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Diagnostic Testing for Functional Dyspepsia

Durre Sabih and Muhammad Kashif Rahim

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1. Introduction

Dyspepsia is defined as predominantly midline pain or discomfort located in the upper abdomen [1]. Discomfort refers to a subjective, negative feeling that is not "painful". Dyspepsia can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Although the term implies a relationship with eating and the majority of patients have symptoms worsened by food, this is no longer necessary to diagnose dyspepsia [2]. During the investigation of dyspepsia, three major structural causes are readily identifiable: peptic ulcer disease (10%), gastroesophageal reflux (20%) (with or without esophagitis), and malignancy (2%) [3]. Thus, most (50%-70%) patients with chronic dyspepsia do not have a significant focal or structural lesion found at endoscopy. When symptoms are chronic or recurrent (table 1) but without an identifiable structural cause using standard diagnostic tests (usually endoscopy), the condition is usually labelled functional or functional dyspepsia [4, 5]. Hence functional dyspepsia is a diagnosis of exclusion, the implication being that symptoms have been investigated without demonstrating an organic or anatomical cause [5].

Functional dyspepsia is not life-threatening and is not associated with any increase in mortality. However, the impact of this condition on patients and health care services is considerable. In a recent community survey of several European and North American populations, 20% of people with dyspeptic symptoms had consulted either primary care physicians or hospital specialists; more than 50% of dyspepsia sufferers were on medication most of the time and approximately 30% reported taking days off from work or school due to their symptoms [5, 6]. Patients with functional dyspepsia have a significantly reduced quality of life when compared to the general population [7].

The Rome III criteria for diagnosing functional dyspepsia are persistent or recurrent upper abdominal pain or discomfort for a period of 12 weeks, which need not be consecutive, in the preceding 12 months, with symptoms present more than 25 percent of the time, and an absence

Symptom	Definition		
Pain centered in the upper abdomen	Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other pain sensations could be throbbing, shooting, stabbing, cramping, gnawing, burning or aching. By questioning the patient, pain should be distinguished from discomfort.		
Discomfort centered in the upper abdomen	A subjective, unpleasant sensation or feeling that is not interpreted as pain according to the patient and which, if fully assessed, can include any of the symptoms below.		
	Early satiety	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished.
	Fullness after meal	Unpleasant sensations like the persistence of food in the stomach; this may or may not occur post-prandially (slow digestion).
	Bloating in the upper abdomen	Tightness located in the upper abdomen; it should be distinguished from visible abdominal distension.
	Nausea	Queasiness or sick sensation; a feeling of the need to vomit.

Table 1. The spectrum of dyspepsia symptoms and recommended definitions [4, 5]

of clinical, biochemical, endoscopic, and ultrasonographic evidence of organic disease that would account for the symptoms [1] (Table 2).

12 weeks minimum, that need not be consecutive, in the preceding 12 months of:

• Persistent or recurrent symptoms (pain or discomfort centred in the upper abdomen);

• No evidence of organic disease (including at upper GI endoscopy) that is likely to explain the symptoms;

• No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel).

Table 2. Rome III diagnostic criteria for functional dyspepsia [1, 9]

On the basis of the most bothersome or predominant single symptom, identified by the patient, functional dyspepsia is further classified into various subgroups [4, 9]:

1. Ulcer-like dyspepsia

Pain centred in the upper abdomen is the predominant (most bothersome) symptom [9].

2. Dysmotility-like dyspepsia

An unpleasant or troublesome non-painful sensation (discomfort) centred in the upper abdomen is the predominant symptom; this sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea [9].

3. Unspecified (non-specific) dyspepsia

Symptoms do not fulfil the criteria for ulcer-like or dysmotility-like dyspepsia [9].

2. Functional dyspepsia: Pathophysiologic mechanisms and their relation to symptom pattern

Several pathophysiologic mechanisms explain underlie dyspeptic symptoms. These include delayed gastric emptying, impaired gastric accommodation to a meal, and hypersensitivity to gastric distension, *H. pylori* infection, altered response to duodenal lipids or acid, abnormal duodenojejunal motility, or central nervous system dysfunction. At present, the pathophysiology of functional dyspepsia is only partially elucidated. However, there is growing evidence that functional dyspepsia is in fact a very heterogeneous disorder and different subgroups can be identified based on different demographic, clinical, and pathophysiologic features [2].

1. Delayed gastric emptying

Delayed gastric emptying is traditionally considered a major pathophysiologic mechanism underlying symptoms in functional dyspepsia and idiopathic gastroparesis [10]. Several large single-centre studies from Europe found association between delayed gastric emptying and the prevalence and severity of symptoms like post-prandial fullness, nausea, and vomiting [10]. Similarly, other reports have investigated the relationship between delayed gastric emptying and symptom pattern and severity [2]. Depending on the study, the percentage of dyspeptic patients with delayed gastric emptying ranges from 20% to 50%. In a meta-analysis of 17 studies involving 868 dyspeptic patients and 397 controls, significant delay of solid gastric emptying was present in almost 40% of patients with functional dyspepsia [11]. Various causes of delayed gastric emptying are summarized in table 3.

2. Impaired gastric accommodation to a meal

The motor functions of the proximal and distal stomach differ remarkably. The proximal stomach (body) serves mainly as a reservoir. In contrast, the distal stomach (antrum) regulates gastric emptying of solids by grinding and sieving the contents until the particles are small enough to pass the pylorus. The stomach accommodates to a meal by relaxing of the proximal stomach, providing the meal with a reservoir and enabling an increase in volume without an increase in pressure. Scintigraphic and ultrasonographic studies have shown an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach. These findings suggest defective postprandial accommodation of the proximal stomach [12, 13].

3. Hypersensitivity to gastric distension

Physiologic stimuli during the digestive process are not normally perceived but in some circumstances may induce conscious sensations. Patients with functional gastrointestinal diseases may have a sensory dysfunction of the gut (termed visceral hypersensitivity), with normal physiological stimuli perceived as discomfort or pain [14]. Patients with functional dyspepsia appear to have enhanced sensitivity to gastric distension [10, 15, 16].

4. Altered duodenal sensitivity to lipids or acid

The symptoms of dyspepsia are usually exacerbated by meals which are rich in fat [20]. Similarly the duodenum is more sensitive to acid in those with functional dyspepsia. The

duodenal motor response to acid is decreased in patients with functional dyspepsia, resulting in reduced clearance of exogenous duodenal acid [21].

5. Inflammation

About a third of patients with irritable bowel syndrome or dyspepsia describe the onset of symptoms after an acute enteric infection. It is possible that mucosal inflammation may have a part in the creation of the visceral hypersensitivity.

6. H. Pylori infection

The discovery of *H. pylori* led to uncovering a causal relationship between *H. pylori* infection and the occurrence of duodenal and gastric ulcers [17]. The role of *H. pylori* is less clear in functional dyspepsia. Systematic reviews of the epidemiologic evidence on a relationship between *H. pylori* infection and functional dyspepsia have found no evidence for a strong association [18, 19].
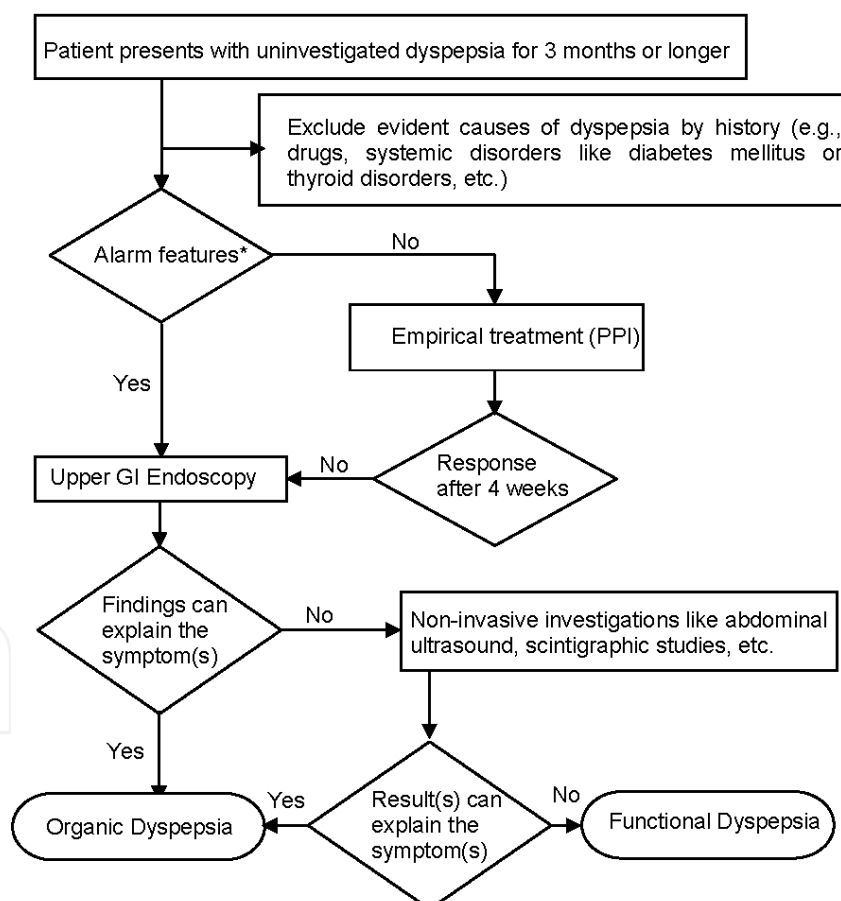
*The alarm features are unintended weight loss, progressive dysphagia, recurrent or persistent vomiting, evidence of gastrointestinal bleeding, anemia, fever, family history of gastric cancer, new onset dyspepsia in the subjects over 40 years of age in population with high prevalence of upper gastrointestinal malignancy and over 45 and 50 years in populations with intermediate and low prevalence, respectively. **Adapted from reference [22]

Figure 1. Diagnostic algorithm for functional (functional) dyspepsia**

3. Causes of delayed gastric emptying

The various causes that are related to delayed gastric emptying are summarized here in Table 3 [23].

Acute (Transient) Delayed Gastric Emptying	Cigarette smoking, Alcohol, Viral gastroenteritis, Hyperglycemia, Acidosis, Hypokalemia, Immobilization, Myxoedema, Hypocalcaemia, Hypercalaemia, Hypomagnesaemia, Hepatic coma, Postoperative ileus, Parenteral nutrition,
Chronic Delayed Gastric Emptying	Gastric ulcer disease, Functional dyspepsia, Gastroesophageal reflux disease, Diabetes Mellitus, Hypothyroidism, Post gastric surgery, Addison's diseases, Pernicious anaemia, Achlorhydria, Connective tissue diseases, Anorexia nervosa, Depression, Neurologic disorders (Multiple sclerosis, Parkinsonism, paraneoplastic syndrome etc).
Pharmacological Agents and Hormones	Antacids (aluminium hydroxide), Opiates, Anticholinergics, Tricyclic antidepressants, Beta adrenergic agonists, Levodopa, Calcium channel blockers, Progesterone, Birth control pills, Gastrin, Cholecystokinin, Somatostatin

Table 3. Causes of Delayed Gastric Emptying [23].

4. Diagnostic investigations of dyspepsia

Functional dyspepsia is usually a diagnosis of exclusion; the diagnosis is made after eliminating organic disease or a structural basis for symptoms. The physician must decide how many investigations to order before deciding that the patient has a functional disorder (Table 4). The heterogeneity of presentation and the extensive differential diagnosis including significant organic disease mandates rapid exclusion of pathologies like peptic ulcer disease, reflux esophagitis and malignancy of the stomach or esophagus. Another perspective is the test-and-treat approach that includes acid suppression, treatment of *H.pylori* infection and early endoscopy. Patients with "alarm features" (Fig 1), or those older than 40-50 years (depending on ethnicity) require a more aggressive strategy such as early endoscopy. It must also be understood that there are many patients who can have both organic as well as functional components of dyspepsia.

Initial investigations may include blood counts, electrolytes, fasting blood sugar, renal function tests and thyroid function tests. Testing for celiac disease and stool examination for occult blood or parasites may also be considered. *H.pylori* infection can be diagnosed by serology, breath or stool testing.

Gastric accommodation can be assessed by gastric barotest. The barotest measures gastric tone and comprises of a bag that can be maintained at a constant pressure by feedback mechanisms (termed a barostat). Volume changes in the bag thus represent variation in gut - the bag

becomes bigger with gut relaxation and smaller with contraction. "Barotesting" is the "gold standard" for visceral hypersensitivity, but is invasive and uncomfortable, so non-invasive means have been developed that include SPECT (Single Photon Emission Tomography) imaging and 3-D ultrasound.

SPECT can be used to assess intragastric volume although correlation with barotest has not been consistently established and the volumes determined do not reflect muscle activity of the stomach. 3D ultrasound can also be used for volume determination of the stomach but this remains a highly operator dependent technique and there is limited data available in the literature.

Chemical hypersensitivity tests can be done by a duodenal infusion of lipid to provoke early symptoms of gastric distension in patients with functional dyspepsia and relief by administering a cholecystokinin receptor antagonist (loxiglumide). CCK-8 (cholecystokinin octapeptide) intravenously can be used instead of the lipid infusion to provoke symptoms in patients with functional dyspepsia, but this does not affect normal individuals.

Scintigraphic imaging lends itself elegantly to the evaluation of functional-dyspepsia due to the inherent strength of dynamic imaging and generating physiological data. Currently, it remains the only method to quantitatively measure the rate of gastric emptying.

Gastric scintigraphy employs a radiolabeled meal to measure emptying [24]. Gastric scintigraphy has evolved to include an evaluation of compartmental or antral motility, and more recently to SPECT to evaluate postprandial gastric accommodation. As a physiologic, quantitative, and non-invasive test, gastric emptying scintigraphy is well suited for evaluating patients before and after medical or surgical treatment. This procedure is now widely considered the gold standard for evaluating gastric emptying. The advantages of radionuclide imaging are:

1. The method is simple and non-invasive from the patient's point of view, requiring a single oral administration of the radionuclide.

2. The meal used in this method is physiological and does not alter the normal physiology of the gut.

3. Reaction to the radiopharmaceutical is rare.

4. Both solid and liquid meals can be studied and the gastric emptying can be quantified.

5. The radiation dose is very low so that repeated studies can be done to follow the progress of the disease or the response to treatment and the method can therefore be used as a research tool.

6. This method can be used to assess the amount of original meal in the stomach irrespective of the gastric secretions or the duodenal reflux.

7. There is no documented complication reported as the result of the gastric emptying studies.

8. There are different protocols with a 2, 3 or 4 hour end points (3 and 4 hour end points are emerging as more diagnostic).

Figure 2. Position of patient and camera during acquisition of images for scintigraphic evaluation of gastric emptying times.

Test	Strengths	Weaknesses
Radiological method (Barium meal)	• Gastroparesis can be diagnosed with barium meal	• Contraindicated in acid peptic disease and partial intestinal obstruction • Can cause barium appendicitis
Ultrasonography	• Non invasive • Does not involve ionizing radiation • Equipment used is available in most of the hospitals	• Operator dependent • Relatively time consuming as it requires repeated and prolonged observations
Endoscopy	• Permits direct visualization of the oesophagus, gastric and duodenal mucosa • First-line diagnostic procedure for patients with alarm features	• Invasive procedure • Not well accepted by patients • Requires trained personnel • Limited availability of equipment
Gastric emptying scintigraphy	• Simple and non-invasive • Physiological meal used • No reaction to pharmaceutical • No documented complication	• Ionizing radiation used • Time consuming • Equipment widely available • Degree of delayed gastric emptying does not correlate well with symptomatology
C-13 Acetate breath test	• Non invasive • No radiation involved • Can be adapted for solid or liquid emptying (C-13 sodium acetate for liquid and C-13 octanoic acid for solids)	• Variability similar to other tests • Good reproducibility • Needs special equipment (mass spectrophotometer) but cheaper alternates have been developed (NDIRS* and LARA**)

*NDIRS Non-dispersive isotope-selective infrared spectroscopy

**LARA Laser-assisted ratio analysis

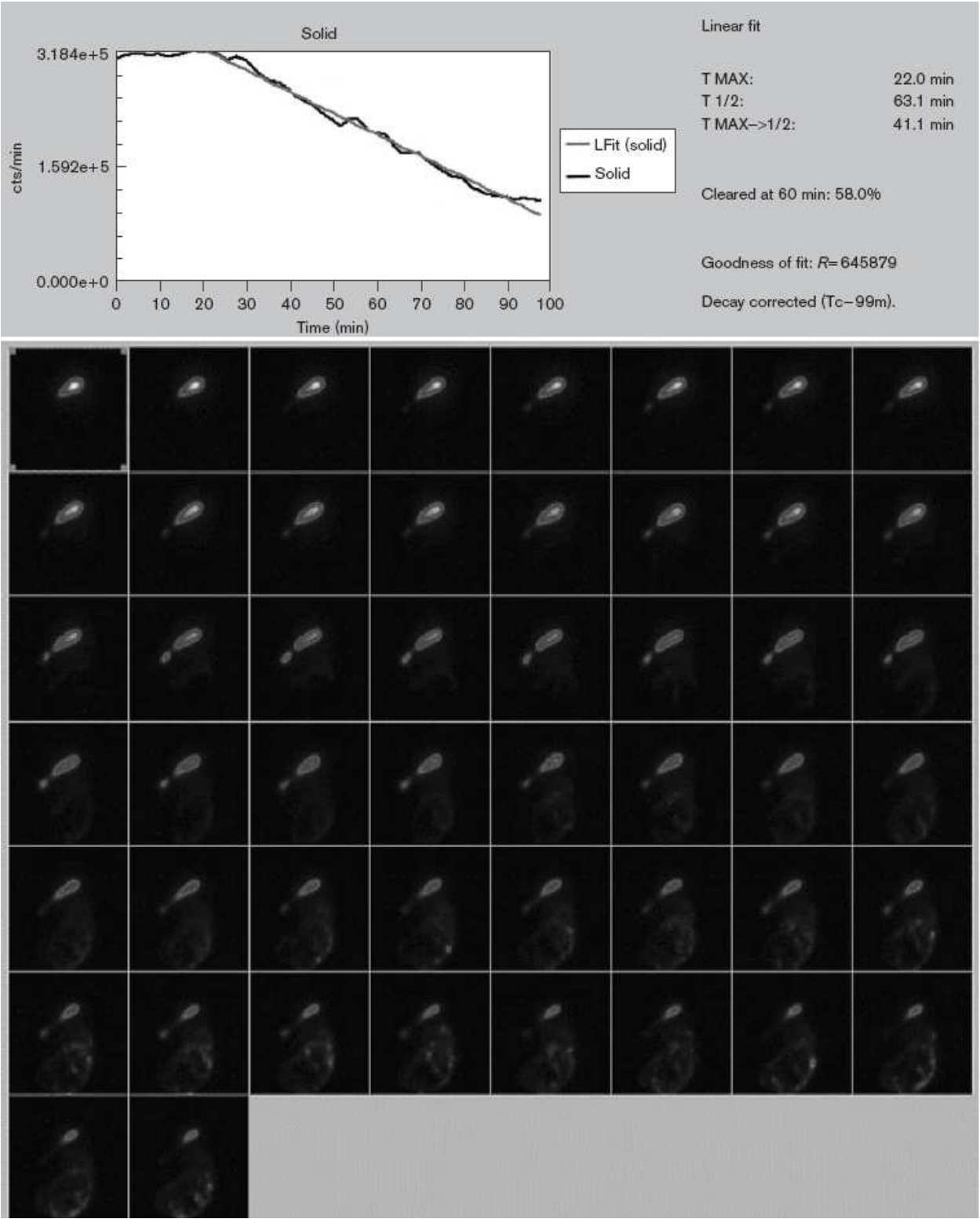**Table 4.** Investigations for the work-up of functional dyspepsia with their strengths and weaknesses

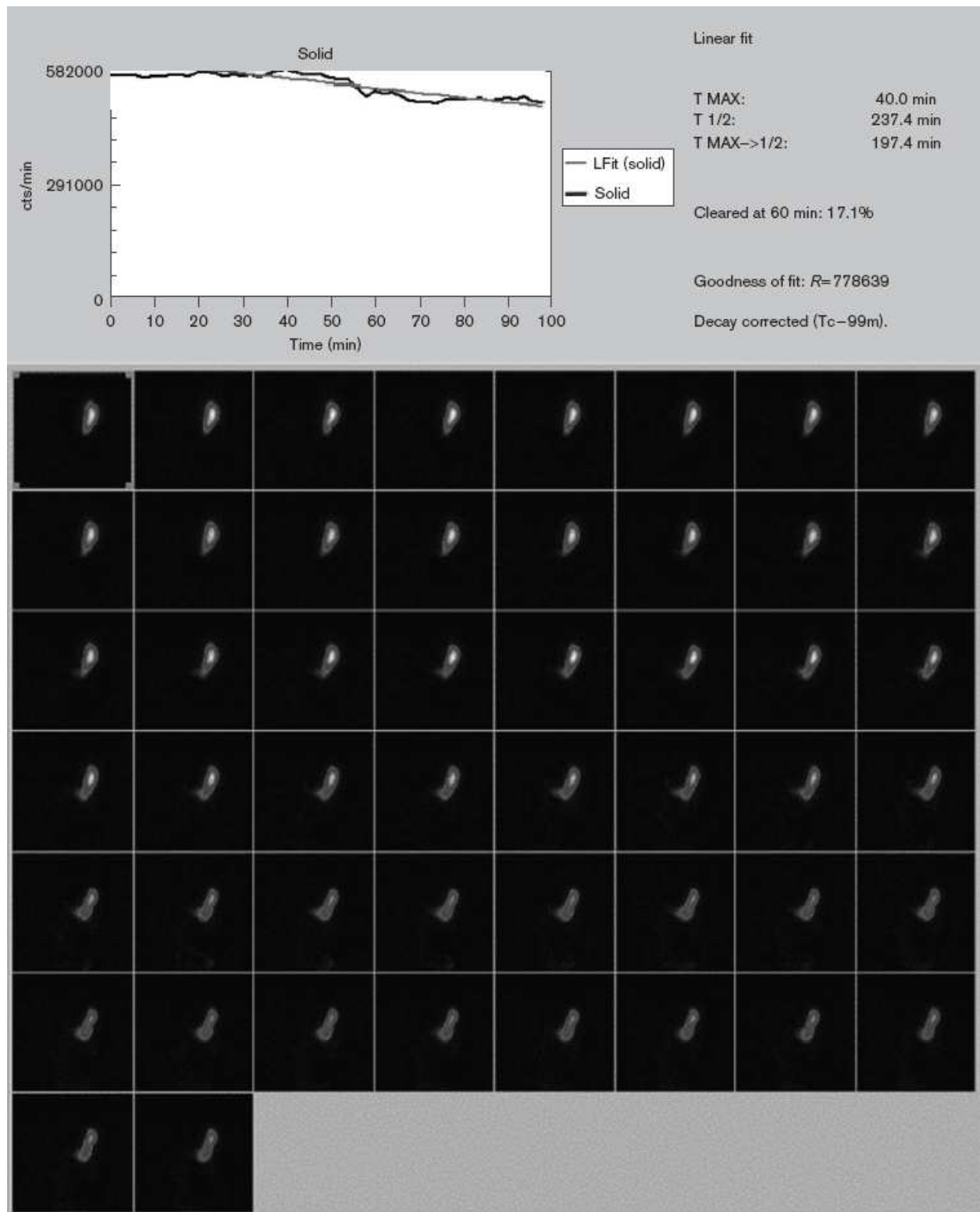**Figure 3.** Figure Dynamic images and time–activity curves of a normal person.

Figure 4. Dynamic images and time–activity curves of a patient with impaired gastric emptying.

5. Conclusion

Functional dyspepsia is a common problem with a significant impact on individuals and society. A variety of diagnostic tests are available to exclude organic disease and characterize underlying pathophysiologic abnormalities. Further work is needed to validate existing diagnostic tests in different populations. The goal of having an objective test that correlates with the symptom severity remains elusive. Physicians must remain cognisant that functional disorders create the same or perhaps even more distress in the patient when compared to conditions that can yield evidence of organic pathology.

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