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Experience with Esophago-Gastro-Intestinal Transit Scintigraphy – Initial 229 patients: Multiple Regions of Dysmotility are Common

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Running Head: Comprehensive GI Transit Scintigraphy

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Key words: gastric scintigraphy, gastrointestinal transit, intestinal transit scintigraphy

ABSTRACT

Objective: The purpose of this investigation was to review our experience with our "Comprehensive Gastrointestinal Transit Study" in the first 229 patients. This scintigraphic study analyzes motility of the entire gut, from esophagus through the rectosigmoid colon.

Methods: Data were reviewed for our first two years of experience (184 females, 45 males), age 20-79 (mean 44±16) with this exam. Patients were referred with symptoms suggestive of a motility disorder. Patients first swallowed In-111 DTPA in water for the esophageal swallow study, then 300 cc for a 30 minute In-111 water only study, followed by 120 cc of In-111 water simultaneous with the solid standardized Tc-99m egg substitute meal. Images and quantification were obtained for esophageal transit, water-only gastric emptying, water with solid gastric emptying, small bowel, and colonic transit.

Results: Of the 229 patient studies, 45 (20%) were normal. The remaining 184 (80%) had at least one region of dysmotility, for a total of 336 regions of abnormal motility. A single region of dysmotility was seen in 92 patients (50%), two regions in 50 (27%), three regions in 26 (14%), four regions in 12 (7%), and five regions in 4 (2%) of dysmotility. There was a poor correlation between the results of water only study and water with the solid meal. Three different patterns of delayed colonic transit were seen. Patient symptoms were often not predictive of the scintigraphic findings.

Conclusion: This study highlights the frequent occurrence of dysmotility in more than one region of the gastrointestinal tract in patients with a suspected motility disorder and the frequent concurrence of both upper and lower tract dysmotility in the same patients. It provides information to referring physicians regarding which motility disorders may be causing the patient symptoms, why the patient is or is not responding to their present therapy, and if and what additional workup and therapy may be needed.

INTRODUCTION

Gastric emptying scintigraphy is a commonly requested nuclear medicine study at most imaging centers because it provides important functional information regarding gastric motility not available from other methodologies. However, there has been a concern that only 30-60% of symptomatic patients with clinically suspected functional gastroparesis have an abnormal radionuclide gastric emptying study (*1-3*).

More recently, there has likely been an increase in the positivity rate of gastric emptying studies, for two reasons. First, a consensus recommendation for a 4 hour gastric emptying study was published in the nuclear medicine and gastroenterology literature and is now standard (*4,5*). The four hour study has proven to be more sensitive for detection of gastroparesis than shorter length studies, e.g., 2 hours, commonly used in the past (*6,7*). A 30% increase in positivity has been reported at 4 compared to 2 hours (*8*). Furthermore, the addition of a clear liquid (water) emptying study increases the sensitivity for detection of gastroparesis. Multiple investigations have found that of patients referred with a suspected gastric motility disorder who have a normal solid gastric emptying study, 25-30% will have delayed liquid emptying (*9-12*).

However, a gap still persists in our ability to detect abnormal emptying in patients referred with symptoms suggestive of a gastric motility disorder. While gastric dysmotility symptoms are commonly associated with post-prandial upper abdominal symptoms of nausea, vomiting, and abdominal discomfort, and intestinal disorders are most commonly associated with lower abdominal pain, bloating, diarrhea and constipation, there may be overlap of upper and lower intestinal dysmotility symptoms (*13-15*). Thus, the addition of small and large bowel intestinal transit scintigraphy to the gastric emptying study may be of value, by confirming or excluding dysmotility in these additional regions and pinpointing the regions of the gastrointestinal tract causing the patient's adverse symptoms.

"Whole gut transit" radionuclide studies that combine gastric emptying and small and large bowel transit studies into a single study have been described and are routinely performed at a few centers (*16-17*)**.** We have been providing our "Comprehensive Esophago-Gastro-Intestinal transit" study since 2014. Our unique methodology has been previously published, along with our normal values, and our initial clinical experience (*18*).

In the first two years of offering this test, 229 patients completed the comprehensive study. This manuscript describes the results of this scintigraphic study for those patients. Of particular interest was that many patients were found to have abnormal motility at more than one site and not infrequently in both the upper and lower gastrointestinal tract.

MATERIALS AND METHODS

Patient Population

The institutional review board (IRB) at Johns Hopkins University approved this retrospective study and the requirement to obtain informed consent was waived.

The patients described in this retrospective review completed the Esophago-Gastro-Intestinal Transit Study between August 2014 and November 2016, and included 45 males and 184 females; age 20-79 (mean 44±16). The majority of patients were referred from the Johns Hopkins Gastrointestinal Motility Clinic, some by other Hopkins gastroenterologists, and a minority from the rheumatology clinic. Patients usually had either predominantly lower abdominal complaints (49%), a combination of upper and lower abdominal complaints (31%), and/or a poor response to their present treatment after having had a prior radionuclide gastric emptying study (20%).

Scintigraphic Methodology

All patients were asked to fast overnight prior to beginning the study. The studies were started on a Monday morning. Patients were asked not to take laxatives the day prior to or for the duration of the study. Other medications that might affect gastrointestinal motility were withheld for at least 3 days prior to and during the study.

The first day of the study included an esophageal transit study, then liquid-only (water) gastric emptying, followed by simultaneous liquid and solid gastric emptying, and then small bowel transit, for a total imaging time of six hours. After this first day of imaging, there were no food or activity limitations for the duration of the study. Imaging was subsequently performed at 24, 48, and 72 hours to quantify colonic transit, requiring only one 5 minute anterior and posterior morning image. Our methodology and quantification are detailed in Table 1.

The abnormal values used for this study were derived from our prior publication (*18*): Esophageal swallow (< 83% transit of counts 10 sec after maximum counts), liquid only gastric emptying (t1/2 > 25 min), liquid with solid meal (< 39% emptying at 1 hour), solid gastric emptying (< 90% emptying at 4 hours), small bowel transit (< 49% arrival at the ileocecal valve by 6 hours), and large bowel transit (< 67% by 72 hours).

RESULTS

Of the 229 patient studies (184 females, 45 males), 45 (20%) were interpreted as normal. The remaining 184 patients (80%) had at least one region of dysmotility, with a total of 336 abnormal regions. A single region of dysmotility was seen in 92 patients (50%) (Table 2). The regions involved were the esophagus (6 patients) (Fig. 1), gastric liquid-only (10 patients) (Fig. 2 A), gastric liquid with the solid meal (1 patient) (Fig. 2 B), solid gastric emptying (6) (Fig. 2 C), small intestine (10) and large intestine (59 patients) (Figs. 3, 4, 5) (Table 2).

Two regions of gastrointestinal dysmotility were detected in 50 patients (27%) (Table 3), 3 regions in 26 patients (14%) (Table 4), 4 regions in 12 patients (7%) (Table 5), and 5 abnormal motility regions were detected in 4 patient (2%) (Table 6). Forty-three of 49 patients with solid meal gastroparesis had additional regions of gastrointestinal dysmotility, (Tables 3-6).

The liquid-only and the liquid with the solid gastric meal studies did not correlate well with each other. The liquid-only study was positive in 45 patients. The liquid with the solid meal was positive in 32 patients. Both were positive in the same patients in only 14 patients.

Delayed transit was the predominant finding in the patients with dysmotility. Rapid transit was less common. Rapid transit was not seen in the esophagus, present only once with liquid-only gastric studies, 3 times in patients where liquid was combined with solid food, 6 times with solid gastric emptying, 7 times in the small bowel, and 3 times with colonic transit.

In the 15 patients with systemic sclerosis, all but two had delayed esophageal transit. These patients also had various other motility abnormalities. Eight had delayed solid meal emptying. Six had delayed colonic transit, and nine had multiple regions of dysmotility, including liquid-only, liquid with solid gastric emptying, and small bowel.

Three patterns were seen in patients with quantitatively delayed colonic transit (Figs. 3-5). Some patients had images showing colonic transit throughout the entire colon and rectosigmoid, but with no or little excretion from the body (62%), while others had proximal regional abnormal transit, that is, the radiotracer was seen transiting only to the ascending, transverse, or splenic flexure (31%). A few patients had delayed excretion manifested by retention in the rectosigmoid region (7%).

Some patient's symptoms predicted the scintigraphic findings, e.g., in the colon, those with symptoms of diarrhea often had rapid colonic transit, while those with constipation often had delayed transit. However, in other patients, symptoms did not predict the scintigraphic findings. The majority of patients in this study had both upper and lower gastrointestinal symptoms. While patients with delayed gastric emptying often had typical symptoms of dyspepsia, bloating, early satiety, and weight loss, many also had constipation (83%) and diarrhea (17%). Patients with delayed liquid only studies often had symptoms of dyspepsia, nausea and vomiting, but many also had constipation and/or diarrhea. With small bowel delayed transit, abdominal cramping was the dominant symptom (90%), but many also complained of constipation (75%). In patients with more than one region of dysmotility, symptoms overlapped and often were not predictive of the scintigraphic findings. Diffuse dysmotility was seen predominantly in patients with diabetic gastroparesis and poor glycemic control

Patient management changed in patients with positive studies, particularly those with multiple regions of dysmotility. A change in management occurred in 17% of patients with one region of dysmotility, in 34% of patients with 2 regions of dysmotility, 38% with 3 regions, and > 50% of patients with 4-5 regions of dysmotility.

DISCUSSION

Various radionuclide solid gastric emptying methodologies have been used over the years at different imaging centers, with different study length, meals, quantification, and normal values. However, a specific standardized 4 hour protocol published by Tougas, et al., with multicenter normal values based on 123 subjects, is now recommended (*19*); Consensus Recommendations have been published in both the nuclear medicine and gastroenterology

literature (*20,21*). At a few centers, combined solid and liquid gastric emptying studies are routinely performed (*22,23*). Small and large intestinal transit studies have been described and are performed at a limited number of imaging centers, often using different methodologies, radiotracers and normal values (*24-27*).

"Whole gut transit" scintigraphy was first described by the Mayo Clinic in 1995 and subsequently at Temple University in 2000 (16,17). This terminology refers to combining gastric and small and large intestinal transit into one study. The Mayo Clinic uses a radiopharmaceutical not approved by the Food and Drug Administration, a pH-sensitive methacrylate-coated capsule containing In-111 labeled activated charcoal particles. The capsule dissolves upon reaching the alkaline terminal ileum, releasing the radionuclide. It can be combined with a Tc-99m labeled solid gastric emptying meal to examine both the upper and lower gastrointestinal tract (*28*). Temple uses In-111 DTPA in water combined with a solid meal for their whole gut studies (*16*). The utility of In-111 DTPA is that it is not absorbed in the gastrointestinal tract and has a relatively long half-life (2.8 days), allowing for the 3-4 day imaging study. The rate of transit of In-111 DTPA correlates well with both radiopaque markers and I-131 cellulose (*29,30*).

At Johns Hopkins, we have been performing our Comprehensive Esophago-Gastro-Intestinal Scintigraphy since 2014. We published our methodology and initial experience in 18 patients in 2015 (*18*). This methodology varies from other published "whole gut" scintigraphic methods in several ways. First, we perform an initial esophageal transit study. Then, we study liquid gastric emptying in two ways, clear liquid (water) only, followed by simultaneous ingestion of additional In-111 water with the solid meal. Our quantitative method for colonic transit is also different from prior described methods. We do not calculate a geometric center of activity as some centers have described, but rather we calculate the percent transit, i.e., the amount of activity that has left the body at 24, 48, and 72 hours, calculated similar to gastric emptying. In addition, we provide a visual description of the extent of transit of the radionuclide at each time point. The geometric center method requires drawing 5-7 regions of interest for the colon. It is time-consuming and invariably different ROIs are drawn by different technologists and physicians. We have shown that the two different methods correlate quite well (*18*).

The reason that we include two different liquid studies, a 30-minute water (300 cc) only study with In-111 DTPA followed by In-111 water (120 cc) ingested simultaneously with the

solid meal and measured at time 0, 1, 2, 3 and 4 hours, is that past our experience suggested that the two methods often provided different results. This was confirmed in this investigation and suggests to us a different pathophysiology for the two methods, although the explanation for this difference is uncertain and requires further study.

Demand for our comprehensive study continues to grow so that we are now doing 5 to 7 studies a week or approximately 250 studies a year. A bias in our referral pattern may be that many patients are referred with suspected lower gastrointestinal disease, others because of symptoms suggestive of both upper and lower gastrointestinal tracts, and others because of poor therapeutic response to gastroparesis reported on a prior gastric emptying study.

This paper highlights the frequent occurrence of upper and lower gastrointestinal transit motility disorders in the same patients. A report from Temple University in 2000 describing their whole gut transit scintigraphy study reported that "some patients had a diffuse dysmotility disorder of the gastrointestinal tract" (*15*). This was similarly observed by Stivland, et al. (*31*), but neither publication specified its frequency, or that dysmotility could occur in multiple separate regions of the gastrointestinal tract, e.g., stomach and colon. Studies with the wireless motility capsule have also reported that some patients have a diffuse motility disorder, but also that patients may have dysmotility in more than one region of the gastrointestinal tract, upper and lower, and the clinical presentation is often not predictive of regional transit delays (*32*). Different patterns of delayed colonic transit have been previously described, including a diffusely delayed pattern, delay limited to the proximal colon, and rectosigmoid dysfunction (*33*). This is the first scintigraphic study to describe and quantify these three patterns of colonic dysmotility.

CONCLUSION

Esophago-gastro-intestinal transit scintigraphy provides valuable information to referring physicians regarding which motility disorder(s) may be causing their patients' symptoms, why their patient is or is not responding to their present therapy, and if and what additional workup and treatment may be needed. Most importantly, this is the first scintigraphic study which has reported that many patients have dysmotility in more than one region of the gastrointestinal tract, helping to explain patient symptoms or poor response to therapy.

KEY POINTS

QUESTION: The aim of this investigation was to determine the clinical value of our comprehensive esophago-gastro-intestinal transit scintigraphic study in our first 229 patients.

PERTINENT FINDINGS: Of the 229 patients, one region of dysmotility in the gastrointestinal tract was detected in 50% of patients, 2 regions in 27%, 3 in 14%, 4 in 7% and 5 regions in 2%. Upper and lower gastrointestinal dysmotility was commonly seen in the same patient.

IMPLICATIONS FOR PATIENT CARE: This study permits referring physicians to appreciate which motility disorders may be causing the patients' symptoms, why a patient is or is not responding to present therapy, and what additional workup or therapy may be needed.

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FIGURE LEGENDS

Figure 1. Delayed esophageal transit. (Above) Single 0.5 sec dynamic frame for esophageal transit showing retained activity in the esophagus and some transit to stomach. (Below) Time-activity curves show poor transit in the middle (yellow) and lower third of the esophagus (blue), but better emptying in the lower third. Percent emptying was 43% (abnormal <83%).

Figure 2 A, B, C. Abnormal clear liquid only emptying, normal liquid with solid emptying, and normal solid emptying in the same patient. A**:** Clear liquid only shows poor emptying with delayed time-activity curve and half-time of clearance of 61 minutes (normal less than 25 min). B: Clear liquid ingested with solid meal shows a normal multi-exponential pattern of clearance. C: Solid meal emptying is normal with 95% emptying at 4 hours.

Figure 3. Entire colon delayed transit. Regions-of-interest are drawn around the activity at 360 min, 24, 48, and 72 hours in the anterior and posterior views. The activity at 360 min (upper left) is mostly at the ileo-cecal value. It used as the denominator for calculation of the percent colonic transit at each subsequent time interval. The percent transit (excretion from the body) is 0%. Image review shows transit of activity to the descending colon on the anterior view and to the rectosigmoid on the posterior view.

Figure 4. Proximal colon delayed transit. The anterior images are shown at all imaging time points. In the immediate image, the stomach is seen superiorly. At 60 min to 180 minutes, most of the activity is in the proximal small bowel. By 240 minutes, activity is in the distal small bowel. By 360 minute, most of the activity is at the ileal-cecal valve. A ROI is placed around this activity to quantify small bowel transit (activity that has reached the ileocecal value and beyond at 360 minutes). At 24 hours, most of the activity is in the cecum. At 48 hours, the activity has reached the transverse colon. At 72 hours the activity distribution is similar; most is more distal, although it has not reached the splenic flexure. Figure 5 shows quantification for this patient.

Figure 5 Colonic images/quantification from patient in Fig. 4 (posterior views not shown but used for geometric mean quantification) shows no transit (0 percent) out of the body and a regional transit delay. The time-activity curve rises slightly due to imperfect attenuation correction. The blue dotted horizontal line represents 50% emptying.

Table 1 Methodology for Esophago-Gastro-Intestinal Transit Study

Patients are instructed to fast overnight prior to the exam, not to eat or drink anything further on day one. Normal eating can resume on days 2, 3, and 4. Laxatives are prohibited on exam days until completed.

Esophageal transit –	In-111 DTPA 3.7 MBq in 15 ml water 0.5 second frames x 60 Quantification: % transit (percent of counts 10 sec after maximum counts
Liquid-only gastric emptying –	In-111 DTPA 3.7 MBq in 300 ml water 1 min frames x 60 acquired in left anterior oblique view Quantification: Half-time of emptying and fitted t1/2
Combined Liquid/Solid gastric emptying –	In-111 DTPA 3.7 MBq in 120 ml water and the consensus standardized egg-white solid meal ingested over 10-15 minutes 1.0 min anterior and posterior images immediately, and at 1, 2, 3, and 4 hours after meal ingestion Quantification: Liquid: % emptying at 1, 2, 3, and 4 hours and emptying half-time. First hour value used.
Solid gastric emptying –	Tougas, et al. protocol (19). 74 MBq Tc-99m SC labeled egg white meal. GM attenuation correction and % emptying at 0, 1, 2, 3, and 4 hours
Small intestinal transit index –	1 min anterior and posterior images on In-111 photopeaks at 5 and 6 hours. Geometric mean attenuation correction. Quantification at 6 hours: % activity reaching the region of ileocecal valve and beyond.
Large intestinal transit –	5 min anterior/posterior images on In-111 photopeaks acquired in AM at 24, 48, and 72 hours. Geometric mean attenuation correction. Quantification: % activity present at 6 hours that transits out of the body at 24, 48, and 72 hours. Also a visual description of extent of transit at each time interval is reported.

Table 2. Distribution and frequency of 1 abnormal motility region in patients

Region of GI tract involved	Esophagus	Stomach Liquid only	Stomach Liquid with solid	Stomach Solid	Small bowel	Colon/Recto -sigmoid
Total patients 92	6	10	1	6	10	59

Table 3 Distribution and frequency of patients with 2 abnormal regions of motility

Number of Patients	Esophagus	Stomach Liquid only	Stomach Liquid With solid	Stomach Solid	Small bowel	Colon/Recto-sigmoid
2	X	X				
2	X			X		
3	X				X	
10	X					X
1		X		X		
1		X			X	
9		X				X
3			X	X		
1			X		X	
4			X			X
1				X	X	
10				X		X
3					X	X
50 patients						

Table 4 Distribution and frequency of patients with 3 abnormal regions of motility

Patients	Esophagus	Liquid only	Liquid With solid	Solid	Small bowel	Colon/Recto-sigmoid
3	X	X		X		
2	X	X				X
4	X			X		X
4	X				X	X
4		X	X			X
3		X			X	X
2			X	X	X	
4			X	X		X
Total patients 26						

Table 5 Distribution and frequency of patients with 4 abnormal regions of motility

Patients	Esophagus	Liquid only	Liquid with solid	Solid	Small bowel	Colon/Recto-sigmoid
1	X	X		X		X
1	X	X	X	X		
1	X	X			X	X
1		X	X	X	X	
1	X	X	X		X	
2	X		X	X		X
1		X	X	X	X	
1		X	X		X	X
1			X	X	X	X
1	X		X	X	X	
1		X		X	X	X
Total patients 12						

Table 6 Distribution and frequency of patients with 5 abnormal regions of motility

Patients	Esophagus	Liquid only	Liquid with solid	Solid	Small bowel	Colon/Recto-sigmoid
1		X	X	X	X	X
3	X	X	X	X		X
Total patients 4						

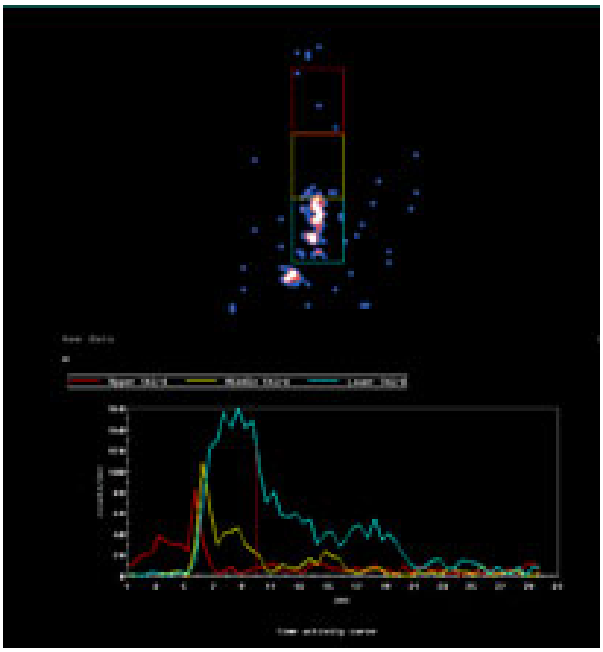
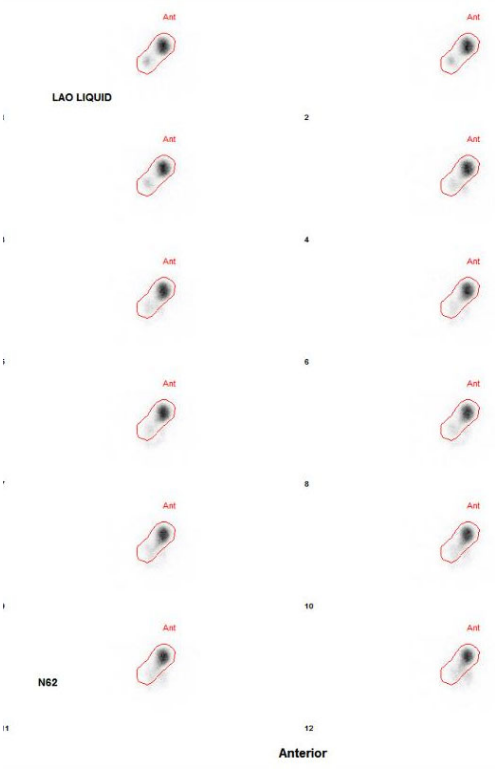
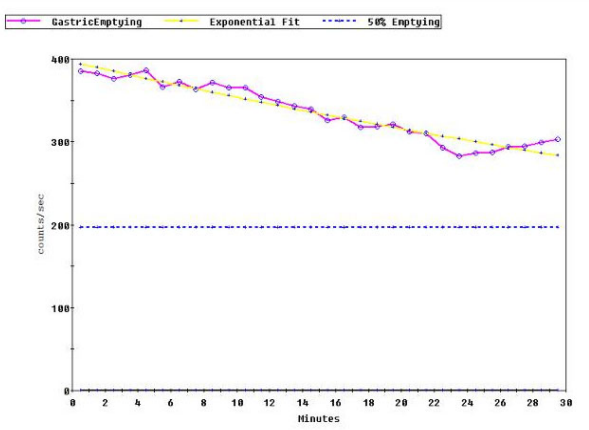


Figure 1. Delayed esophageal transit. (Above) Single 0.5 sec dynamic frame for esophageal transit showing retained activity in the esophagus and some transit to stomach. (Below) Time-activity curves show poor transit in the middle (yellow) and lower third of the esophagus (blue), but better emptying in the lower third. Percent emptying was 43% (abnormal <83%).

Fig. 2 A





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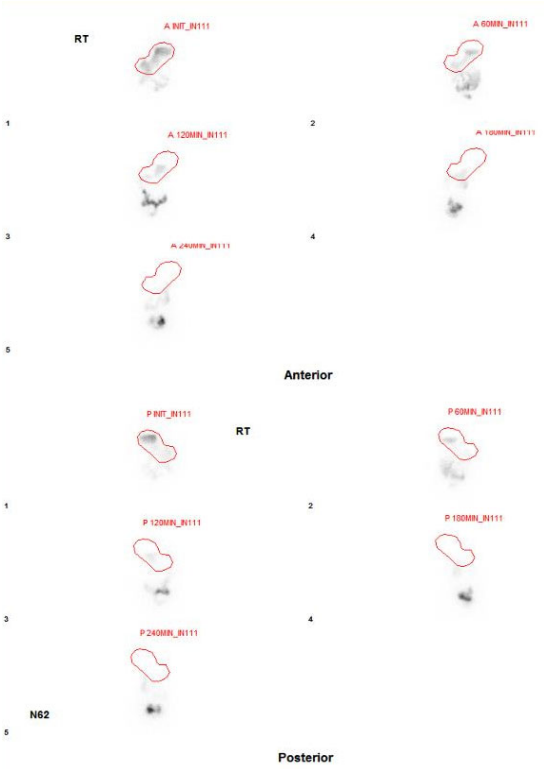
Raw Data T 1/2 (min) = None

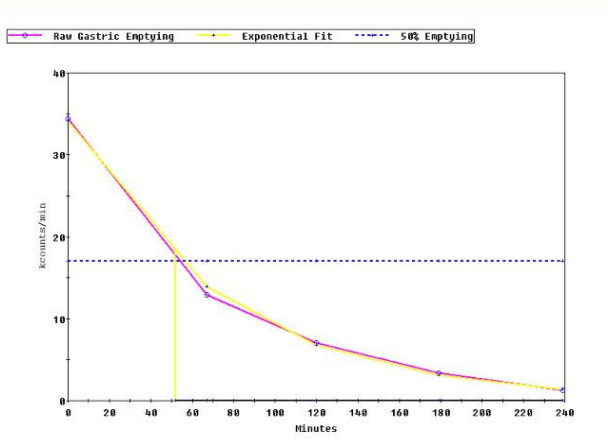
In-111

** Anterior Only

Frame/Time		Fit / Raw % Empty		KCounts/sec**
3	2.5	2	2	0.377
6	5.5	6	5	0.366
9	8.5	9	3	0.372
12	11.5	12	8	0.354
15	14.5	15	12	0.340
18	17.5	18	18	0.318
21	20.5	20	19	0.312
24	23.5	23	26	0.283
27	26.5	26	24	0.294
30	29.5	28	21	0.303

Fig. 2 B





Decay Corrected by Xeleris: Yes

Expon Fit T 1/2 (min) = 51.65

Raw Data T 1/2 (min) = 53.53

Frame/Time		Fit / Raw % Empty		In-111 ** Geometric Mean KCounts/min**	Anterior / Post	
1	0.0	0	0	34.46	42.00	28.28
2	67.0	59	63	12.89	16.81	9.89
3	120.0	80	80	7.06	9.90	5.03
4	179.0	91	90	3.42	5.55	2.11
5	239.0	96	96	1.28	1.55	1.06

Fig. 2 C

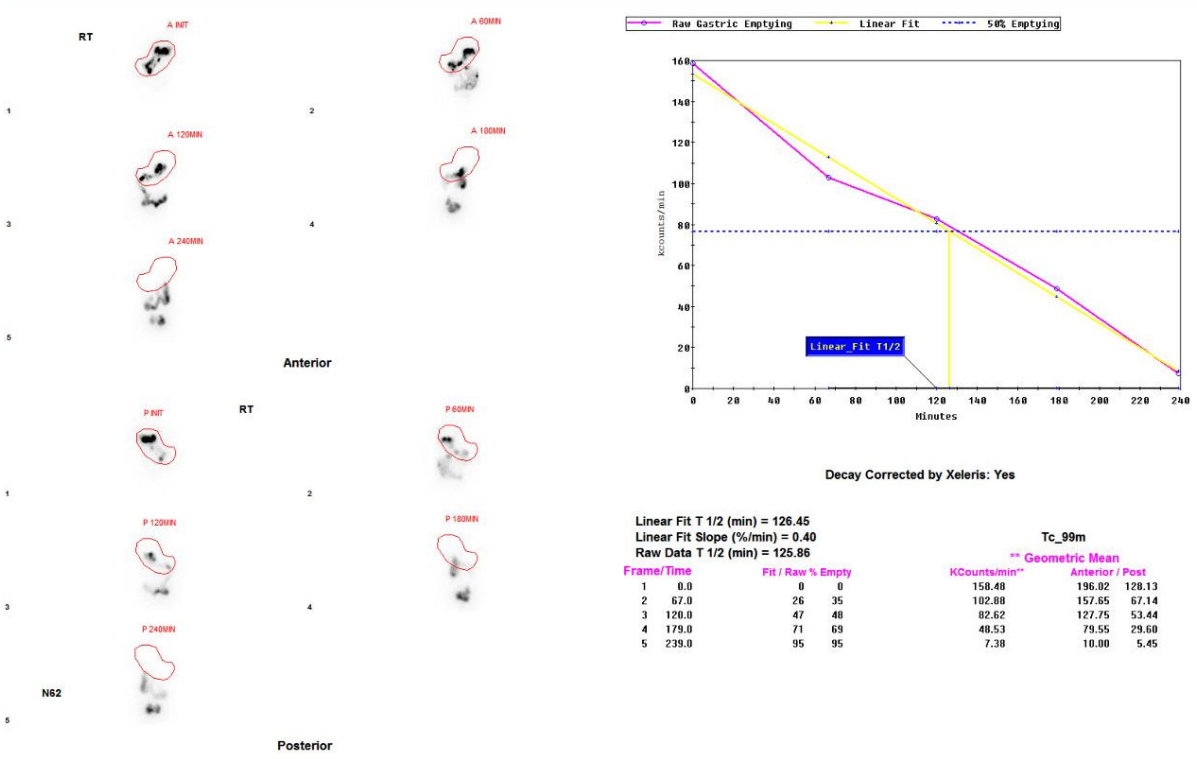


Figure 2 A, B, C. Abnormal clear liquid only emptying, normal liquid with solid emptying, and normal solid emptying in the same patient. A**:** Clear liquid only shows poor emptying with delayed time-activity curve and half-time of clearance of 61 minutes (normal less than 25 min). B: Clear liquid ingested with solid meal shows a normal multi-exponential pattern of clearance. C: Solid meal emptying is normal with 95% emptying at 4 hours.

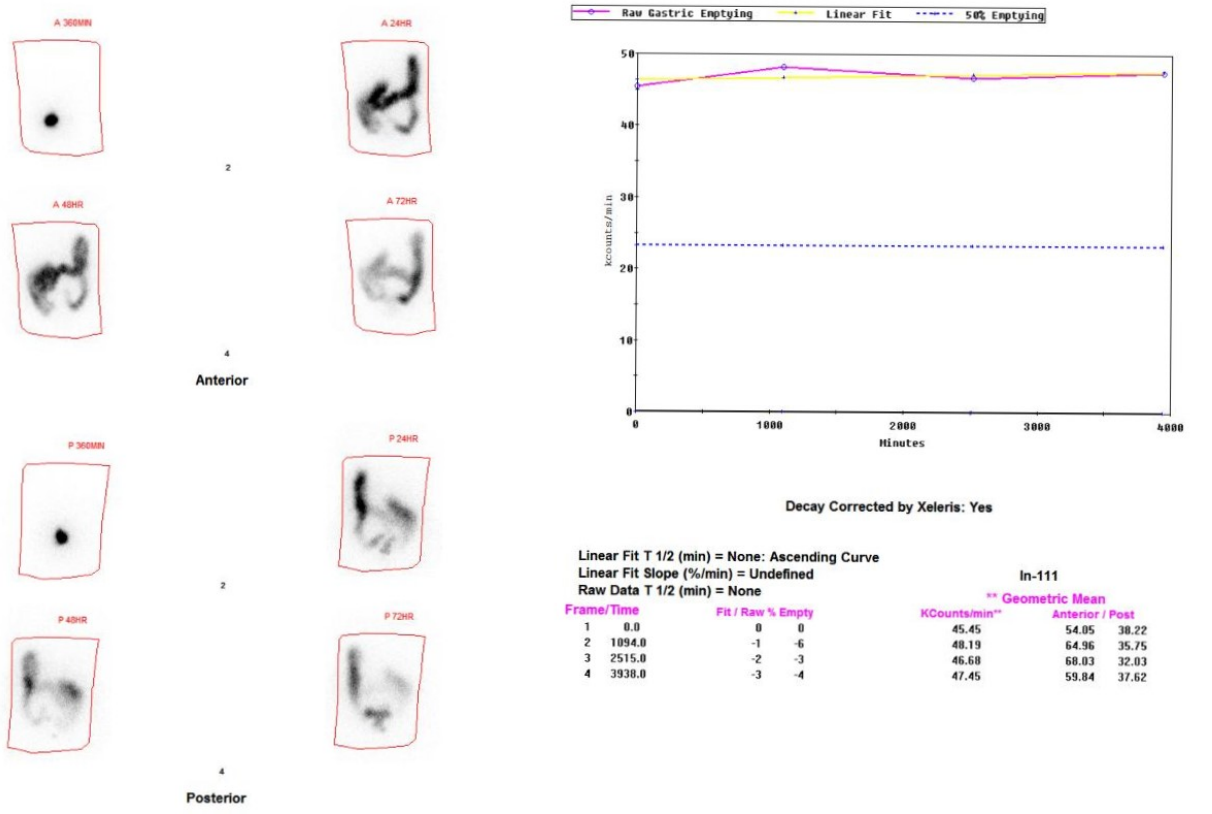


Figure 3. Entire colon delayed transit. Regions-of-interest are drawn around the activity at 360 min, 24, 48, and 72 hours in the anterior and posterior views. The activity at 360 min (upper left) is mostly at the ileo-cecal value. It used as the denominator for calculation of the percent colonic transit at each subsequent time interval. The percent transit (excretion from the body) is 0%. Image review shows transit of activity to the descending colon on the anterior view and to the rectosigmoid on the posterior view.

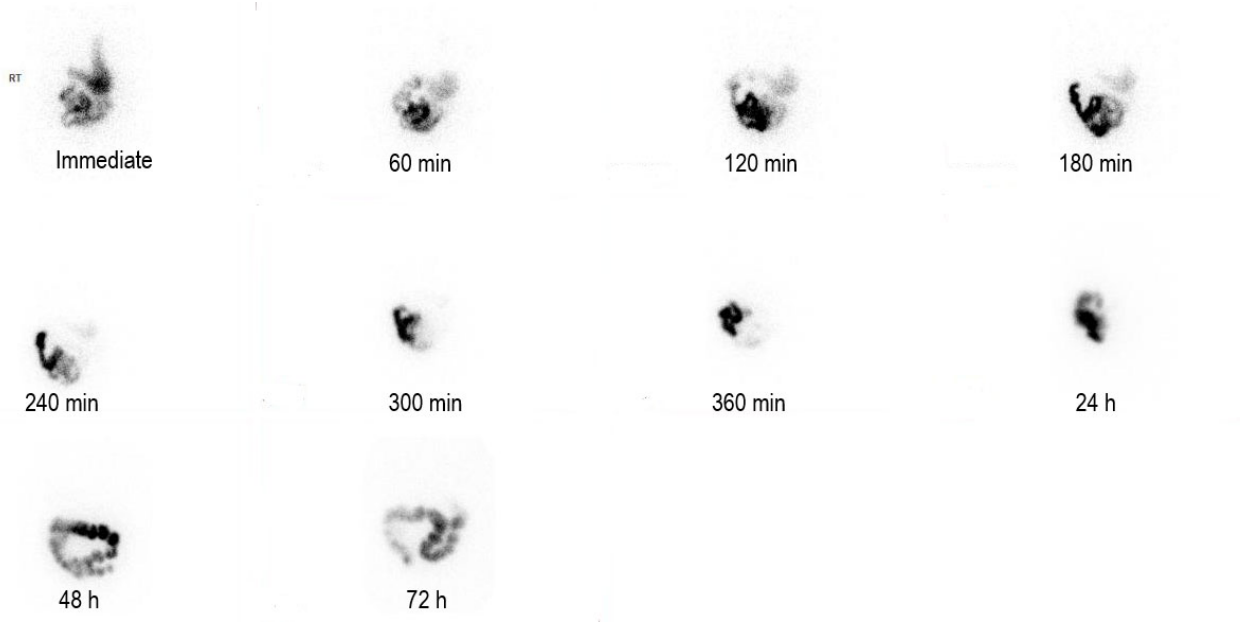


Figure 4. Proximal colon delayed transit. The anterior images are shown at all imaging time points. In the immediate image, the stomach is seen superiorly. At 60 min to 180 minutes, most of the activity is in the proximal small bowel. By 240 minutes, activity is in the distal small bowel. By 360 minute, most of the activity is at the ileal-cecal valve. A ROI is placed around this activity to quantify small bowel transit (activity that has reached the ileocecal value and beyond at 360 minutes). At 24 hours, most of the activity is in the cecum. At 48 hours, the activity has reached the transverse colon. At 72 hours the activity distribution is similar; most is more distal, although it has not reached the splenic flexure. Figure 5 shows quantification for this patient.

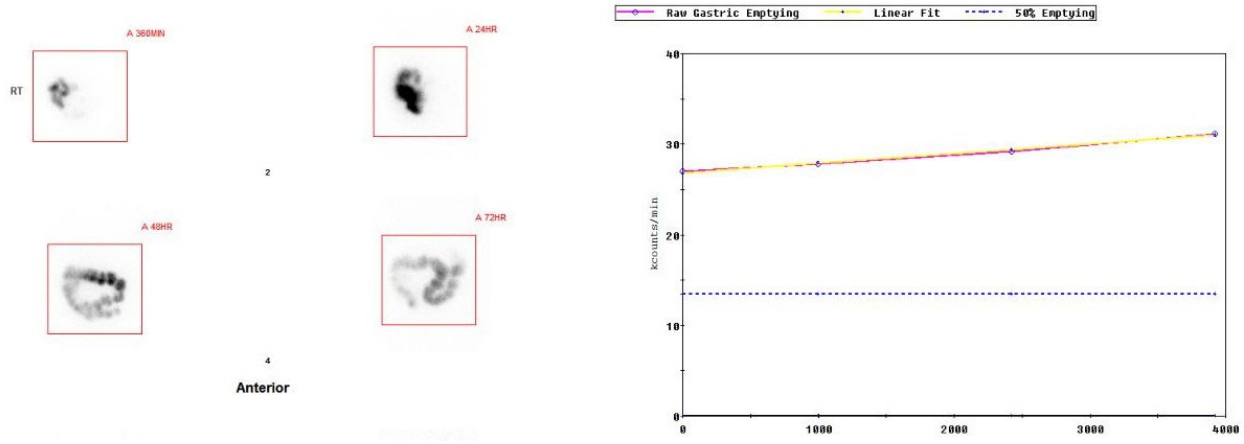


Figure 5. Colonic images/quantification from patient in Fig. 4 (posterior views not shown but used for geometric mean quantification) shows no transit (0 percent) out of the body and a regional transit delay. The time-activity curve rises slightly due to imperfect attenuation correction. The blue dotted horizontal line represents 50% emptying.