Optimal timing of imaging in gastric emptying scintigraphy for the detection of delayed emptying

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Keywords: Gastric emptying scintigraphy
- Delayed gastric emptying
- Gastroparesis

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Received:
1 December 2021
Accepted revised:
17 December 2021

Abstract

Objective: The purpose of this study was to evaluate a standard 4-h imaging protocol for gastric emptying scintigraphy (GES) in detecting delayed gastric emptying (GE). **Subjects and Methods:** Gamma camera imaging was performed in the anterior and posterior views at 0, 0.5, 1, 1.5, 2, 2.5 and 4-h as per established Miami method (MIA) and National Standard Protocol (NSP), in accordance with the consensus guidelines of the ANMS/SNM [SNMMI] Societies. Patients (N=1002) received a standardized solid meal radiolabeled with 1mCi of technetium-99 (^{99m}Tc) sulfur colloid. Quantitative analysis was performed using geometric mean calculation of decay-corrected counts at each imaging time point, expressed as percent emptying or retention. **Results:** In our patient cohort, 21% had delayed GE at 4h, whereas 79% had normal emptying with less than 10% retention at 4h. There was a 25% increase in delayed GE studies at 4h versus 2h. From those patients who had delayed GE at 2h, 30% normalized at 4h, while 10% of patients with normal GE at 2h became delayed at 4h thus indicating that more studies changed from abnormal to normal than from normal to abnormal at 4h. Greater than 90% GE was found in 9% of patients at 2h and 25% of patients at 2.5h and this persisted at 4h. The study at 2h as compared with 4h, had 56% sensitivity, 95% specificity, 70% PPV and 91% NPV. **Conclusion:** The 4-h imaging was very important in detecting cases that were delayed at 2h but normalized at 4h, and also cases with normal GE at 2h that became abnormal at 4h. These findings support the ANMS/SNM [SNMMI] recommendations. Gastric emptying value 90% at 2.5h can be used as threshold in predicting normal GE and the study could be terminated without additional imaging.

Hell J Nucl Med 2021; 24(3): 234-238

Published online: 28 December 2021

Introduction

Radionuclide gastrointestinal imaging studies provide unique functional and quantitative diagnostic information non-invasively [1, 2]. Gastric emptying scintigraphy (GES) was introduced more than 50 years ago [3] and remains the standard method for comprehensive assessment of gastric emptying (GE) and/or motility [2, 4] in patients of all ages. The test utilizes a radiolabeled physiologic meal, either solid or liquid, that enables scintigraphic imaging to measure the gastric counts and assess the volume of the meal remaining in the stomach over time, without any assumptions of its geometric shape [2]. Gastric emptying scintigraphy can be used as a baseline test to determine delayed, normal or rapid GE, while serial studies can be used to assess the response to treatment [1].

Gastroparesis (GP) is a motility disorder of the stomach with delayed food emptying from the stomach without any evidence of mechanical obstruction [5]. The clinical manifestation of GP may include postprandial symptoms of fullness, bloating, early satiety and abdominal pain along with the more common and debilitating symptoms of nausea, vomiting and weight loss. This disorder is more strictly characterized by a delay in GE with an absence of a mechanical obstruction. Objective evidence of delayed GE as seen on scintigraphy, with classic symptoms as described above and poor digestion are the hallmarks of GP [2, 6, 7].

Although GES is considered an effective method for assessing GE, historically it has been underutilized by clinicians due to lack of protocol standardization and universal acceptance of normal values [2, 8, 9].

There has been great variability in GES protocolsin terms of the type and content of the meal, acquisition parameters including patient positioning, frequency of imaging time points, total duration of imaging [2] and quantitative analysis with reported results [6]. Some recent studies from the National Institute of Health's (NIH) gastroparesis research consortium have maintained that patients with GP and functional dyspepsia -a disorder of brain-gut interaction rather than a true motility disorder - are virtually indistinguishable by symptoms or GES findings over time, further complicating the literature [9]. Other studies maintain that when scintigraphy is performed correctly, patients with GP can be differentiated from functional etiologies [9,10]. Some even propose that scintigraphic measurement of gut transit predicts patients most at risk of repeated ER visits and hospitalizations, i.e. those with higher morbidity associated with GP based on severity of GE delay [11].

In 2008, the Society of Nuclear Medicine (SNM), currently Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the American Neurogastroenterology and Motility Society (ANMS) published consensus recommendations for GES [2] based on a standardized low-fat egg-white meal of specific caloric content, and, a standard imaging protocol with time points at 0,1,2 and 4h after meal ingestion. The ANMS/SNM [SNMMI] consensus statement aimed to facilitate uniformity in the methodology with the ability to generate credible normal vs. abnormal results, enabled the comparison of GE data from various facilities [12] and overall enhance the clinical utility of GES.

The normal GE values supported by the ANMS/SNM [SNMMI] statement were derived by a multi-institutional and multi-national study based on a large number of normal subjects published by Tougas et al. (2000). This study defined delayed GE in terms of gastric retention to be >90% at 1 h, >60% at 2h, and >10% at 4h [2, 6]. An important aspect of Tougas et al.'s (2000) study is extending the duration of the study to 4h as a more sensitive time point in detecting delayed GE as compared to other protocols that imaged only up to 2h [6,13,14]. The 4-h finding was supported by a number of other studies as well [15-17].

In our Institution, based on our Miami Method (MIA), we have been using for over 25 years a GES protocol with imaging time points and corresponding normal GE value ranges as follows: at 0-min (0%), 30-min (8%-18%), 60-min (15%-40%), 90-min (33%-61%), 120-min (50%-80%) and 150-min (62%-85%). This established MIA method was augmented in 2012 by incorporating the delayed 4-h imaging and including as reporting criteria for delayed GE at 1-h, 2-h and 4-h the Tougas et al. (2000) values, as a combined MIA and NSP GES protocol.

The aim of our study was to retrospectively analyze a large number of GES cases performed over 7 years using a standard meal as per NSP and a modified imaging protocol based on a combined MIA and NSP protocol that uses the ANMS/SNM [SNMMI] criteria for the detection of delayed GE.A main objective of the study was to determine the importance of the 4-h imaging in detecting additional delayed GE or additional normal GE with respect to previous imaging time points. Another objective was to examine the predictive significance of imaging points at 2h and 2.5h in the evaluation of delayed GE and potentially optimizing the GES protocol by reducing the total duration of the study.

Subjects and Methods

The study included n=1002 adult patients (age ≥18 years) who had GES at the University of Miami Hospital and Clinics from 2012 to 2019. The patient characteristics are shown in Table 1. Institutional Review Board approval was obtained for this retrospective analysis. The patients were referred to nuclear medicine by their gastroenterologist or primary care physician for ruling out GP in the evaluation of upper GI symptoms after absence of mechanical obstruction as determined either by imaging or prior upper endoscopy. As per protocol, prokinetic agents and certain pain medications such as opiates and antispasmodic agents were stopped 2 days prior to the scan, with rare exceptions if patients were unable to be taken off these medications. The GES studies started in the morning with the patients asked to fast after midnight and/or to remain NPO for 6 hours prior to the scan. The fasting glucose level was measured at the start of the study to be under 275mg/dL in order to proceed with the exam. Diabetic patients on insulin were asked to bring their medication with them to the test.

Table 1. *Characteristics of the patient population.*

No. Sex, Age, y	All	Male	Female
Patients (n)	1002	298	702
Mean Age (y)	52	52	52
Median Age (y)	53	54	53
Range (y)	18-91	18-87	18-91

The patients received a low-fat egg-white meal (equivalent to 2 large eggs) radiolabeled with 1mCi of technetium-99 (^{99m}Tc) sulfur-colloid. The egg-whites were stirred appropriately during preparation to reach consistency and an internal temperature of 160 degrees. The radiolabeled egg-whites were made into a sandwich using 2 slices of white bread and 28g strawberry jam so that the total caloric content of the meal was approximately 255Kcal as recommended by the ANMS/SNM [SNMMI] guidelines [6]. The patient was asked to ingest the meal in under 10 minutes and could also drink 120mL of water. In case the patient could not eat the entire meal, the percent of the ingested portion was estimated and recorded; at least 50% meal consumption was required for the study to proceed.

Imaging was performed with the patient in a standing upright position using a large field of view (FOV) dual-detector gamma camera (Skylight; Philips Healthcare) so that anterior and posterior views could be acquired simultaneously using 1-min static images in a 128x128 matrix, around a 20% ^{99m}Tc energy window (140keV ±10%) with a low-energy high-resolution (LEHR) collimator. The imaging time points were at 0h (just after completion of the meal), 0.5h, 1h, 1.5h, 2h, 2.5h and 4h. The position of the detectors was recorded and reproduced at each imaging time point so that the stomach, distal esophagus, proximal small bowel would be encompassed and in the same area of the FOV in each image; this was useful when the patient would rest in between image acquisitions or when additional GES studies were staggered on the same gamma camera. The images acquired every 30min, from 0 to 2.5h were part of the original institutional MIA protocol, while the 4-h time point was introduced as part of this study in accordance with NSP criteria of the ANMS/SNM [SNMMI] consensus statement. Patients who vomited at any point during the meal ingestion or the exam were not included in this cohort for retrospective analysis.

Regions of interest (ROI) to outline the stomach in the anterior and posterior views at each time point were drawn on a standard nuclear medicine clinical workstation. Quantitative analysis was performed by calculating the geometric mean, as (anterior counts X posterior counts)1/2, of the decay-corrected counts at each imaging point (0-, 30-, 60-, 90-, 120-, 150- and 240-min), as the square root of the product of the anterior times the posterior counts, expressed as percent emptying or percent retention with respect to the initial 0h baseline.

The potential increase in the number of delayed cases from 2h to 4h was examined based on the difference in the rate of positives (at 95% CI) between the two time points. Data analysis using McNemar's Chi-squared test with continuity correction was performed to evaluate the significance of the 4-h imaging in detecting studies that changed from normal at 2h to abnormal at 4h, and, abnormal studies at 2h that changed to normal at 4h. Additionally, time imaging points of 1h, 1.5h, 2h and 2.5h were examined for their predictive significance in detecting normal or abnormal GE at 4h using <10% retention as the objective criterion. Receiver operating characteristic (ROC) analysis was performed and optimal thresholds at 95% confidence interval (CI) were determined based on the Youden index for the 1h, 1.5h, 2h, and 2.5h GE with <10% retention at 4h considered the standard of truth. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the curve (AUC) values were computed for the respective time points. The percentages and 95% CI were calculated for those patients who reached >90% GE at 2 or 2.5h and maintained <10% retention at 4h to obtain certainty regarding these estimates.

Results

In our cohort of n=1002 patients, 919/1002 (92%) had normal GE at 1h and 83/1002 (8%) had delayed GE at 1h according to NSP criteria. At 2h, 836/1002 (83%) had normal GE and 166/1002 (17%) had delayed GE, while at 4h, 795/1002 (79%) had normal GE and 207/1002 (21%) had delayed GE (Table 2). The increase in delayed GE cases from 2h to 4h was 25% (41/166), which was significant based on the corresponding rate of positives at the 95% CI, which was 4.9% (3.7%-6.5%) at 2h and 11.6% (9.7%-13.7%) at 4h, respectively.

Of the 207/1002 who were delayed at 4h, 103 (approximately half of them) had mildly delayed GE (10%-19% retention), 46 (22%) had moderately delayed GE (20%-29%) and 58 (28%) had severely delayed GE (retention 30%) based on the Navas et al. (2021) classification scale for delayed GE [10].

From the normal studies at 1h, 136/919 (15%) became delayed at 4h, while those with normal studies at 2h, 77/836 (9%) became delayed at 4h. Of those with delayed studies at 1h, 26/83 (31%) became normal at 4h, and similarly, those with delayed studies at 2h, 50/166 (30%) became normal at 4h (Table 2). Applying McNemar's Chi-squared test with continuity correction yielded a smaller percent change in either normal to delayed GE, or, delayed to normal GE, at 2h as compared to 1h using the 4-h as the standard criterion. The analysis also demonstrated that a higher percentage of patients changed from abnormal to normal (30%) vs. normal to abnormal (9%) from 2 to 4h, which was significant (P< 0.001).

Receiver operating characteristic curve analysis for sensitivity, specificity, PPV and NPV for 1h and 2h GE with respect to the 4-h criterion of <10% retention [Tougas et al. (2000)] are shown in Table 3.

Table 2. *Normal and delayed gastric emptying at imaging points 1, 2 and 4 hours. Total n=1002.*

	Normal		Delayed	
Time Point (h)	**Total**	**Normal to Delayed***	**Total**	**Delayed to Normal†**
1	919	136	83	26
2	836	77	166	50
4	795		207	

**Patients normal at 1 or 2h who had delayed GE at 4h. †Patients with delayed GE at 1 or 2h who normalized at 4h.*

Table 3. *Receiver operating characteristic curve analysis for sensitivity, specificity, PPV and NPV for 1h and 2h GE with respect to the 4-h criterion of <10% retention.*

Gastric Retention	Sensitivity	Specificity	PPV	NPV
> 90% at 1h	28% (57/207)	98% (783/795)	69% (57/83)	85% (783/919)
> 60% at 2h	56% (116/207)	95% (759/795)	70% (116/166)	91% (759/836)

In our patient population, greater than 90% GE (<10% retention) was found in 21/1002 (2%) at 1.5h, 93/1002 (9%) at 2h and 250/1002 (25%) at 2.5h, respectively. In these cases, the GE at 4h persisted with <10% retention and therefore the outcome remained unchanged. Statistical analysis at the 95% CI yielded that the corresponding confidence level

***Table 4.** The sensitivity, specificity, PPV, NPV and AUC values (95% CI) for 1h and 2h relative to the 4h standard of truth of <10% retention along with the calculated threshold values (Youden criterion) for optimal accuracy.*

Gastric Emptying	Threshold	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
1h	21%	0.806	0.789864	0.6787565	0.9115549	0.4352159	0.7684631
1.5h	36%	0.867	0.7948084	0.7720207	0.9359534	0.4730159	0.7904192
2h	52%	0.913	0.8096415	0.865285	0.9618209	0.5202492	0.8203593
2.5h	68%	0.94	0.789864	0.9378238	0.9815668	0.5156695	0.8283433
*** 2.5h**	64%		0.8529048	0.8549223	0.9610028	0.5809859	0.8532934

** Indicates analysis predicting threshold that would result in equal sensitivity and specificity.*

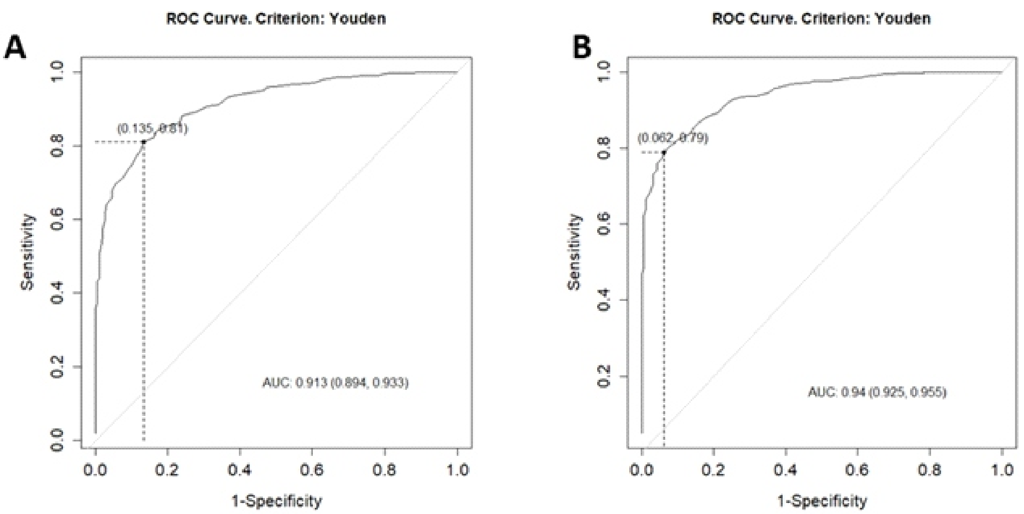

Figure 1A and 1B. ROC curves for 2-h (A) and 2.5-h (B) of gastric emptying with respect to the 4-h criterion of more than 10% retention indicating delayed GE. AUC values were 0.91 for 2h and 0.94 for 2.5h, respectively.

was 16% for 1.5h, 4% for 2h, and approximately 0% for 2.5h indicating the incremental stability towards the later time points, particularly the 2.5h.

The sensitivity, specificity, PPV, NPV and AUC values (95% CI) for 1h and 2h relative to the 4h standard of truth of <10% retention along with the calculated threshold values (Youden criterion) for optimal accuracy are shown in Table 4. The ROC graphs and AUC for 2h and 2.5h vs. 4h are shown in Figures 1A and 1B.

Discussion

Gastric emptying scintigraphy has been widely utilized and accepted for many years as the gold standard method for evaluating upper gastrointestinal motility and transit in patients with symptoms of nausea, vomiting and postprandial pain. Gastric emptying scintigraphy faced a wide range of variability in its imaging methodology, choice of meal, and lack of normal reference values for both delayed and rapid gastric emptying. Efforts to standardize the protocol for GES begun to materialize in the early 2000's. A multicenter study by Tougas et al. (2000) [6] of 123 healthy volunteers, used a simplified protocol with imaging at 0, 1, 2, and 4h after the ingestion of a low-fat radioactive meal, generated normal limits of GE at each imaging point. It also determined that gastric retention >10% at 4h indicates significantly delayed GE. The Tougas et al. (2000) protocol, due to its simplicity in acquisition and quantification, was adapted by many centers as the standard and a number of investigators have since reported on its clinical utility and ability to detect delayed GE [13, 14, 16].

In our investigational study of a 1002 patient cohort, the MIA protocol, which included imaging at time points 0-min, 30-min, 60-min, 90-min, 120-min and 150-min, was extended to include the 4-h imaging as per the ANMS/SNM [SNMMI] recommendations. Essentially, our protocol included all imaging time points of the standard NSP as well as in between imaging at 30-min, 90-min, and 150-min, which could provide additional useful information for the study; in particular the 90-min and 150-min images were examined for potential contribution to the process of determining delayed GE.

Similar to previous studies [13,14,16], our investigation detected additional cases with delayed GE at 4h than 2h with a statistically significant (P<0.01) relative increase of 25%. There was a small number of patients who were abnormally delayed based on the 2h criterion and became normal with <10% retention at 4h; this represented a 9% decrease in delayed cases from the 2h to 4h. Overall, these findings further support the importance of the 4-h imaging time point.

A previous published study [13] reported on 3-h GE values that were found to be at least as sensitive as the 4-h time point while another study [14] reported an AUC of 0.97 comparing the 3h to the 4h. Our MIA protocol includes a 2.5h imaging point which when examined using ROC analysis yielded an AUC of 0.94 as compared to the 4-h imaging point, suggestive of a strong correlation.

In our cohort, 25% of the patients already had less than 10% gastric retention at 2.5h thereby obviating the need to perform additional imaging at 4h. In order to implement this as part of the workflow, it is recommended that the acquired images and real-time quantification results up to 2.5h are inspected by the Nuclear Medicine Physician to determine if the study can be safely terminated.

Our ROC analysis using plots and AUC calculations determined GE thresholds for optimal accuracy and associated metrics of sensitivity, specificity, PPV and NPV for 1, 1.5, 2, and 2.5h by using the Tougas (<10% retention at 4h) as the gold standard (Table 4). This type of analysis can be useful in validating that the NSP criteria are applicable to their patient populations, provided that their protocol implementation including patient preparation, standardized meal, imaging methodology are based on the ANMS/SNM [SNMMI] guidelines.

In conclusion, this clinical investigation provided a confirmation of the NSP criteria of the ANMS/SNM [SNMMI] consensus statement in a large patient cohort at our Institution. This study demonstrated the importance of the 4-h late image in detecting additional delayed GE cases as compared to the 2h.The 2.5-h imaging time point can detect a significant number of normal cases with already <10% retention and allow for earlier than 4-h termination of the gastric emptying study.

The authors declare that they have no conflicts of interest.

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