater at 4 hours than at 24 hours, but not significant. The specificity of 4 hour imaging also tended to be greater than or the same as that of 24 hour imaging. At both 4 and 24 hours, SPECT orthogonal imaging had significantly higher sensitivity than did planar imaging (4 hour, 84% vs 62%, $p=0.01$; 24 hour, 78% vs 44%, $p<0.001$), but planar imaging had better specificity (4 hour, 89% vs 98%, $p<0.05$; 24 hour, 88% vs 94%, p=ns). ***Conclusion*** In patients with gastrinoma, 4 hour In-111 pentetreotide imaging with SPECT provides the greatest diagnostic efficacy. SPECT imaging significantly increased the sensitivity of In-111 pentetreotide imaging with minor reductions in specificity. We conclude that a single imaging session at 4 hours after In-111 pentetreotide administration which includes SPECT imaging of the upper abdomen is sufficient for screening patients with gastrinoma. Guidelines for imaging this group of patients are presented.

Key words : In-111 pentetreotide, ROC curve analysis, gastrinoma, somatostatin receptor imaging

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INTRODUCTION

Gastrinomas express a high density of somatostatin rece

ptors and are good candidates for receptor imaging with radiolabeled somatostatin analogues.[1-4] The detection rate of gastrinoma using In-111 pentetreotide imaging varies from 70 to 100% depending on the reported series.[5-9] Most institutions obtain images at multiple time points over several days (4 hours, 24 hours, 48 hours) and may or may not include SPECT imaging.[7,10,11] The differences between imaging protocols among various institutions may be one of the factors contributing to the different detection rates reported for gastrinoma.[12] In addition, these multiple imaging sessions over several days require increased camera and technologist time as well as patient time, all of which increase costs. Currently, there are no studies that evaluate the optimal imaging protocol in these patients.

The purpose of this study was to compare the results of planar and SPECT imaging at several time-points to determine whether the imaging protocol could be simplified without compromising our ability to detect lesions. The different imaging modalities were compared using receiver operating characteristics (ROC) curve analysis and by calculation of sensitivity and specificity.

MATERIALS AND METHODS

Seventy nine In-111 pentetreotide studies from 77 gastrinoma patients (49 males and 28 females) were evaluated. These patients were enrolled in a prospective study of Zollinger-Ellison syndrome (ZES) that began in 1974 at the National Institutes of Health. The characteristics of this group of patients has been reported earlier. These are not different from other larger series of patients with ZES. The mean age was 52.5 years (range: 16-78 years) old. 51 patients had elevated basal or secretin stimulated serum gastrin levels and were considered to have active disease. Some of these patients had previously undergone surgery for gastrinoma. 26 patients had normal basal and stimulated serum gastrin levels after surgery for gastrinoma and were considered to have inactive, cured disease. Eleven patients had MEN-1 with gastrinoma.

In-111 Pentetreotide Imaging:

For In-111 pentetreotide imaging, patients were hydrated before and after the intravenous injection of In-111 pentetreotide and were given a laxative on the night of radiopharmaceutical administration to avoid artifacts from radioactive accumulation in the intestines. Approximately 222 MBq (6 mCi) of In-111 pentetreotide (Mallinckrodt Diagnostic Imaging Service Radiopharmacy, Beltsville, Maryland) was administered intravenously to each patient and images were acquired using TRIONIX (Twinburg, Ohio) or ADAC (Milipitas, California) dual or triple headed gamma cameras with medium-energy parallel hole collimators and centered over both Indium-111 photon peaks (173 and 247 KeV) with 20% windows. At both 4 and 24 hours, 30 minute whole body images (anterior and posterior), 10 minute planar spot images of the abdomen (anterior and posterior), and SPECT images of abdomen were obtained. 120 sequential, 30 second images using dual headed gamma cameras, or 120 sequential, 40 second images using triple headed gamma cameras were obtained for SPECT. These were stored in 128 x 128 matrix. The images were reconstructed with the manufacturer's software by using a standard filtered back projection algorithm. A Hanning filter was used. SPECT images were displayed as reprojected and orthogonal images. Reprojected images were reviewed with cine display on workstation monitors. Orthogonal image sets included transverse, coronal and sagittal sections.

Interpretation of In-111 Pentetreotide Images:

Each patient study was divided into the following 8 sets of images: 4 and 24 hour whole body images, 4 and 24 hour planar spot images, 4 and 24 hour reprojected SPECT images, and 4 and 24 hour orthogonal images from SPECT. In many patients the 24 hour whole body images were not obtained. After patient identifiers, scan dates and times were removed, a random number was assigned to each image set. The image sets were placed on

a work-station for review. Thus, each image set was evaluated independent of the other images obtained in that patient. On the work-station, the intensity of the images were manipulated. Reprojected images were displayed in cine mode and co-ordinate orthogonal images were displayed simultaneously.

Three nuclear medicine physicians independently evaluated each image set and graded each lesion with a 5 point scale: 0-negative image, no lesion; 1-unlikely lesion (physiologic site or faint uptake); 2-possible lesion; 3-probable lesion; 4-definite lesion (Figure 1).

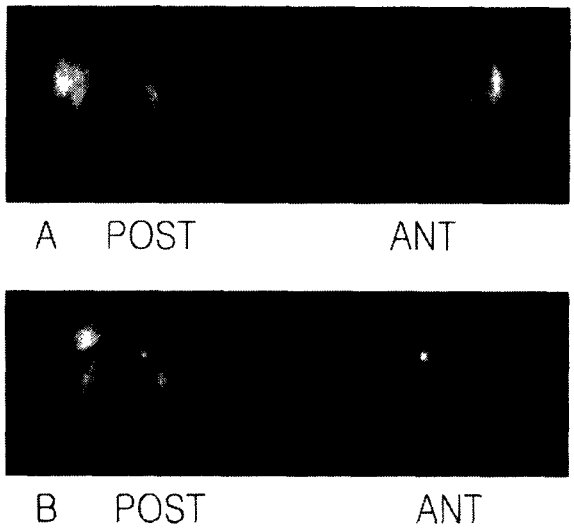

Figure 1. Examples of Grading System. This images show the examples of planar abdomen image for grading. The upper images show physiologic distribution of In-111 pentetreotide in the spleen, both kidneys, and the liver. We graded it as 0, negative image. The lower images show definite lesion on superior and medial to right upper kidney We graded it as a 4. (A. Grade 0: Negative Image; B Grade 4: Definite Lesion)

If more than one lesion was noted in an image set, each was given its own grade. To simplify the analysis, the readings of the 3 nuclear medicine physicians were combined into a single final score which was the most frequently assigned grade if 2 or 3 physicians agreed or the median score if the 3 scores were discordant. A combined SPECT grade was also obtained by choosing the higher grade between reprojected and orthogonal SPECT. We also obtained combined 4 and 24 hours study grades by choosing the higher grade between 4 and 24 hours of the whole body, planar spot, reprojected and orthogonal images. The true positive, true negative, false positive, false negative status of each lesions was based on pathologic (surgery or autopsy), and/or radiologic findings (CT, MRI, and angiography) as well as serum gastrin levels (40-200 pg/ml).

Statistical Analysis:

Intra-observer variability of In-111 pentetreotide scan interpretation was evaluated using the Wilcoxon signed rank test for 17 patients whose scans were separately read two times. Inter-observer variability for all randomized readings of three physicians was evaluated using the kappa statistic.[13] We used the computer programs by Metz et al.[14-16] to calculate the area under the ROC curve (AUC) and to compare two ROC curve's AUC This CORROC2 program calculates estimates of the parameters of a model for correlated ROC data and calculates the statistical significance of the difference between the two ROC curves. We reported the results of a univariate z-score test of the difference between the areas under the two ROC curves.

Analyses were performed on a lesion by lesion basis. In patients with elevated gastrin levels, only those findings which could be confirmed pathologically or radiographically were scored as true positive. All positive findings in patients with normal gastrin levels and inactive disease were considered to be false positive. Image sets receiving a grade of 0 in patients with active disease in whom no surgery was performed and in whom the radiologic studies were negative were scored as if they contained a single false negative lesion. Likewise, image sets receiving a grade of 0 in previously cured patients were scored as if a single, true negative lesion had been found. Lesions identified on In-111 pentetreotide scan in patients with active disease in whom no surgery was performed and in whom the

radiographic studies were negative were considered "uncertain", and excluded from ROC and sensitivity/specificity analyses.

The sensitivity and specificity of each imaging method was compared by using the Mantel-Haenszel tests.17) Lesions with final scores of 0, 1, 2 were categorized as negative; those graded 3 or 4 were categorized as positive.

Two tailed P values are reported.

RESULTS

A total of 541 image sets from 79 studies of 77 patients were reviewed. For the analysis there were 112 lesions, 51 positive lesions and 61 negative lesions. 24 of the positive lesions were confirmed radiographically; 24 were confirmed at surgery and 1 was confirmed at autopsy. In 2 other patients, the In-111 pentetreotide scans were negative, but since secretin stimulated serum gastrin levels were elevated, these were considered false negative. In 7 patients with elevated serum gastrin levels, 9 In-111 pentetreotide positive areas could not be confirmed by radiographic imaging or surgery. These designated uncertain lesions and were excluded from analysis. Of these patients with positive In-111 pentetreotide scans, 36 patients had single lesion, 6 patients had 2 lesions and 1 patient had 3 lesions.

1. Intra- and inter-observer variability

Analysis of repeat readings of 136 image sets from 17 patients showed consistent interpretation with no significant intra-observer variability ($p>0.05$). Inter-observer agreement was substantial (kappa value; 0.56 - 0.71, $p<0.01$).

2. ROC Curve Analysis

4 versus 24 hour images: Table 1 shows the AUC (area under the curve) of the ROC curve for each imaging method. The 4 hour AUCs were always greater than the 24 hour AUCs, but the differences were not significant.

Table 1. Comparison of the areas under ROC curves of In-111 pentetreotide imaging: 4 versus 24 hours images

Image Set		4 hours AUC*	24 hours AUC*
Whole Body			
Planar	Abdomen	0.82	0.80
SPECT	Orthogonal	0.94	0.89
SPECT	Reprojected	0.87	0.82
SPECT	Combined	0.94	0.90

2-tailed p value is not significant.

* AUC: Area Under ROC (Receiver Operating Characteristic) Curve

SPECT versus Planar images: A comparison of orthogonal SPECT images, reprojected SPECT images and planar images is shown in Table 2. At both 4 and 24 hours the AUC's for the orthogonal SPECT orthogonal images were greater than for the planar spot images, but the difference between the two imaging methods was significant only at 4 hours (0.94 vs 0.82, $p<0.05$). The AUC's for the reprojected SPECT images at both 4 and 24 hours were also greater than the planar spot images but these were not significantly different.

Table 2. Comparison of the areas under ROC curves of In-111 pentetreotide imaging: SPECT versus planar abdominal images 2-tailed p value in parenthesis.

Image Set	Orthogonal AUC*	Reprojected AUC*	Planar AUC*
4 hours	0.94 (<0.05)	0.87 (ns†)	0.82
24 hours	0.89 (0.09)	0.82 (ns†)	0.81

* AUC: Area Under ROC (Receiver Operating Characteristic) Curve

† ns: non-significant

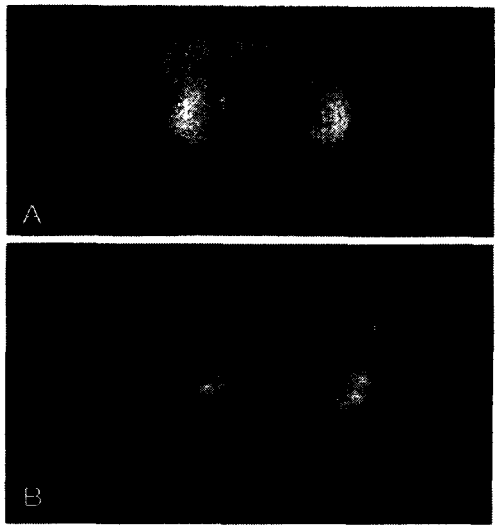

Figure 2. Comparison 4 hours versus 24 hours Images. This figure shows the anterior view of planar abdomen images of 4 and 24 hours The abnormal lesions is noted on medial to right upper kidney at 4 hours study. But at 24 hours study, the lesion is obscured by a lot of bowel activity (A. 4 hours Image; B 24 hours Image)

3. Comparison of the Sensitivity and Specificity

4 versus 24 hours images: Table 3 shows the sensitivities and specificities of the various imaging methods and compares the results at 4 versus 24 hours. The sensitivity was always greater at 4 hours than at 24 hours, but not significant. The specificity of 4 hour imaging also tended to be greater than or the same as that of 24 hour imaging.

Table 3. Comparison of sensitivity and specificity of In-111 pentetreotide imaging : 4 versus 24 hours images

Image Set	Sensitivity		Specificity	
	4hours	24hours	4hours	24hours
Whole Body	51%	50%	100%	100%
Planar Abdomen	62%	44%	98%	94%
SPECT Orthogonal	84%	78%	89%	88%
SPECT Reprojected	75%	67%	93%	93%

The difference is not significant ($p>0.05$).

SPECT versus Planar images: In Table 4 the sensitivity and specificity of orthogonal SPECT imaging and planar imaging are compared. At both 4 and 24 hours, SPECT imaging was significantly more sensitive than whole body or planar spot imaging. At 4 hours the sensitivity of SPECT orthogonal imaging was 84% compared to 51% ($p<0.001$) for whole body imaging and 62 % ($p<0.01$) for planar imaging. At 24 hours, the sensitivity of orthogonal imaging was 78% compared to 50% whole body imaging ($p=0.06$) and 44% for planar imaging ($p<0.001$).

The specificity of planar imaging, however, was greater than that of SPECT imaging. At both 4 and 24 hours the specificity of whole body imaging was 100%. Planar imaging specificity was 98% at 4 hours and 94% at 24 hours. The specificity of SPECT orthogonal imaging was 89% ($p<0.05$ vs planar imaging) at 4 hours and 88% at 24 hours (not significantly different than planar imaging)

Table 4. Comparison of sensitivity and specificity of In-111 pentetreotide imaging : SPECT versus planar Images

Image Set	Sensitivity			Specificity		
	SPECT Orthogonal	Planar	P value	SPECT Orthogonal	Planar	P value
4hours	84%	51% WB*	<0.001	89%	100% WB*	<0.01
4hours	84%	62% Abdomen	0.01	89%	98% Abdomen	<0.05
24hours	78%	50% WB*	0.06	88%	100% WB*	ns†
24hours	78%	44% Abdomen	<0.001	88%	94% Abdomen	ns†

* WB: whole body image

† ns: not significant

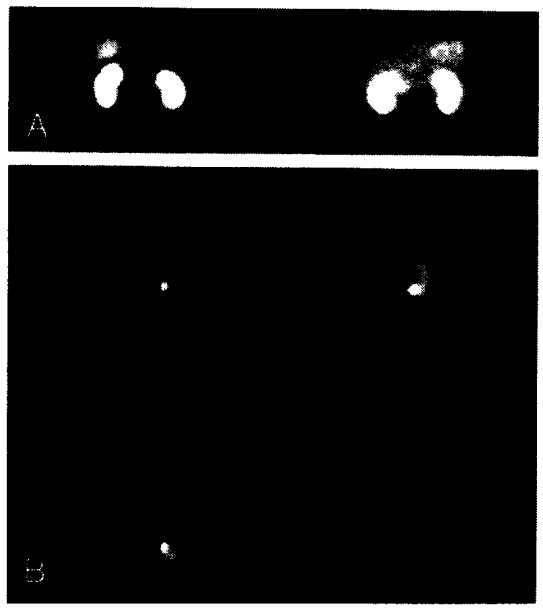

Figure 3. This figure shows the comparison between planar and orthogonal images. The planar image shows only physiologic distribution of radioactivity and was graded as 0. But the orthogonal images show the lesion anterior to left lower kidney clearly. The lesion is overlapped with renal activity on planar image. (A. Planar Images; B. Orthogonal Images)

Discussion

Our objective in this study was to compare planar vs. SPECT and 4 vs 24 hour imaging with In-111 pentetreotide scan, and to see whether we could determine the optimal imaging protocol to be used in patients with ZES. Using ROC analysis, we demonstrate that 4 hour imaging is superior to 24 hour imaging, as is SPECT when compared to planar imaging. Sensitivity and specificity are also generally greater at 4 hours than at 24 hours. SPECT significantly increased the sensitivity of In-111 pentetreotide imaging, although at the cost of a reduction in specificity. Overall, 4 hour SPECT imaging provided the greatest diagnostic efficacy in these patients.

ROC curve analysis is generally considered to be the most appropriate methodology for evaluating the diagnostic performance of medical imaging procedures.[18] Simple sensitivity and specificity calculations alone do not provide a measure of diagnostic efficacy because they depend on the arbitrary selection of a decision threshold to distinguish between positive and negative. Our sensitivity and specificity analysis used a cutoff between 2 and 3, such that lesions with grades 0-2 were scored as negative and those graded 3-4 as positive, and showed that SPECT had greater sensitivity but lesser specificity than planar imaging. Using ROC curve analysis, it was clear that SPECT provided the better diagnostic efficacy.

Previous reports have discussed the usefulness of SPECT vs. planar imaging and recommended the use of various imaging times, ranging from 4 to 48 hours.[10,19,20] However, none of these studies were performed in a blinded or randomized fashion. In the present study, blinded, randomized readings allowed us to independently compare the usefulness of the different types of image sets. However, this meant that each set was interpreted without benefit of the other images obtained in that patient. Under normal circumstances, all parts of a scan are viewed and taken into account before a final interpretation is given. Thus, the random, independent review method used in this study was somewhat artificial, and could have resulted in higher false positive and/or false negative rates than would otherwise have been obtained under normal conditions. In addition to the above, in patients with active disease who did not undergo surgery, we excluded lesions seen on In-111-pentetreotide scan which could not be confirmed radiographically. Previous work has shown that In-111 pentetreotide scan is more sensitive than ultrasound, CT, MRI, and angiography and even more sensitive than when those conventional imaging modalities are combined.[6] Therefore, it is likely that our exclusion of those unconfirmable lesions caused us to underestimate the sensitivity of In-111 pentetreotide scan. Our data shows that 4 hour images are generally superior to 24 hour images. We believe that the major reason for this is the lesser amount of bowel visible at 4 hours, since bowel activity can both obscure small lesions and cause false positive results. Adrian et al[21] reported

that 25% of patients demonstrated intestinal activity 4 hours after injection of In-111 pentetreotide, as compared to 85% of patients at 24 hours. Others have shown that tumor to background activity ratios are greater at 24 hours as compared to 4 hours, suggesting that 24 hour imaging may be preferable to 4 hour imaging.[7,11] Although we did not specifically address this issue, it should be noted that only 3 true positive lesions were better seen at 24 hours than at 4 hours in our study, whereas 13 were seen better at 4 hours. Our data also show that SPECT is of utmost importance in these patients, often detecting lesions not seen on planar imaging. This is in contrast to studies by de Kerviler et al[22] and Lebtahi et al[20], which concluded that planar imaging was superior to SPECT. One reason for these discrepant results may be that those studies were performed using single headed SPECT gamma cameras.

Conclusion

In summary, we feel that the optimal In-111 pentetreotide scan imaging protocol in patients with ZES should include 4 hour whole body planar imaging with SPECT of the abdomen. 24 hour SPECT should be obtained as necessary, usually to further evaluate equivocal lesions seen at 4 hours. Whole body planar images, while insensitive, are necessary to screen for distant metastases, and should be used to guide additional SPECT imaging. Early 4 hour imaging and SPECT should always be performed. Lastly, although our study was limited to gastrinomas, we feel that these recommendations can probably be extended to include In-111 pentetreotide scanning of other abdominal neuroendocrine tumors as well.

국문 초록

배경 In-111 pentetretide 스캔시 여러날에 걸쳐 다양하게 영상을 얻는 것은 시간과 비용을 증가시킨다. 저자들은 영상법과 영상시기를 비교하여 진단능은 유지하면서 영상과정을 단순화할 수 있는지 평가하고자 하였다.

방법 혈청 가스트린이 정상으로 완치된 가스트린 종 환자 26명과 혈청 가스트린이 상승되어 있는 51명의 환자를 합한 77명의 가스트린종 환자로부터 얻은 79 검사를 평가하였다. 222 MBq의 In-111 pentetreotide를 주사한 후 4시간과 24시간에 각각 얻은 전신 영상, 복부 평면 영상, SPECT 영상을 분리하여 분석하였다. 환자와 영상의 시간정보를 숨긴 후 무작위로 모두 541 영상 을 분석하였다. 병소를 5단계로 점수를 매겼다: 0 - negative; 1 - unlikely; 2 - possible lesion; 3 - probable lesion; 4 - definite lesion. 수신자특성곡선(ROC) 분석과 민감도, 특이도를 각각 비교하였다. 생검과 방사선학적 영상으로 112 병소(51 가스트린종, 61 음성)에 대한 최종 진단을 내렸다.

결과 4시간 영상의 곡선하 영역(AUC)이 24시간보다 컸으나 통계학적으로 유의하지는 않았다. 4, 24시간 모두에서 SPECT의 곡선하 영역이 평면 영상보다 컸다(4 hour, 0.94 vs 0.82, $p<0.05$; 24 hour, 0.89 vs 0.81, $p=0.09$). 3, 4점을 양성으로 기준을 정했을 때, 민감도는 4시간에서 24시간보다 컸으나 유의하지는 않았다. 4시간 영상의 특이도는 24시간 영상보다 크거나 같았다. 4, 24시간 모두에서 SPECT영상은 평면 영상보다 민감도가 높았으나(4 hour, 84% vs 62%, $p=0.01$; 24 hour, 78% vs 44%, $p<0.001$), 평면 영상의 특이도가 높았다(4 hour, 89% vs 98%, $p<0.05$; 24 hour, 88% vs 94%, p=ns).

결론 가스트린 종 환자에서 SPECT를 포함한 4시간 In-111 pentetrotide 영상이 가장 좋은 진단 효용성을 나타내었다. SPECT 영상은 특이도를 약간 감소시키나 민감도를 유의하게 높였다. 따라서, 가스트린 종 환자에서 In-111 pentetreotide 주사후 SPECT를 포함한 4시간째 영상이 선별 검사로 충분할 것으로 사료된다.

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