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The Role of Nuclear Medicine in the Detection of Acute Gastrointestinal Bleeding

Douglas M. Howarth, FRACP

The clinical consequences of lower gastrointestinal bleeding range from trivial to life-threatening. Nuclear medicine imaging techniques allow identification of those patients who are actively bleeding. The demonstration of active bleeding not only provides important prognostic information but also allows for a coordinated imaging approach using angiography and aids localization of the bleeding site. ^{99m}Tc-labeled erythrocytes and ^{99m}Tc sulfur colloid are 2 commonly used techniques to detect active bleeding. Each has its respective advantages and disadvantages, but the medical literature indicates that both tests are useful. More prolonged or delayed imaging is possible using ^{99m}Tc-labeled erythrocytes but care is required to prevent misinterpretation of the bleeding location because of a higher likelihood of radiotracer movement through the bowel away from the bleeding site. These forms of scintigraphy may be helpful in risk-stratifying patients and planning radiological and surgical interventions. Careful selection of patients to include those who have a high likelihood of active bleeding greatly increases the clinical utility of these tests. In addition, ^{99m}Tc pertechnetate imaging may be diagnostic of ectopic gastric mucosa in a Meckel's diverticulum as a potential source of bleeding. Patients also should be carefully selected for this test, based on age and exclusion of other causes of bleeding.
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Acute gastrointestinal hemorrhage (AGH) is potentially a life-threatening event that may require swift surgical intervention. When AGH has occurred from the upper gastrointestinal tract, defined as bleeding from a source proximal to the ligament of Trietz, the patient most commonly presents with hematemesis. Upper gastrointestinal endoscopy is often diagnostic in suspected upper gastrointestinal hemorrhage and also has been advocated in asymptomatic patients with a positive fecal occult blood test and negative colonoscopy.[1]

When AGH has occurred from the lower gastrointestinal tract, the patient may present with frank (bright red) rectal bleeding, altered blood from a more proximal site, or in a moribund state with clinical evidence of blood volume loss from an indeterminate site. Clinical examination of the abdomen may reveal tenderness to palpation, abdominal guarding and, where bleeding is active, increased bowel sounds. In some circumstances a mass may be palpable, but often there is a relative paucity of diagnostic clinical features. Rectal examination together with sigmoidoscopy or colonoscopy at the bedside may reveal a bleeding source such as tumor, colitis, diverticulae, trauma or angiodysplasia, so that further imaging is unnecessary before therapeutic intervention. However, where there is no direct evidence of active bleeding in the distal gastrointestinal tract, or where active bleeding hampers adequate visualization of the bowel, other imaging investigations may be required.

Endoscopic examination of the colon can be extremely difficult where there is active bleeding unless the source of bleeding is very obvious, such as a large readily accessible colonic mass.[2,3] Angiodysplasia, patchy colitis, diverticulae, or smaller polyps may be rendered invisible by the colonic bleeding. Similarly, in an acute clinical setting, barium enema or computed tomography (CT) imaging is usually of limited use. Under ideal conditions anatomical imaging, such as arteriography, can be used to determine the site of bleeding. This technique can be of use by accurately localizing an actively bleeding vessel. Animal experimental arteriography studies have determined the critical minimal bleeding rate to be at least 0.5 mL/min.[4] Clinical studies, however, indicate that active bleeding can only be detected by angiography in the majority of patients where the rate of bleeding is in excess of 1 mL/min.[5]

Selective mesenteric angiography,[6] first described in 1965, has more recently been incorporated into the therapeutic modality of selective (or superselective) mesenteric emboli-

Hunter Imaging Group, Pacific Medical Imaging, Warners Bay, NSW, Australia.

Address reprint requests to Douglas Howarth, FRACP, PO Box 744, Warners Bay, NSW 2282, Australia. E-mail: Howdoug@bigpond.com

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Table 1 Basic Differences in Methodology of ^{99m}Tc-Labeling of Erythrocytes (Red Blood Cells) and the Relative Advantages and Disadvantages of Each Technique

In Vivo	Modified in Vitro	In Vitro
Technique		
Intravenous stannous chloride.	Intravenous Stannous chloride.	Draw 1-3 mL of blood.
10- to 20-minute interval.	10- to 15-minute interval.	Label according to UltraTag© Red Blood Cell kit instructions.*
Intravenous ^{99m}Tc pertechnetate 740 MBq (20 mCi).	Draw 3 mL of venous blood.	Readminister ^{99m}Tc-labeled blood to patient.
	Add ^{99m}Tc pertechnetate 740 MBq (20 mCi).	
	Readminister labeled blood to patient.	
Advantages		
Rapid and simple to administer.	Improved labeling efficiency.	Excellent labeling efficiency.
	Improved target to background ratio.	Optimal target-to-background ratio.
Disadvantages		
Free ^{99m}Tc pertechnetate may degrade image quality.	Good-but-suboptimal image quality.	More costly.

*Mallinckrodt Inc, St. Louis, MO.

zation, or use of vasoconstrictive agents such as vasopressin to facilitate natural coagulation.[7] Accurate localization of the site of bleeding is also important when a surgical approach to therapy is used. A descriptive, retrospective study of 31 high-risk patients with massive lower AGH who underwent either segmental colectomy (n = 21) or subtotal colectomy (n = 10) showed high mortality in both groups.[8] These results indicate that surgical intervention should be an option only when the risk-benefit has been carefully considered and angiographic intervention techniques are unsuccessful. Furthermore, on the basis of more marked mortality in the subtotal colectomy group, these authors suggest that, when possible, segmental colectomy should be performed where bleeding has been localized by angiography rather than the option of subtotal colectomy, where localization of bleeding is not possible.

Both the final diagnosis and accurate localization of bleeding are crucial in a patient who presents with clinical features indicating AGH. When the bleeding has either temporarily or permanently ceased, however, this may be problematic. As many as 35% of patients admitted to a university-affiliated teaching hospital with AGH will be discharged without a final diagnosis.[9,10] For diagnosis, both the timing of bleeding and the location of bleeding are important factors, particularly when the source of bleeding is distal to the stomach. When a patient presents with clinical features of subacute or chronic gastrointestinal bleeding, establishing a diagnosis may be even more challenging.

Nuclear medicine plays a role of varying importance in AGH. For the detection of AGH both dynamic and equilibrium imaging techniques can be employed. Radiolabeled sulfur colloid particles or ^{99m}Tc-labeled erythrocytes are the physiological agents used most commonly to detect active gastrointestinal bleeding. When there is clinical suspicion of bleeding attributable to a Meckel's diverticulum, ^{99m}Tc pertechnetate imaging can be used to confirm or exclude the presence of ectopic gastric mucosa.

^{99m}Tc-Labeled Autologous Erythrocyte Scintigraphy

Because of the ready availability of good quality commercial kits, enabling rapid and reliable erythrocyte labeling and the ability to image in dynamic early-phase followed by extended equilibrium-phase, this technique is currently the most popular method. Variations in the technique exist, including in vivo, modified in vitro, and in vitro imaging protocols (Table 1). These imaging protocols have previously been well described.[11-14] This test is commonly indicated when, in the presence of AGH, the cause of bleeding cannot be determined by endoscopy and when angiography is either negative or unavailable. This scintigraphy technique also can be used as a first-line test to demonstrate active bleeding and so facilitate angiographic confirmation and intervention.[15,16] Active bleeding at a rate of greater than 0.3 mL/min can be detected using this technique.[17] Some evidence is also available to suggest that this bleeding rate threshold is as low as 0.1 mL/min but, to be detected, more than 3 mL of blood needs to pool at one site.[18] Other authors have suggested a range of volumes from 5 mL to as much as 50 to 70 mL are required for scintigraphic detection in adults.[19,20] Not only is this test more sensitive than angiography for the detection of active bleeding, but also the blood pool phase allows either continuous or intermittent imaging to be undertaken where bleeding is not continuous, thus increasing the likelihood of detecting intermittent bleeding over a relatively long period. This period is only limited by the half-life of the radiotracer used and the availability of scanning time in the Nuclear Medicine department.

^{99m}Tc-Labeled Sulfur Colloid Scintigraphy

This technique was first described in animal experiments in 1977[21] A recommended imaging protocol is shown in Table 2.

Table 2 ^{99m}Tc Sulfur Colloid Gastrointestinal Bleeding Study Protocol[21,22]

1. Patient receives 770 MBq (10 mCi) ^{99m}Tc sulfur colloid intravenously
2. Imaging with large field of view gamma camera, and low-energy, all-purpose collimator.
3. Patient is positioned supine, including pelvis and abdomen, with only lower edge of liver visible.
4. Dynamic flow sequence: 2 seconds per frame for 30 frames (128 × 128 word mode matrix).
5. Continuous static images 1-2 minutes each (>750,000 counts each) for up to 30 minutes.
6. Additional static images: obliques or upper abdomen views as required. For interpretation, image intensity threshold set on computer to show radiotracer within bone marrow.

The principle of radiolabeled sulfur colloid imaging relates to the use of this radiotracer as an early phase vascular imaging agent that is rapidly cleared from the vascular space by extraction to liver, spleen and bone marrow. Consequently, extravasation from a vascular source, such as that which occurs during active gastrointestinal bleeding, will potentially yield a high target-to-background count ratio because the extravasated radiolabeled blood will not be cleared as rapidly.[22] Successful identification of the bleeding site is therefore dependent on active bleeding occurring within a time-window of several minutes after radiotracer administration. Although this technique allows rapid identification of bleeding sites, intense radiotracer activity within the liver and spleen may be problematic in the identification of bleeding sites from stomach, proximal duodenum or colonic flexures. The authors of a retrospective comparative study of ^{99m}Tc sulfur colloid scintigraphy (n = 193) versus ^{99m}Tc red cell-labeled scintigraphy (n = 138), in addition to an additional 28 studies where both tests were performed in the same patient, concluded that there was no practical advantage of ^{99m}Tc-labeled red blood cell scintigraphy over ^{99m}Tc sulfur colloid scintigraphy.[23] The authors indicate that a greater risk of inaccurate localization of bleeding is possible using the former technique attributable to an increased likelihood of radiotracer peristaltic movement with the more prolonged imaging time.

Other Techniques

^{99m}Tc-labeled albumin was the earliest intravascular agent used to detect gastrointestinal bleeding.[20] This technique showed promising results but was soon surpassed by techniques using more reliable labeling techniques.[24] ^{99m}Tc-labeled heat-damaged erythrocytes also have been used as an intravascular technique where a high target-to-background ratio is achieved by clearance of damaged erythrocytes by the spleen and extravasation of labeled-heat-damaged erythrocytes at a site of active gastrointestinal bleeding.[25] The intravascular half-life of this radiotracer is longer than ^{99m}Tc sulfur colloid.[25] Indium-111 labeled erythrocytes also have been used with the aim of using the longer physical half-life of In-111 to facilitate prolonged imaging in the hope of detecting intermittent gastrointestinal bleeding.[26,27] The increased cost and increased radiation burden, however, limit the potential clinical utility of this technique.[28]

Meckel's Diverticulum

Bleeding from a Meckel's diverticulum can potentially occur at any age but is more likely to occur in infancy or early childhood. A Meckel's diverticulum is an embryological remnant caused by incomplete closure of the omphalomesenteric duct, most commonly located in the distal ileum. It is not known what proportion of these diverticulae contain ectopic mucosa, but estimates range from 10% to 60%.[29-31] The most common type of ectopic tissue in Meckel's diverticulae is gastric mucosa, and less commonly pancreatic–gastric, pancreatic, and duodenal mucosa can be present.[30] Ectopic gastric mucosa may give rise to potential parietal cell production of gastric acid and pepsin and subsequently result in mucosal damage and bleeding.[32] Ectopic gastric mucosa also can rarely be found within other abdominal malformations, including enteric duplications, duplication cysts, and gastrogenic cysts.[33]

The true incidence of bleeding from Meckel's diverticulum is not known but, suffice to say, it is a rare disorder, with this congenitial abnormality occurring in less than 3% of most populations.[29] Published data give some perspective to the true incidence. A 12-year review of 88 pediatric patients admitted to Chang Gung Memorial Hospital, Taipei, Taiwan, found 39 patients with histologically proven ectopic gastric mucosa.[33] This number equates to approximately 3 patients per year in this population. A 22-year review of children admitted to Mott Children's Hospital, Ann Arbor, Michigan, with suspected diagnosis of Meckel's diverticulum found 70 with a confirmed final discharge diagnosis.[34] This number also equates to approximately 3 per year in this population. The incidence of bleeding from Meckel's diverticulum in adult patients in even more obscure but is likely to be much rarer than in pediatric patients.

Scintigraphic imaging to detect ectopic gastric mucosa as a source of lower gastrointestinal hemorrhage is based on the fact that ^{99m}Tc pertechnetate is actively secreted by the mucous cells found within gastric mucosa.[35] The technique has been well described previously.[36] The test generally is credited as being the most accurate noninvasive technique to make a diagnosis of ectopic gastric mucosa. Diagnostic accuracy of 90% has been reported.[37,38] Relatively lower diagnostic accuracy, based on a range of diagnostic sensitivities as low as 50% and as much as 86% also has been reported.[34,36,39] The use of this test in adults has been reported to be of even lower diagnostic accuracy, with sensitivity of 63% and specificity of 9%.[31] The low specificity has been attributed to the greater likelihood of encountering a range of other pathological conditions in adults.[40] The use of pentagastrin (recommended dose 6 μg/kg subcutaneous injection) or H-2 antagonists such as cimetidine or ranitidine before imaging has been reported to increase detection rates.[41-43] Pentagastrin accelerates and increases uptake into gastric mucin-producing cells but also may increase gastric secretions and motility, which potentially may reduce the diagnostic accuracy

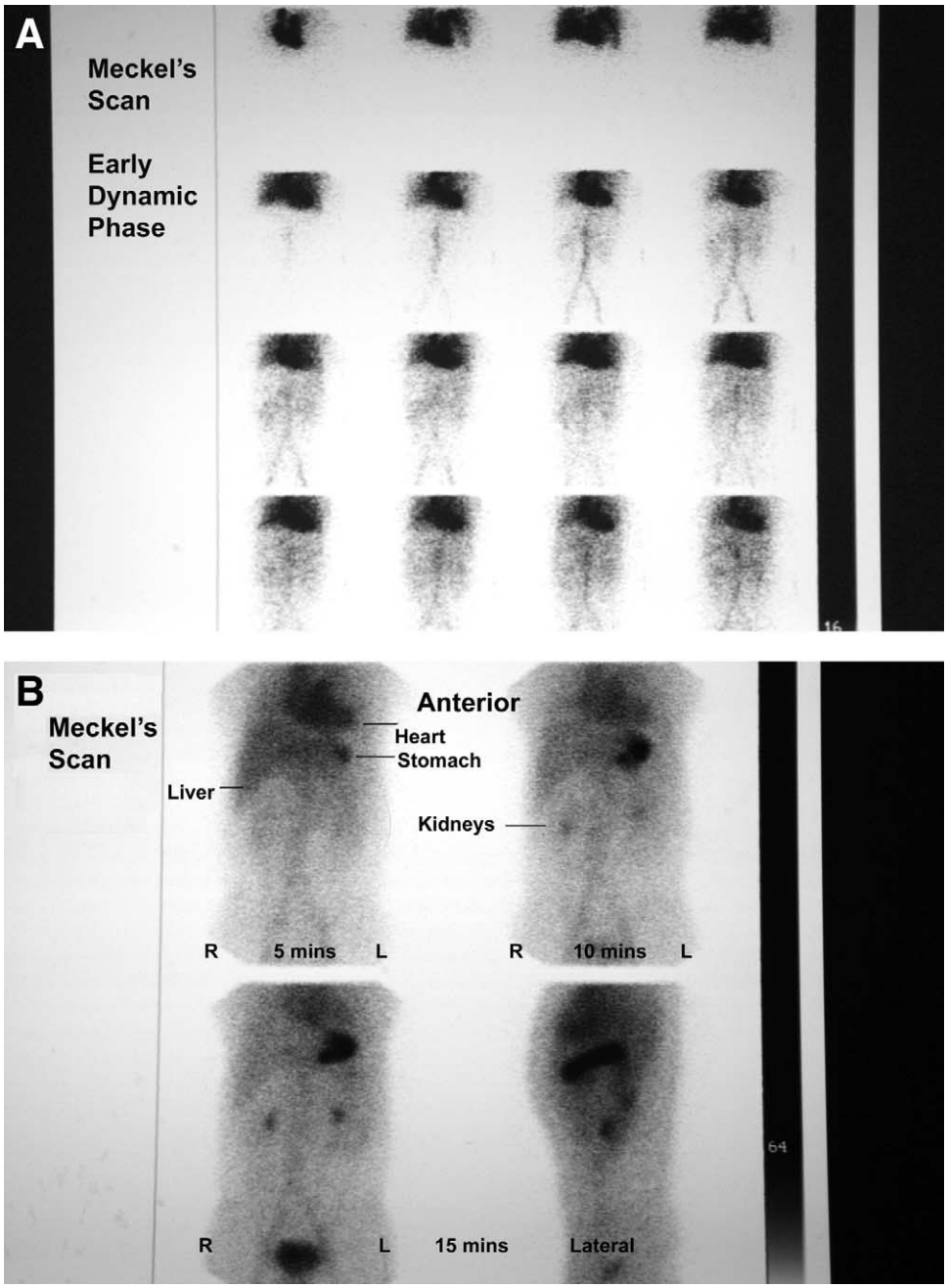


Figure 1 Meckel's scan in a 20-year-old male patient with intermittent malena stool. The scan shows no abnormal radiotracer uptake to indicate the presence of ectopic gastric mucosa. (A) Early dynamic phase images during the arterial phase showing no active bleeding. (B) Images at 5 and 10 minutes are shown, demonstrating the normal distribution of ^{99m}Tc pertechnetate during the early phase of the study.

of the scintigraphy study unless glucagon (50 μg/kg, intravenous) is given 10 minutes after the start of the study or, alternatively, hyoscine butyl-bromide.[44,45] The use of H-2 blocking drugs is based on the principle of reducing intraluminal secretions without affecting radiotracer uptake.[43,46] Although these pharmacological modifications may potentially improve both the detection rate and specificity of the scintigraphy study, the evidence supporting the routine use of these agents remains rudimentary.

As is implied from the previous discussion, a major pitfall in ^{99m}Tc pertechnetate scintigraphy arises from the progressive secretion of radiotracer from stomach to bowel over time that may potentially mask a focus of abnormal radiotracer uptake (Fig. 1). The location of ectopic gastric mucosa also may be variable although the most common location is the central abdomen (Fig. 2). Occasionally, ectopic gastric mucosa can be found in the low pelvis obscured by the urinary bladder unless post void or lateral images are included in the study (Fig. 1). ^{99m}Tc pertechnetate imaging has been recommended to be performed before ^{99m}Tc-labeled red blood cell scintigraphy, where both tests are likely to be performed, because stannous pyrophosphate, often used in the latter study, may reduce ^{99m}Tc pertech-

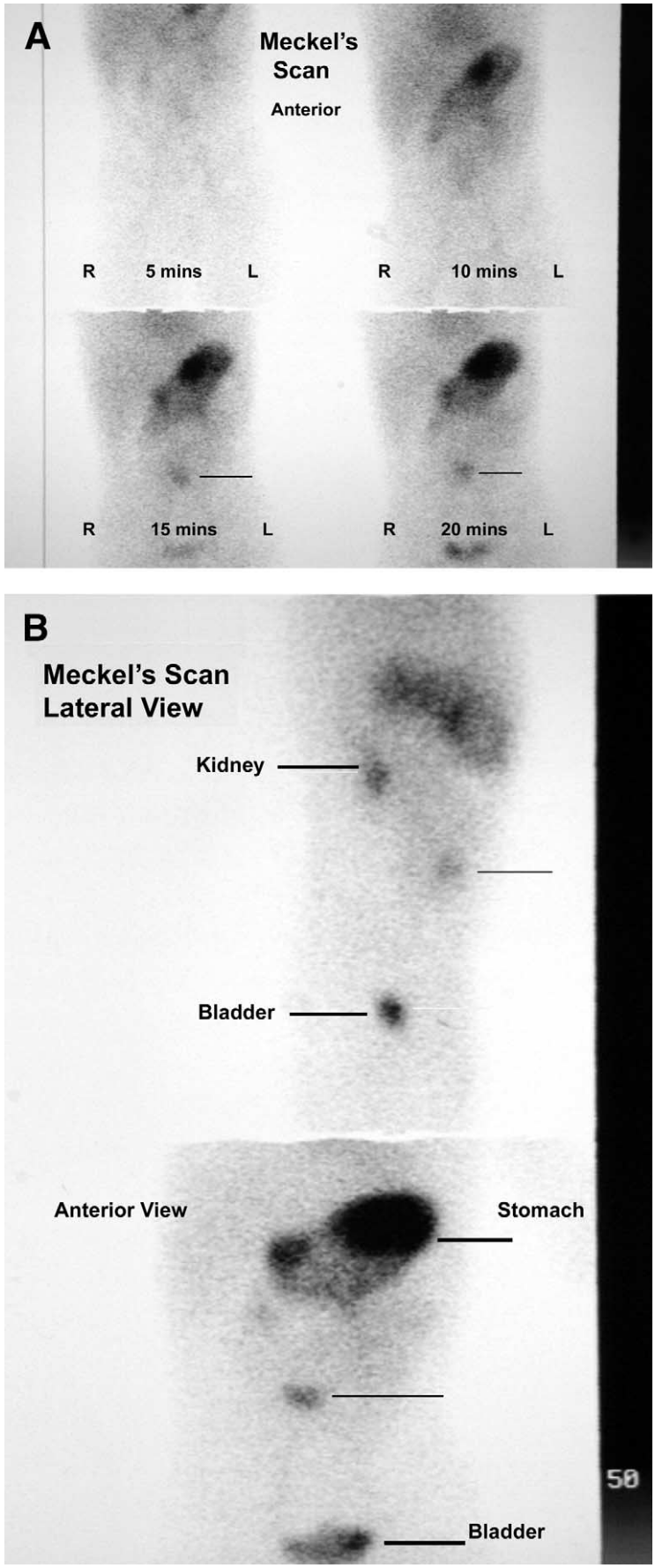


Figure 2 Meckel's scan (^{99m}Tc pertechnetate) in a 6-year-old male patient whose presenting clinical feature was severe unexplained anemia (hemoglobin 2.1 mg/dL). (A) Static images of the abdomen at 5, 10, 15, and 20 minutes showing gradually increasing abnormal accumulation of radiotracer in the central abdomen consistent with ectopic gastric mucosa (arrows). (B) Lateral and anterior static images showing moderately intense accumulation of radiotracer in the anterior central abdomen (arrows), consistent with ectopic gastric mucosa. ^{99m}Tc pertechnetate is also observed in the stomach, kidneys, and urinary bladder.

netate uptake in the stomach for several weeks after administration.[47] ^{99m}Tc pertechnetate uptake also can be seen in obstructed loops of bowel, intussusception, arteriovenous malformations, ulcers, inflammatory lesions, and some bowel tumors, giving rise to false-positive studies.[31]

Image Interpretation Pitfalls

Interpretation of ^{99m}Tc sulfur colloid imaging in the upper abdomen may be problematic in certain clinical settings because of reticuloendothelial cell uptake of this radiotracer within liver and spleen. Also, potential false-positive interpretation of focal abnormal uptake has been reported as the result of an accessory spleen.[48] Unexpected bleeding from a ruptured spleen also has been reported using ^{99m}Tc labeled erythrocyte scintigraphy,[49] as well as a photopenic region seen in the spleen on ^{99m}Tc sulfur colloid imaging indicating splenic rupture.[50] Other unsuspected causes of bleeding also have been documented, including bleeding around a peritoneal dialysis catheter in the abdominal wall of a patient with end-stage renal failure.[51] Trauma can potentially account for bleeding detected in soft tissues adjacent to but outside the abdominal cavity.[52-55] Gluteal hematoma and other soft tissue hemorrhages also have been reported on ^{99m}Tc-labeled erythrocyte scintigraphy.[56,57] Nonenteric bleeding secondary to the use of anticoagulant use or the presence of inherent coagulopathy also has been detected using scintigraphic techniques.[58-60] When such bleeding occurs in the abdominal wall, interpretation may be difficult without the use of oblique or lateral images.[61] Retroperitoneal abdominal varices may mimic gastrointestinal bleeding on both ^{99m}Tc sulfur colloid imaging and ^{99m}Tc-labeled erythrocyte imaging.[62,63] Intraperitoneal bleeding also has been reported using ^{99m}Tc-labeled erythrocytes to study possible AGH in a patient with pancreatitis as well as liver and renal failure complicated by sepsis.[64] Bleeding into a pancreatic pseudocyst also has been reported.[65] Other structures that have been reported to have the potential to reduce the specificity of ^{99m}Tc-labeled erythrocytes include a horse-shoe kidney,[66] the left ovarian vein,[67] dilated abdominal aorta,[68] ischemic bowel,[69] hepatic hemangioma,[70] diverticula abscess, and uterine leiomyoma[71] (Fig. 3). Bleeding from a ruptured abdominal aortic aneurysm also has been reported as an interpretation pitfall.[72] In addition, normal or aberrant vasculature supplying genitalia may be confused with abnormal accumulation, particularly if patient positioning is suboptimal. Attenuating structures such as barium sulfate from previous barium enema examination may potentially result in a false negative study (Fig. 4).

Gallbladder visualization during ^{99m}Tc-labeled erythrocyte scintigraphy has been more widely reported in both adults and a neonate.[73-78] Hematobilia may account for this scan finding, or alternatively transfusion-related labeling of the porphyrin group of degraded hemoglobin, with subsequent liver and biliary excretion, particularly in patients with severe renal impairment.[73,79]

Not only does ^{99m}Tc-labeled erythrocyte scintigraphy have the potential to detect active bleeding from gastrointestinal tumors, but it also may help demonstrate other large vascular tumors.[80,81] However, correlative imaging often is required to assist with interpretation of the scan findings.[82]

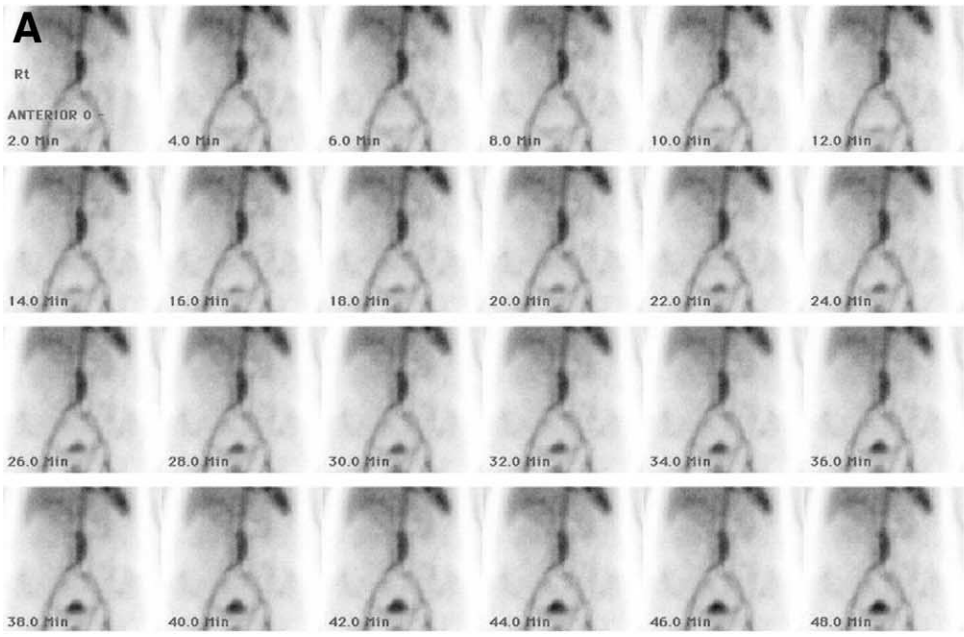
Pitfalls also commonly occur, not only in establishing a diagnosis of AGH but also in attempts to localize the site of bleeding. Cinegraphic loop viewing of dynamic imaging can help to reduce incorrect interpretation of bleeding sites by demonstrating the onset of bleeding and the subsequent peristaltic passage of radiotracer along the bowel.[83-86] Static imaging may demonstrate blood in the bowel lumen without definite evidence of its site of origin. Great care must be taken with interpretation of the apparent site of bleeding because blood within the gut lumen stimulates strong peristaltic action resulting in both antegrade and retrograde spread of the blood from the site of bleeding (Fig. 3). Furthermore, the timing of a static image may show blood in the gut that has already traveled distal to the actual site of bleeding. Dynamic imaging minimizes, but does not eliminate, such timing errors. Incorrect image interpretation may therefore place the patient at increased risk if urgent surgery is undertaken on this basis, without angiographic correlation.

Controversies

Patient Risk Stratification

A retrospective study of 565 hospitalizations (488 patients) for AGH in a large tertiary referral hospital during a 7-year period showed that in 89% of cases bleeding stopped spontaneously,[87] which is an indicator as to the vagaries of AGH and the difficulties involved in establishing protocols for the management of patients. A large proportion of patients admitted to hospital with AGH will be discharged from hospital without a satisfactory diagnosis for the cause of bleeding.[88] Consequently, it can be argued that if such a large proportion of patients have a good outcome irrespective of the investigations undertaken, the rationale for investigating these patients in the first place can be called into question. Unfortunately, predicting which patients will fall into the favorable

Figure 3 Dynamic imaging sequence after the intravenous administration of ^{99m}Tc-labeled erythrocytes in a 76-year-old man whose presenting symptom was recurrent rectal bleeding. (A) Imaging 0 to 48 minutes showing no active gastrointestinal bleeding. A small infra-renal abdominal aortic aneurysm is noted. (B) Imaging 61 to 90 minutes shows active bleeding in the hepatic flexure. Radiotracer is most avid at this location but radiotracer is also seen distal and, to a lesser extent, proximal to the site of bleeding. (C) Additional sequence after 4 hours shows more marked antegrade and retrograde movement of the radiotracer from the site of bleeding (hepatic flexure). (D) Additional sequence after 5 hours showing persistent but widespread distribution of radiotracer in the colon.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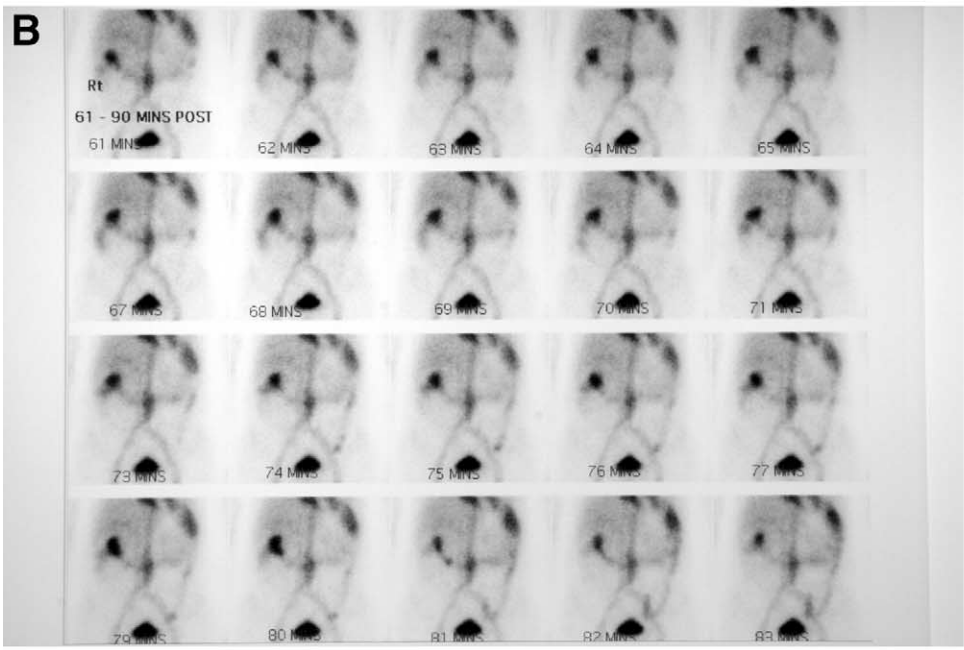
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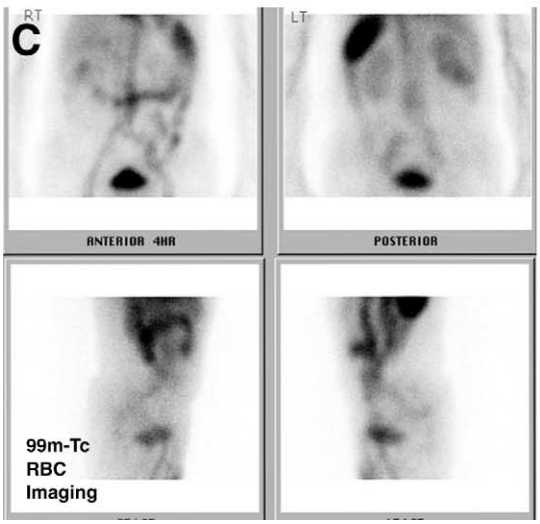
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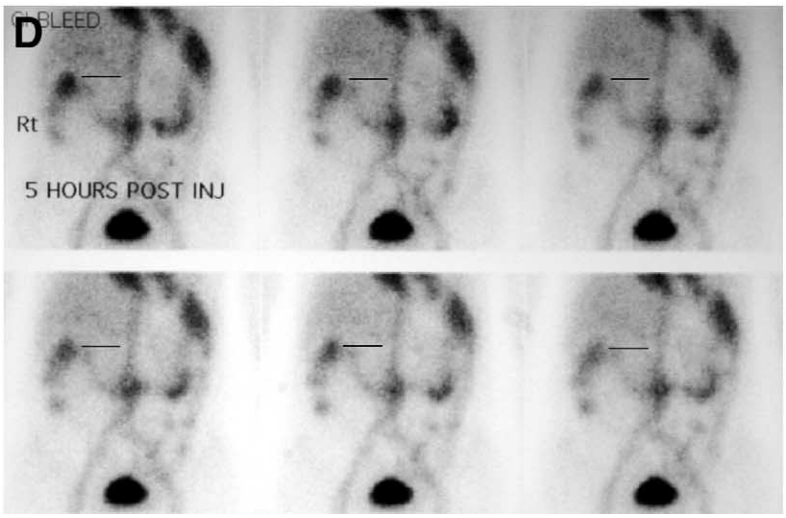
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outcome group is not always easy, and despite several recommended clinical classification tools, currently no reliable triage or risk stratification technique exists.[89-91] However, a negative ^{99m}Tc-labeled red blood cell scintigraphy study has been shown to be predictive of a good outcome.[92] These authors calculated approximate bleeding rates based on scintigraphic appearance and blood transfusion requirements in 62 patients with anemia and grossly bloody or guaiac-positive stools. They were able to risk-stratify these patients on the basis of estimated bleeding rates according to overall transfusion requirements and surgical outcome. Although their data provide only useful guidelines, as a result of the inherent technical difficulties of such calculations, the study does, however, provide good evidence to indicate that the optimal time for ^{99m}Tc red blood cell-labeled scintigraphy is less than 24 hours after the patient has received a minimum of 2 units (500 mL) of red blood cell transfusion. Other, more recent, evidence also is available to support this assertion.[93]

The Role of Nuclear Medicine Imaging in Planning Surgery

^{99m}Tc-labeled red blood cell scintigraphy has been called into question in its role in assisting surgical intervention of patients with acute lower gastrointestinal bleeding.[94] This retrospective study showed that of the 249 patients who had scans during a 10-year period, 40 underwent laparotomy for ongoing bleeding. Of these patients 28 (70%) were positive on ^{99m}Tc-labeled red blood cell scintigraphy. These authors regarded a negative scan as unhelpful if the surgeon chose to operate despite this scan result, and 3 of the 12 patients with negative scans (25%) died as the result of perioperative complications directly unrelated to blood loss, which further raises the issue of appropriate risk stratification before surgical intervention. Operative intervention usually is considered appropriate for patients with massive gastrointestinal bleeding defined as patients who are hemodynamically unstable. For example, those requiring more than 5 units of packed red blood cell replacement. The risk-benefit ratio should always be taken into account, particularly where a more circumspect approach may have a favorable outcome. A negative scan may indicate no need for acute surgical intervention. A positive scan has been shown to be predictive of increased in-hospital mortality and morbidity compared with a negative scan.[84,95] If by corollary, a negative scan is associated with relatively reduced in-hospital mortality, the use of surgical intervention in this group of patients can be brought to question.

When the localization accuracy of positive nuclear medicine scans have been evaluated by endoscopy, angiography, or surgery, a range of 40% to 100%, and mean value of 80% have been reported.[96-103] By most standards this implies a very satisfactory ability to accurately localize the site of bleeding. Alternatively, looking at the percent of inaccurate localization in these studies, the range was 6% to 59% and mean value was 25%.[96,103,104] If it can be safely assumed that the mean values are truly representative, these values indicate accurate localization will occur in approximately 75% to 80% of cases, and inaccurate localization will occur in 20% to 25% of cases. Furthermore, in the absence of other clinical means of identifying the site of bleeding, these data indicate that scintigraphy offers incremental advantage irrespective of the test's imperfections.

The Role of ^{99m}Tc-Labeled Red Blood Cell Scintigraphy to Detect Bleeding From the Lower Gastrointestinal Tract

Despite the apparent advantages of this form of imaging compared with angiography and ^{99m}Tc sulfur colloid imaging, which allows longer periods of imaging, its role remains controversial. There has been great variation in reported diagnostic accuracy for the detection of active bleeding.[6,13,105] Inherently, the use of numerically expressed diagnostic accuracy (sensitivity and specificity, positive and negative predictive values) for comparative purposes with this test suffers from the following problems: (1) The definition of a "positive" test is relatively loose; (2) comparison to other imaging tests is only valid when both tests share a similar measurable study endpoint; (3) the clinical relevance of detectable bleeding without localization of the bleeding site is not clearly established; and (4) because of the unpredictability of bleeding, the results of scintigraphy are highly dependent on both the appropriate selection of the patient and correct timing of the test. Consequently, the published literature contains a broad range of sensitivities and specificities in an attempt to convey comparative imaging value to scintigraphy imaging as well as other imaging modalities.[24,96,106-113]

Theoretically, ^{99m}Tc-labeled red cell scintigraphy can be used to detect intermittent lower gastrointestinal hemorrhage where other methods have a low probability of detecting active bleeding.[11] In practice, however, more often than not, prolonged imaging using ^{99m}Tc-labeled red blood cell scintigraphy is negative. Consequently, the use of potentially costly imaging time can be wasteful unless there is a relatively high probability that the patient will actively bleed during the allocated imaging time. Therefore, patients who have not had significant blood loss over a short period of time are unlikely to bleed actively during the imaging period. The number of positive scans in published series range from 26% (52/203) to 82% (85/103), whereas the mean is 56%.[96,103,114] This variation of results has contributed to the debate as to the true utility of this form of imaging. In reality, however, the variation largely reflects how well patients were selected for imaging, rather than the true utility of the imaging test. Other factors such as imaging protocols and interpretative skills may also influence such results.

Use of ^{99m}Tc-Labeled Red Blood Cell Scintigraphy as a Screening Test to Predict the Likelihood of Positive Angiography

Because of the ability of angiography to detect active bleeding but a reduced ability to detect intermittent bleeding, ^{99m}Tc-labeled red blood cell scintigraphy has been advocated as a useful test to precede angiography.[115] The rationale is based on both its higher sensitivity to detect bleeding compared with angiography and its higher likelihood to detect intermit-

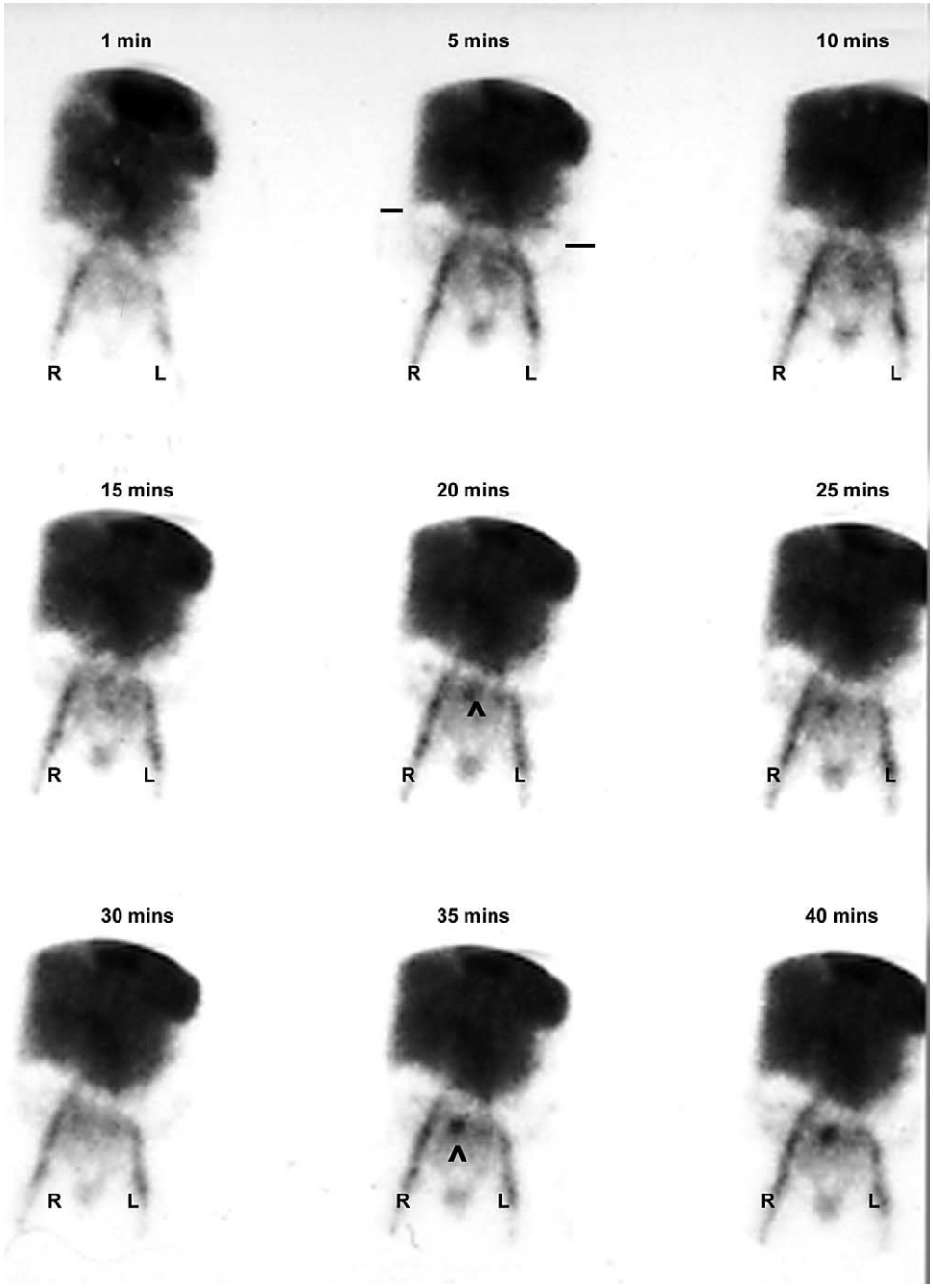

Figure 4 Dynamic imaging sequence after the intravenous administration of ^{99m}Tc-labeled erythrocytes in a 75-year-old man whose presenting symptom was intermittent bright rectal bleeding. The day before, he had been investigated by barium enema. Abdominal imaging sequence 5 to 40 minutes showing no evidence of active gastrointestinal bleeding until about 15 to 20 minutes (/\). The central abdominal bleeding stops, and is again seen at 35 minutes (/\). Attenuation artifact due to barium within the transverse colon is noted (–). Although the barium artifact partially obscures the bleeding site, it indicates a bleeding source from small bowel rather than colon.

tent bleeding.[116,117] The authors of a review of 249 patients who had ^{99m}Tc red blood cell-labeled scintigraphy and 271 who had visceral arteriography reported a significant benefit of scintigraphic screening, although the methodology allowed bias to influence the results.[118] Despite this apparent sound rationale, other studies have indicated no clear-cut advantage in this diagnostic approach.[99,103,114] Factors such as patient selection, imaging techniques, timing of angiography relative to radionuclide scintigraphy, and skill of the angiographer are likely to contribute to the lack of consensus on this issue. It can be argued that radionuclide scintigraphy has more of a role in patients who clearly may require surgical intervention where angiography is negative. Consequently, angiography is indicated for all suitable patients before surgery, or with a view to being an interventional alternative to surgery. In some circumstances, however, bleeding may be

life-threatening but intermittent. In this situation, ^{99m}Tc-labeled red blood cell scintigraphy before angiography may be helpful in establishing correct timing of the angiography. Accurate logistical coordination of both imaging tests is, however, required for this to be successful.

The authors of a study of 86 patients with positive ^{99m}Tc red blood cell scintigraphy suggested that this test can be used to predict which patients will have detectable bleeding on angiography on the basis of the presence or absence of a scintigraphic "blush" seen within the first 2 minutes of the study.[119] They reported respective positive and negative predictive values of 75% and 93%, thus allowing greater selectivity of patients who should undergo angiography. The overall predictive values and clinical utility, however, are likely to be considerably lower in practice, when considering the inclusion of patients who are negative on ^{99m}Tc red blood cell scintigraphy.

Optimal Duration Of Imaging With ^{99m}Tc-Labeled Red Blood Cells

Diagnostic benefits have been suggested for imaging over a longer time period than the usual 1 to 2 hours.[105,115,120] Furthermore, a report of 2 cases showed the value of a second radiotracer injection that apparently enabled the detection of AGH on delayed scintigraphy in patients with intermittent bleeding.[121] The author argues that reinjection at 18 to 24 hours after the original dose of radiotracer, by virtue of enhanced count statistics, reduces the likelihood of misinterpretation due to previously extravasated red blood cells and increases the likelihood of localization of bleeding. A study of 137 patients, including 24 whose imaging time extended beyond 3 hours (intermittent imaging), showed that 11 of these patients had positive scans that would otherwise have been missed.[122] However, controversy exists regarding the clinical utility of delayed imaging. A retrospective study of 67 emergency room patients who had ^{99m}Tc-labeled erythrocyte scintigraphy studies performed with additional delayed imaging, using endpoints of clinical outcome and patient management, compared patients with positive scans to those with negative scans.[123] No statistical significance was found between the 2 groups, and it was concluded that delayed imaging had no significant influence on outcome for those patients whose initial scan (over the course of 1 to 2 hours) was negative or equivocal. These authors report mortality values of 8% for positive scans versus 0% for negative scans, with $P < 0.32$ calculated by χ^2 or Student t-test. Proportionality statistic calculation for 3/37 versus 0/30 yields a P value of 0.105.[124] Although this study attempts to objectively measure the benefit of delayed imaging, it fails to measure true incremental benefit by comparison to patients who did not have delayed imaging and, also, because of selection bias within both patient groups, as well as the retrospective nature of the study. In another retrospective study of 48 patients with negative ^{99m}Tc-labeled erythrocyte scintigraphies during the first 60 to 90 minutes of imaging who subsequently underwent delayed imaging, late positives were observed in 22 (46%).[125] These authors also indicated that patients with late positive scans had a higher rate of surgery and increased transfusion requirements than late negative patients. Furthermore, late positive bleeding was more likely to occur from proximal gut than colon. Similar potential selection bias and shortcomings related to a retrospective analysis also limit the application of data from this study.

Other retrospective studies have also been published advocating prolonged or delayed imaging with ^{99m}Tc-labeled erythrocytes,[120,126] and although the weight of relatively weak evidence supports the use of delayed imaging, it is apparent that a prospective, and possibly multicenter, study approach is required, using unambiguous outcome markers, to assess any true incremental advantage of delayed imaging.

Role of Nuclear Medicine Scintigraphy in Small Bowel Hemorrhage

The colon is relatively peripheral in its location within the abdominal cavity and also has easily located landmarks, such as the hepatic and splenic flexures. The sigmoid colon is more variable but is generally predictable in its location. The small bowel, although located more centrally, is more variable in location and more prone to overlap with vascular structures. Other physiological considerations, such as a potentially more rapid rate of transit in small bowel and a greater tendency for both antegrade and retrograde radiotracer propulsion with peristalsis, also may be important. Consequently, detection and localization of bleeding in small bowel may be more difficult. A lower diagnostic rate has been demonstrated for the detection of foregut bleeding (7/21, 33%) using ^{99m}Tc-labeled red blood cells compared with colonic bleeding (15/20, 75%).[122]

Recommended Roles of Imaging Modalities

The role of nuclear medicine scintigraphy in the detection of lower gastrointestinal hemorrhage fits into a neat theoretically algorithm. This algorithm places the scintigraphy study as one of the first imaging investigations to be performed with the aim of determining a sufficient rate of bleeding to facilitate successful angiography and possible angiographic intervention.[16] However, gastrointestinal bleeding is a law unto itself with respect to timing, severity, and clinical context. Consequently, algorithms are only useful as guidelines and, often, each case has to be individually evaluated. Furthermore, a lack of consensus among emergency room physicians, surgeons, interventional radiologists, and nuclear medicine physicians also often adds to the difficulties in prescribed patient management. The use of ^{99m}Tc-labeled erythrocyte scintigraphy as a tool for risk stratification may assist an algorithmic approach to management and also may assist in preventing an overaggressive surgical approach to management that may reduce both morbidity and mortality. Most of the literature, understandably, tends to focus on the role of a positive scintigraphy study, rather than negative studies. However, iatrogenic morbidity and mortality may be minimized by a more measured approach to surgical intervention.

There are clear-cut situations in which emergency surgical intervention is required without time for scintigraphic imaging procedures. More often, however, the patient has been stabilized by transfusion and supportive care while undergoing surgical assessment. A negative scintigraphy study in this group of patients is predictive of good outcome, and may be a very useful means of risk stratifying patients who do not need to be put at unnecessary risk of emergency surgery.[120]

^{99m}Tc-labeled erythrocyte scintigraphy or ^{99m}Tc sulfur colloid imaging have a role in assisting both radiological and surgical interventions, and scintigraphy is highly recommended before angiography. Optimal timing and good coordination, by use of standardized institutional protocols, will help ensure that the patient benefits from both tests. The surgical team should adopt a realistic approach when using scintigraphy to assist surgical planning and should assume that the test will potentially benefit surgical management in approximately 25% of cases.[96,127] Moreover, this proportion can be improved where those patients referred for scintigraphy imaging are more carefully selected.[128]

The role and benefits of delayed scintigraphy are enticingly apparent but unconfirmed by scientific clinical assessment. The procedure guidelines of the Society of Nuclear Medicine currently suggest that the use of delayed imaging is optional.[129] Some may argue that ^{99m}Tc-labeled red blood cells scintigraphy has its most practical application in patients with minimal or moderately severe hemorrhage, whereas patients with massive hemorrhage should either have angiography with a view to therapeutic intervention or surgery.[130] The group of patients who present with anemia and intermittent rectal bleeding or malena stool and no diagnosis despite endoscopic examination are another group often referred for ^{99m}Tc red blood cell scintigraphy. It is this group of patients who tend to lower the overall diagnostic sensitivity of the test in many published series. Unless there is good objective clinical evidence that the patient is actively bleeding, or likely to bleed during the course of the study, there is no point in performing the test in this group of patients. Similarly, investigating patients with ^{99m}Tc pertechnetate Meckel's scan should be restricted to those patients where there is (1) a high likelihood of bleeding ectopic gastric mucosa based on the clinical scenario and (2) a positive scan result will result in a management plan that will benefit the patient without inappropriately increasing iatrogenic risk. These are particularly important considerations in children. In view of the extremely low overall likelihood of a positive Meckel's scan, particularly in adults, performing the test to exclude bleeding from this source, in most cases, is not an appropriate indication for the test despite a reported specificity of 90%.[35]

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