Role of scintigraphy in inflammatory bowel disease

Maria I Stathaki, Sophia I Koukouraki, Nikolaos S Karkavitsas, Ioannis E Koutroubakis

Author contributions: Stathaki MI, Koukouraki SI reviewed the literature, wrote the first draft of the paper; Karkavitsas NS and Koutroubakis IE provided the idea, performed the review, and edited the manuscript.

Correspondence to: Ioannis E Koutroubakis, MD, PhD, Department of Gastroenterology, Medicine University Hospital of Heraklion, PO Box 1352, 71110 Heraklion, Crete, Greece. kjohn@her.forthnet.gr

Abstract

The diagnosis of inflammatory bowel disease (IBD) depends on direct endoscopic visualization of the colonic and ileal mucosa and the histological study of the obtained samples. Radiological and scintigraphic methods are mainly used as an adjunct to endoscopy. In this review, we focus on the diagnostic potential of nuclear medicine procedures. The value of all radiotracers is described with special reference to those with greater experience and more satisfactory results. Tc-99m hexamethylpropylene amine oxime white blood cells remain a widely acceptable scintigraphic method for the diagnosis of IBD, as well as for the evaluation of disease extension and severity. Recently, pentavalent Tc-99m dimercaptosuccinic acid has been recommended as an accurate variant and a complementary technique to endoscopy for the follow-up and assessment of disease activity. Positron emission tomography alone or with computed tomography using fluorine-18 fluorodeoxyglucose appears to be a promising method of measuring inflammation in IBD patients.

Key words: Crohn's disease; Technetium-99m pentavalent dimercaptosuccinic acid; Intestinal inflammation; Scintigraphy; Ulcerative colitis

Peer reviewer: Tsianos Epameinondas, MD, PhD, Professor, 1st Division of Internal Medicine & Hepato-Gastroenterology Unit, Medical school University of Ioannina, PO Box 1186, Ioannina 45110, Greece

Stathaki MI, Koukouraki SI, Karkavitsas NS, Koutroubakis IE. Role of scintigraphy in inflammatory bowel disease. World J Gastroenterol 2009; 15(22): 2693-2700. Available from: URL: http://www.wjgnet.com/1007-9327/15/2693.asp DOI: http://dx.doi.org/10.3748/wjg.15.2693

INTRODUCTION

The diagnosis and follow-up of patients with inflammatory bowel disease (IBD) is mainly based on endoscopy and the histological study of the obtained biopsy specimens. Ileocolonoscopy, gastroscopy and evaluation of small bowel by wireless capsule endoscopy or double balloon enteroscopy offer a successful diagnostic approach in the majority of IBD patients.

Radiological methods have a secondary role and they are used additionally to endoscopy. They are indicated in cases of suspected complications or small bowel involvement in patients with Crohn's disease (CD). They include conventional radiological methods such as double-contrast barium studies and cross-sectional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. All of them have been proven valuable techniques for evaluation of the effects of the inflammatory process, not only on the bowel wall, but also on other structures within the abdomen.

Unfortunately, endoscopy as well as the majority of the aforementioned radiological methods are not well tolerated by patients, because of the necessity for adequate bowel preparation and the increased risk of complications, especially when used during the acute phase of bowel inflammation.

Alternatively, several studies have demonstrated the reliability of scintigraphic imaging in the diagnosis and assessment of disease activity in IBD. In comparison with other modalities, they are non-invasive techniques and produce no patient discomfort related to instrumentation and preparation, they are not contraindicated in the acute phase and can visualize active disease both in the small and the large bowel.

Technetium-99m hexamethylpropylene amine oxime labelled white blood cells (Tc-99m HMPAO WBC) have been accepted widely as a reliable method for the diagnosis of IBD, assessment of disease activity
and treatment response. Pentavalent Tc-99m dimercaptosuccinic acid [Tc-99m (V) DMSA] seems to be an accurate scintigraphic variant and has been suggested as a complementary technique to colonoscopy for the follow-up and assessment of disease activity. Finally, fluorine-18 fluorodeoxyglucose (F-18 FDG) is a promising method for the detection of inflammation in the small and large bowel.

In this article, we review the current data and future prospects on the role of scintigraphy in diagnosis and evaluation of disease activity in patients with IBD.

THE ROLE OF NUCLEAR MEDICINE IN IBD

Nuclear medicine imaging has played a major role in the diagnosis and detection of inflammation, and has a wide availability of radiotracers. However, its contribution to the localization of small and large bowel pathology in IBD is still under investigation.

Indium-111 oxine labeled leukocytes

Indium-111 (In-111) oxine was the first agent used for in vitro leukocyte labeling. The method has been validated by different research groups as a sensitive and specific test for the detection of active intestinal inflammation. However, the high radiation dose, limited availability and poor image quality comprise major disadvantages associated with In-111.

Recently, a dedicated whole-body counter has been proposed as an alternative technique to whole-body gamma-camera counting for quantification of disease activity in IBD. It relies on the assumption that all granulocytes migrating into the bowel wall in IBD do in fact end up in the feces, therefore In-111 retention in IBD patients is less compared to that in normal volunteers.

Tc-99m HMPAO labeled leukocytes

Tc-99m HMPAO has been used clinically as a cerebral perfusion agent. In 1986, Peters et al. used it as an alternative to leukocytes labeling and inflammation imaging. Since then, several groups have verified the utility of this imaging technique for IBD. The published data show that it provides a sensitivity of 95%-100%, a specificity of 85%-100% and an accuracy of 92%-100% in the detection, localization and assessment of disease activity. Therefore, its widespread acceptance has been based on the aforementioned favorable results and the advantages of Tc-99m, such as low radiation dose, availability, cost and superior image quality. It plays an important role in the diagnosis of complications, assessment of disease activity and establishing the extent of small intestine affected. Moreover, it allows a true evaluation of inflammation activity, even during clinical remission or treatment response.

In 2007, Almer et al. compared leukocyte scintigraphy to intraoperative small bowel enteroscopy and laparotomy findings in CD. They confirmed the reliability of Tc-99m HMPAO WBC in the early diagnosis of small bowel inflammation, and proposed its utility as a first-line investigation modality, especially in children and vulnerable adults.

Despite the wide utility of Tc-99m HMPAO WBC in IBD, controversy still exists about the advantageous imaging time. Early scanning (30-60 min) has been recommended by some authors in order to avoid false positive results caused by intestinal migration of the radionuclide, whereas others favor late scanning because of higher sensitivity. Recently, Sans et al. have evaluated the optimal scanning sequence for identification of active disease, evaluation of IBD extent, and quantification of disease activity. They reported only slightly lower specificity but higher sensitivity (85% vs 100%) and accuracy (85% vs 95%) of late scanning (3 h) when compared to early scanning.

Various biomarkers of inflammation have been suggested in selecting patients with suspected IBD for white cell scanning. Given that C-reactive protein constitutes a reliable indicator for the evaluation of inflammatory activity in IBD, patients with ≥ 5 mg/L should be selected for white cell scanning in order to reduce the number of false negative results.

Alonso et al. have applied Tc-99m HMPAO WBC to patients with subclinical gut inflammation. This group studied patients with seronegative spondyloarthropathy without clinical evidence of IBD. They confirmed the utility of the method in the assessment of bowel inflammation, even if it remains subclinical. Moreover, they described a possible role of labeled leukocytes in identifying the patients who are suitable for therapy with sulfasalazine, and in assessing treatment effectiveness and disease relapse. El Maghraoui et al. have certified the aforementioned results and demonstrated a statistically significant correlation between Tc-99m HMPAO-labeled leukocytes and ileocolonoscopy.

The usefulness of this technique in early detection of postoperative asymptomatic recurrence of CD has been suggested. Biancone et al. have demonstrated that, in patients with CD who had an ileocecal resection in the previous 6 mo, the perianastomotic 30 min Tc-99m HMPAO WBC uptake was significantly associated with disease recurrence.

The role of Tc-99m HMPAO-labeled leukocytes single photon emission computed tomography (SPECT) in IBD has also been investigated. SPECT images provide accurate assessment of inflammation in both the small and large bowel and precise anatomical details of CD lesions. Moreover, they are independent of bone marrow activity, thus allowing detailed disease evaluation within the pelvis.

The aim of several groups has been to evaluate and compare the diagnostic accuracy of Tc-99m HMPAO-labeled leukocytes and CT in IBD. They have demonstrated the superiority of scintigraphy in detecting segmental inflammatory activity and proximal extension of bowel involvement. CT displays excellent suitability of bowel involvement. CT displays excellent suitability of bone marrow activity, thus allowing detailed disease evaluation within the pelvis.

Several studies have supported the utility of Tc-
99m HMPAO WBC in pediatric patients with IBD. They have suggested that labeled leukocytes cannot replace endoscopy for initial diagnosis but they do have a place in the decision for colonoscopy[36,37]. Patients with negative 99m HMPAO WBC scans may avoid unnecessary colonoscopy. However, Cucchiara et al[38], after evaluating 48 children, have concluded that a positive test indicates the presence of inflammation but a negative result does not rule out inflammation, since the technique may miss cases with mild disease.

Moreover leukocytes scintigraphy can be considered a reference method for clarifying the extent of inflammation when colonoscopy is not completed successfully, or the findings in contrast radiography are negative[36,37,39]. Although SPECT allows the identification of additional involved segments over planar images, its performance in children seems to be rather difficult[37,40].

The accuracy of 99m HMPAO WBC in differentiating continuous from discontinuous colitis has also been examined[37,41]. In 77 children with active CD, discontinuous uptake was revealed in 63, and among 29 children with ulcerative colitis (UC), continuous uptake was revealed in 23[41]. It should also play an important role in the follow-up of patients and it could be used as a diagnostic tool for assessing recurrence or response to therapy, thus reducing the need for repeated colonoscopy[36,37].

In a report by Charron et al[35], the accuracy of CT and 99m HMPAO WBC scintigraphy versus colonoscopy in IBD has been compared. After evaluating 313 consecutive children who underwent a labeled leucocyte test and comparing with colonoscopy, the sensitivity of scintigraphy was 92%, specificity was 94%, positive predictive value was 96%, negative predictive value was 93% and accuracy was 94%. 99m HMPAO WBC scan is unlikely to miss significant inflammation, while CT has lower sensitivity for detecting inflammation in the bowel wall. However, similar to the adult population, the incidence of complications detected by CT is higher than with scintigraphy[38].

Compared to other modalities, 99m HMPAO WBC scintigraphy is non-invasive, practical, safe, rapid and has excellent diagnostic sensitivity (Figure 1). It requires no bowel preparation, causes no discomfort and exposes patients to less radiation, namely the effective radiation dose for 99m HMPAO WBC imaging is 3 mSv, for barium small bowel follow-through, 6 mSv, and for barium enema, 8.5 mSv[16,39,42]. Additional important advantages are the ability to evaluate the small and the large bowel simultaneously and the superior over small bowel follow-through and CT, in the initial screening and detection of inflammation in patients with IBD[13,38,42]. A concise form of the published data is presented in Table 1.

The high cost, time-consuming in vitro labeling procedure, radiation microdosimetry, as well as the handling and reinjection of blood constitute the main shortcomings of the procedure when compared to other scintigraphic modalities.

### 99m (V) DMSA

99m (V) DMSA is a tumor-seeking agent of low molecular weight developed in 1981. It has been used successfully in the scintigraphic diagnosis of various malignant tumors[43-47]. Moreover, it has been proven advantageous in the diagnosis of inflammatory diseases such as osteomyelitis, psosas muscle abscess, and bone and joint infection[48,49].

The mechanism of 99m (V) DMSA localization in tumors and inflammation remains unclear. In some cases, it resembles the phosphate ion because it accumulates in lesions where calcification is present. However, the increased capillary permeability followed by infiltration of the radiotracer into the interstitial space seems to be the most probable mechanism of uptake in inflammatory lesions[16,17,48,49].

99m (V) DMSA scintigraphy requires no bowel preparation, no blood manipulation and causes no patient discomfort. Moreover it has a low cost, ideal physical characteristics, and simple preparation procedure from cold kits[15,17]. Its utility in the diagnosis

### Table 1 Summary of published studies evaluating the use of Tc-99m HMPAO WBC in IBD

| Study                  | n     | Study design                                                                 | Sensitivity | Specificity |
|------------------------|-------|-----------------------------------------------------------------------------|-------------|-------------|
| Adult population       |       |                                                                             |             |             |
| Sciarretta et al[35]   | 103   | Known active CD compared with colonoscopy                                    | 95%         | 100%        |
| Mairal et al[34]       | 27    | Known IBD compared with In-111 HIG                                         | 100%        | 85%         |
| Giaffer et al[16]      | 31    | Suspected IBD compared with In-111 oxine labeled leukocytes                 | 85% at 40 min| 87% at 40 min|
| Kolkmann et al[40]     | 32    | Known IBD compared with CT                                                 | 94% at 120 min| 71% at 120 min|
| Molnar et al[46]       | 28    | Known active CD compared with spiral CT                                     | 79% for CD  | 98% for CD  |
| Almer et al[30]        | 48    | Known active CD with small bowel inflammation compared with intraoperative | 81% for UC  | 86% for UC  |
|                        |       | small bowel enteroscopy and laparotomy findings                             |             |             |
| Pediatric population   |       |                                                                             |             |             |
| Charron et al[35]      | 215   | Acute intestinal inflammation in patients with and without IBD              | 90%         | 97%         |
| Cucchiara et al[38]    | 48    | Suspected IBD compared with colonoscopy                                     | 76.2%       | NA          |
| Charron et al[35]      | 130   | Exclude inflammation in suspected IBD compared with colonoscopy            | 94%         | 99%         |
| Alberini et al[32]     | 28    | Known IBD compared with endoscopy, ultrasonography and contrast radiology   | 75%         | 92%         |
| Charron et al[35]      | 313   | Known IBD compared with colonoscopy                                        | 92%         | 94%         |

NA: Not applicable; CD: Crohn’s disease; CT: Computed tomography; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.
of inflammation combined with the aforementioned advantages have given a new impulse to research groups to evaluate its role in IBD.

In 2001, Lee et al[15] appraised the potential use of Tc-99m (V) DMSA scintigraphy in the detection and localization of intestinal inflammation. The study enrolled 62 patients with suspected intestinal inflammation, namely IBD, appendicitis, and antibiotic-associated, infective, eosinophilic and ischemic colitis. The scintigraphic findings were compared to colonoscopy and biopsy results. The overall sensitivity was 95%, specificity, 94%, and accuracy, 95%. The three false negative cases were attributed to a mild degree of inflammation. Findings were false positive in two cases as a result of coexisting active bleeding from the gastrointestinal tract and colonic adenocarcinoma, seen at colonoscopy with biopsy[15].

In 2003, Koutroubakis et al[16] evaluated the use of Tc-99m (V) DMSA for the assessment of disease activity in patients with IBD. They examined three groups of patients. The first group enrolled 36 patients who had an exacerbation of previously demonstrated disease or had a first attack of the disease. Tc-99m (V) DMSA scintigraphy was performed after clinical and endoscopic confirmation of active disease and true positive labeled leucocyte scintigraphy. The full agreement among the scintigraphic modalities was 72.5%. The agreement among endoscopy and scintigraphy was 91.9% and 84.4% for Tc-99m HMPAO WBC and Tc-99m (V) DMSA, respectively. The overall sensitivity was 91% for Tc-99m HMPAO WBC and 84% for Tc-99m (V) DMSA. False negative results for Tc-99m (V) DMSA scintigraphy were seen in two patients with UC, probably because of a mild degree of bowel inflammation[16].

Data suggest that Tc-99m (V) DMSA scintigraphy provides a useful approach in the diagnosis of active disease and assessment of disease activity (Figure 2). Despite that, it cannot replace Tc-99m HMPAO WBC for the evaluation of disease localization. Probably, it is not the ideal method for the diagnosis of IBD but it has a place in the follow-up and assessment of disease activity, progression and treatment response[17]. A concise form of the published data is presented in Table 2.

Other radiotracers
A variety of radionuclides has been applied to IBD investigation. Some of them have not gained widespread clinical use because of limitations and disappointing results, while others seem to have a definite role.

Figure 1 Tc-99m HMPAO WBC scintigram. A: Ulcerative colitis (UC) with intense inflammation of the entire large bowel; B: Crohn’s disease (CD) with intense inflammation in the small bowel and the descending colon.

Figure 2 Tc-99m (V) DMSA scintigram. A: UC with intense inflammation mainly in the transverse and the descending colon; B: CD with intense inflammation of the terminal ileum and the ascending colon.
In-111 or Tc-99m human polyclonal immunoglobulin (HIG) has been used in the diagnosis of inflammation and it has been evaluated in IBD. Comparative studies have demonstrated sensitivity, specificity and accuracy of 100%, 85% and 96%, respectively, for labeled leukocytes and 70%, 85% and 74% for In-111 HIG[16]. Tc-99m HIG scintigraphy had 33% sensitivity while Tc-99m HMPAO WBC imaging had 100% sensitivity in the detection of active IBD[51]. On the basis of these results, the role of In-111 HIG is confined to the diagnosis of inflammation only when there is no other alternative modality[62]. On the other hand, Tc-99m HIG has no role in the evaluation of patients with IBD[51].

**In vivo** specific labeling of granulocytes using Tc-99m labeled anti-granulocyte monoclonal antibodies (AGAb) comprises a different approach. They do not require leucocyte isolation, are stored as cold kits and can selectively label granulocytes. Different AGAb have been designed, among them BW 250/183 and Leukoscan[52-55]. Tc-99m BW 250/183 was found to be inferior to Tc-99m HMPAO WBC in the detection of small bowel involvement, although the accuracy between the two scintigraphic methods for the localization of disease in the large bowel was comparable[52]. With respect to Tc-99m Leukoscan, its diagnostic value in IBD is low[55,56]. However, a recent study by Kerry et al[58] has found that Tc-99m Leukoscan has higher sensitivity and specificity at 2 h (44% and 100% respectively) and 4 h (75% and 50% respectively) planar imaging compared to that in previous publications. SPECT images at 4 h showed additional areas of uptake, raising the sensitivity to a value similar to that of Tc-99m HMPAO WBC, namely 88%. Although sensitivity is high, the low specificity limits its application for the investigation of IBD[59].

Research groups have evaluated the role of AGAb imaging in pediatric patients with IBD. Bruno et al[60] have found that the overall sensitivity of Tc-99m BW 250/183 was 94% for CD and 85% for UC. Sensitivity of scintigraphy compared to colonoscopy, radiology and ultrasonography was 90%, 76%, 75% and 55%, respectively. However, it did not appear sufficiently specific in identifying clinical remission, probably because of the presence of tissue inflammation in about 50% of biopsy samples, although patients were considered to be in clinical remission and with negative colonoscopy. The authors have recommended Tc-99m BW 250/183 as a useful tool in the detection of intestinal inflammation in children and young patients with IBD. However, because of its low specificity, endoscopic and histological confirmation is mandatory for all positive cases[60]. The efficacy of Tc-99m Leukoscan has been evaluated in a small series of pediatric patients with IBD. The reported sensitivity per patient was 90% and per bowel segment, 57%. The latter was improved with the use of SPECT[61].

In 1984, Hanna et al[62] worked on the labeling of leukocytes with Tc-99m stannous colloid, and reported the clinical application of this new imaging modality in IBD. Despite its usefulness as an alternative when other agents are not available, the activation of leukocytes, which reduces the in vivo viability, constitutes a shortcoming[63]. Recently, its use in the initial evaluation of children with suspected IBD has been assessed. The combination of the reported results (sensitivity 88%, specificity 90%) and the aforesaid advantages support its utility in the initial assessment of childhood IBD[64].

The primary data on the role of In-111 anti E-selectin monoclonal antibodies are encouraging, given that it can identify areas of inflammation in CD and UC. Still, they are not supported sufficiently to gain acceptance in the field of IBD[65].

### Positron emission tomography (PET)

PET with F-18 FDG is a functional imaging modality which identifies areas of increased glucose metabolism. It has been found to be effective in the evaluation of malignancies, inflammation and infection. Preliminary studies have shown favorable results in the assessment of disease activity in IBD[66].

In a small study of four patients with CD and two with UC, PET scanning demonstrated high radionuclide uptake in the inflamed segments, which had been detected on endoscopy and confirmed by histology. The potential utility of this non-invasive modality, as well as its usefulness for follow-up was suggested[67]. Neurath et al[68] have compared F-18 FDG, hydro-MRI and granulocyte scintigraphy with labeled antibodies (Tc-99m BW 250/183) in the detection of disease activity in 59 patients with CD. The sensitivity and specificity reported for F-18 FDG was 85% and 89%, for hydro-MRI, 67% and 93%, and for Tc-99m BW 250/183, 41% and 100%. It appears to be an accurate modality for detecting inflammation, considering that it allows a simultaneous non-invasive analysis of affected segments in both small and large bowel. Moreover, it is helpful in evaluating possible inflammatory activity in detected stenosis, which is important for its therapeutic application[68].

Recent studies have assessed the role of PET in the investigation of pediatric IBD. It diagnosed active disease in 80% of childhood cases with known IBD, and F-18 FDG uptake correlated with the endoscopic findings in 83.8% of the patients. PET recognized diseased segments that were not detected by other diagnostic methods, probably because of the limited accessibility at endoscopy. Moreover, it is the least invasive technique, can provide additional information to the diagnostic data obtained by other modalities, and exposes patients to...
lower radiation doses[62]. Löfler et al[63], using histology as a reference standard, reported F-18 FDG PET sensitivity, specificity and accuracy to be 98%, 68% and 83%, respectively, for large bowel, and 100%, 86% and 90% for small bowel involvement. Based on these favorable results, the authors have recommended the inclusion of PET in the initial investigative algorithm for the evaluation of bowel inflammation and treatment response. On the other hand, its moderate specificity renders indispensable the endoscopic and histological confirmation of all positive cases[63].

Coupling CT to PET combines the functional data obtained from PET with the anatomical data provided by CT. Its role in the detection and localization of disease activity in IBD has been evaluated. In a pilot study, Meisner et al[64] have validated the results of previous reports concerning the role of PET in IBD, and they have investigated the use of sequential CT. In most cases, the simultaneous transaction of CT was not essential but it allowed better anatomical analysis in patients who had been surgically treated, and in those with inflammation of the small bowel. There was a high correlation between PET activity and disease activity, as determined by other currently used modalities[65].

Louis et al[65] have similarly concluded that coupling PET with CT allows a more accurate anatomical identification and evaluation of F-18 FDG uptake, and it gives more morphological information, namely, the presence of strictures. The technique can detect almost all bowel segments with moderate and severe lesions and a significant proportion with only mild lesions. Of great scientific interest were the combined findings of increased F-18 FDG uptake and bowel wall thickening in PET/CT, which were observed in some segments without endoscopic evidence of lesions. One explanation might be the detection of active disease deeper in the bowel wall, which is an additional benefit of this diagnostic modality[65].

Recently, the role of PET/CT in patients with UC in remission has been evaluated. Although clinical remission was strictly defined, four out of the 10 patients who participated in the study had increased F-18 FDG uptake in the colon. This may be explained by the presence of asymptomatic inflammation, attributed to chronic low-grade activity or to the succession of flare and quiescence. The possibility of representing a normal variant or a false positive result could not be excluded. This finding necessitates further understanding of disease remission. The authors have suggested that PET/CT is a highly sensitive method, however, future studies will define its precise role among all available diagnostic modalities in disease evaluation and treatment monitoring[66].

At present, published data have suggested a high diagnostic value of F-18 FDG PET alone or PET/CT in adult and pediatric patients with IBD. However, the physiological distribution of the radionuclide, mainly in the urinary tract, and to a minor degree in the gastrointestinal tract, may compromise abdominal PET imaging of patients with IBD. In order to avoid any false results, the utility of quantitative analysis using the standardized uptake value (SUV) has been suggested. A cutoff RSUV (ratio between SUV of inflamed bowel and SUV of liver) value of 1.47 seems to be reliable for the identification of areas with significant bowel inflammation[67]. Recently, various methods of labeling leukocytes with F-18 FDG have been reported. F-18 FDG WBC are taken up in the reticuloendothelial tissue and follow the normal leukocyte distribution in vivo. Its role as a method for non-invasive quantification of IBD has been evaluated mainly in animal models[68]. The localization of the inflammatory process and the degree of tracer uptake are correlated with the endoscopic and histological findings. In the future, the method may be useful in determining the cause of pathological abdominopelvic tracer uptake, namely, inflammation versus malignancy. These are preliminary results that require further investigation in humans[67].

CONCLUSION

In this review, we have presented the role and the future prospects of nuclear medicine in IBD. Although it has no primary role in the diagnosis, it might be considered when colonoscopy is not completed successfully or other imaging modalities are negative. However, its contribution to the assessment of disease extent and activity, monitoring treatment response, and differentiating between active CD and UC is well established. Tc-99m HMPAO WBC have gain widespread clinical use while Tc-99m (V) DMSA seems to provide an accurate scintigraphic variant and a complementary technique to colonoscopy for follow-up and assessment of disease activity. The preliminary results on the role of F-18 FDG PET or PET/CT in the diagnosis and follow up of patients with IBD are encouraging. F-18 FDG WBC seem to be a promising future prospect, given that they can differentiate between the cause of pathological tracer uptake, namely, inflammation versus malignancy. Further investigation is essential in order to verify all the aforementioned favorable preliminary results.

REFERENCES

1. Hommes DW, van Deventer SJ. Endoscopy in inflammatory bowel diseases. Gastroenterology 2004; 126: 1561-1573
2. Martin-Comin J, Prats E. Clinical applications of radiolabeled blood elements in inflammatory bowel disease. Q J Nucl Med 1999; 43: 74-82
3. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology 2007; 133: 1670-1689
4. Albert JG, Martin F, Krummenerl A, Stock K, Lesske J, Göbel CM, Lotterer E, Nietsch HH, Behmann C, Fleig WE. Diagnosis of small bowel Crohn’s disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. Gut 2005; 54: 1721-1727
5. Toms AP, Barthrop A, Freeman AH. A prospective randomised study comparing enteroclysis with small bowel follow-through examinations in 244 patients. Eur Radiol 2001; 11: 1155-1160
6. Ambrosini R, Barchiesi A, Di Mizio V, Di Terlizzi M, Leo L, Filippone A, Canalis L, Fossaceca R, Carriero A.
Inflammatory chronic disease of the colon: how to image. *Eur J Radiol* 2007; 61: 442-448

7 Parente F, Greco S, Molteni M, Anderloni A, Bianchi Porro G. Imaging inflammatory bowel disease using bowel ultrasonography. *Eur J Gastroenterol Hepatol* 2005; 17: 283-291

8 Horsthuys K, Bicap S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008; 247: 64-79

9 Madsen SM, Thomsen HS, Munkholm P, Davidsen B, Dorph S, Nielsen SL, Schlüchting P. Inflammatory bowel disease evaluated by low-field magnetic resonance imaging. *Comparison with endoscopy, 99mTc-HMPAO leucocyte scintigraphy, conventional radiography and surgery.* *Scand J Gastroenterol* 2002; 37: 307-316

10 Gani SL, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. *Am J Gastroenterol* 2003; 98: 2363-2371

11 Györke T, Dufek L, Bártafí M, Makó E, Karlinger K, Mester A, Tarján Z. The role of nuclear medicine in inflammatory bowel disease. A review with experiences of aspecific bowel activity using immunoscintigraphy with 99mTc anti-granulocyte antibodies. *Eur J Radiol* 2000; 35: 183-192

12 Schölmerich J, Schmidt E, Schümchen C, Billmann P, Schmidt H, Gerek W. Scintigraphic assessment of bowel involvement and disease activity in Crohn's disease using technetium 99m-hexamethyl propylene amine oxime as leucocyte label. *Gastroenterology* 1988; 95: 1287-1293

13 Giaffer MH, Tindale W, Holdsworth D. Value of technetium-99m HMPAO-labelled leucocyte scintigraphy as an initial screening test in patients suspected of having inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1996; 8: 1195-1200

14 Weldon MJ, Lowe C, Joseph AE, Maxwell JD. Review article: quantitative leucocyte scanning in the assessment of inflammatory bowel disease activity and its response to therapy. *Aliment Pharmacol Ther* 1996; 10: 123-132

15 Lee BF, Chiu NT, Wu DC, Tsai KB, Liu GC, Yu HS, Wang ST. Use of 99mTc (V) DMSA scintigraphy in the detection and localization of intestinal inflammation: comparison of findings and colonoscopy and biopsy. *Radiology* 2001; 220: 381-385

16 Koutroubakis IE, Koukourakis MI, Dimoulooulos PD, Velidaki AA, Karkavitsas NS, Kourounis EL. Active inflammatory bowel disease: evaluation with 99mTc (V) DMSA scintigraphy. *Nucl Med Commun* 2004; 25: 797-804

17 Stathaki BL, Hodgson HJ, Kelly JD, Neirinckx RD, Lavender JP. Clinical experience with 99mTc-hexamethylpropylene-aminoxime for labelling leucocytes and imaging inflammation. *Lancet* 1986; 2: 946-949

18 Allan RA, Sladen GE, Bassingham S, Lazarus C, Clarke SE, Fogelman I. Comparison of simultaneous 99mTc-HMPAO and 111In oxine labelled white cell scans in the assessment of inflammatory bowel disease. *Eur J Nucl Med* 1993; 20: 195-200

19 Sciarratta G, Furno A, Mazzoni M, Basile C, Malaguti P. Technetium-99m hexamethyl propylene amine oxime granulocyte scintigraphy in Crohn's disease: diagnostic and clinical relevance. *Gut* 1993; 34: 1364-1369

20 Sans M, Fuster D, Llach J, Lomeña F, Balsecas JM, Herranz R, Piqué JM, Puig J, Carrió J. Optimization of technetium-99m-HMPAO leucocyte scintigraphy in evaluation of active inflammatory bowel disease. *Dig Dis Sci* 2000; 45: 1828-1835

21 Almer S, Granerus G, Ström M, Oloaion G, Bonnet J, Léamán M, Smedh K, Fransen L, Berthou P, Cattan P, Rain JD, Modigliani R. Leukocyte scintigraphy compared to intraoperative small bowel enteroscopy and laparotomy findings in Crohn's disease. *Inflamm Bowel Dis* 2007; 13: 164-174

22 Kerry JE, Marshall C, Griffiths PA, Scott BB, Griffiths G. White cell scanning for inflammatory bowel disease: are biochemical markers useful referral criteria? *Nucl Med Commun* 2003; 24: 1145-1148

23 Alonso JC, Lopez-Longo FJ, Lampareale JL, González CM, Vegaño O, Carreño L, Almaguer I. Abdominal scintigraphy using 99mTc-HMPAO-labelled leucocytes in patients with seronegative spondyloarthropathies without clinical evidence of inflammatory bowel disease. *Eur J Nucl Med* 1996; 23: 243-246

24 Alonso JC, Soriano A, Rubio C, Cuadra JL, Zarca M, Guerra P, Garcia A, Molino C. Technetium-99m-HMPAO-labeled leucocyte imaging in patients with seronegative spondyloarthropathies. *J Nucl Med Technol* 1999; 27: 204-206

25 El Maghraoui A, Dougdas M, Frenaeux E, Chaussade S, Amor B, Breban M. Concordance between abdominal scintigraphy using technetium-99m hexamethylpropylene amine oxime-labelled leucocytes and ileocolonoscopy in patients with spondyloarthropathies and without clinical evidence of inflammatory bowel disease. *Rheumatology (Oxford)* 1999; 38: 543-546

26 Biancone L, Scopinaro F, Ierardi M, Palouzi P, Marcheggiano A, Di Paolo MC, Porowska B, Colella AC, Pallone F. 99mTc-HMPAO granulocyte scintigraphy in the early detection of postoperative asymptomatic recurrence in Crohn's disease. *Dig Dis Sci* 1997; 42: 1549-1556

27 Weldon MJ, Masoom AM, Britten AJ, Gane J, Finlayson CJ, Joseph AE, Maxwell JD. Quantification of inflammatory bowel disease activity using technetium-99m HMPAO labelled leucocyte single photon emission computerised tomography (SPECT). *Gut* 1995; 36: 243-250

28 Biancone L, Scillacci O, Capocciatti F, Bozzi RM, Fina D, Petruzzello C, Deremia A, Simonetti G, Pallone F. Technetium-99m-HMPAO labeled leucocyte single photon emission computed tomography (SPECT) for assessing Crohn's disease extent and intestinal infiltration. *Am J Gastroenterol* 2005; 100: 344-354

29 Kolkman JJ, Falke TH, Roos JC, Van Dijk DH, Bannink IM, Den Hollander W, Cuesta MA, Peña AS, Meuwissen SG. Computed tomography and granulocyte scintigraphy in active inflammatory bowel disease. Comparison with endoscopy and operative findings. *Dig Dis Sci* 1996; 41: 641-650

30 Molnár T, Papós M, Gyulai C, Ambus E, Kardos L, Nagy F, Palkó A, Pávics L, Lonovics J. Clinical value of technetium-99m-HMPAO-labeled leucocyte scintigraphy and spiral computed tomography in active Crohn's disease. *Am J Gastroenterol* 2001; 96: 1517-1521

31 Charron M, Di Lorenzo C, Rocchis S, CT and 99mTc-WBC vs colonoscopy in the evaluation of inflammation and complications of inflammatory bowel diseases. *J
Charron M. Technetium leukocyte imaging in inflammatory bowel disease. Curr Gastroenterol Rep 1999; 1: 245-252.

Alberini JL, Badran A, Freneaux E, Hadji S, Kalifa G, Devaux JY, Dupont T. Technetium-99m HMPAO-labeled leukocyte imaging compared with endoscopy, ultrasonography, and contrast radiology in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2001; 32: 278-286.

Cucchiara S, Celentano L, de Magistris TM, Montisci A, Iula VD, Fecarotta S. Colonoscopy and technetium-99m white cell scan in children with suspected inflammatory bowel disease. J Pediatr 1999; 135: 727-732.

Charron M. Pediatric inflammatory bowel disease imaged with Tc-99m white blood cells. Clin Nucl Med 2000; 25: 708-715.

Charron M, del Rosario FJ, Kocoshis SA. Pediatric inflammatory bowel disease: assessment with scintigraphy with 99mTc white blood cells. Radiology 1999; 212: 507-513.

Charron M, del Rosario FJ, Kocoshis S. Use of technetium-tagged white blood cells in patients with Crohn’s disease and ulcerative colitis: is differential diagnosis possible? Pediatr Radiol 1998; 28: 871-877.

Charron M, Di Lorenzo C, Kocoshis S. Are 99mTc leukocyte scintigraphy and SBFT studies useful in children suspected of having inflammatory bowel disease? Ann J Gastroenterol 2000; 95: 1208-1212.

Mojiminiyi OA, Udelmann R, Soper ND, Shephstie B, Dudley NE. Pentavalent Tc-99m DMSA scintigraphy. Prospective evaluation of its role in the management of patients with medullary carcinoma of the thyroid. Clin Nucl Med 1991; 16: 259-262.

Ohta H, Endo K, Fujita T, Nakajima T, Sakahara H, Torizuka K, Shimizu Y, Hata N, Masuda H, Horiiuchi K. Imaging of soft tissue tumors with Tc(V)-99m dimercaptosuccinic acid. A new tumor-seeking agent. Clin Nucl Med 1984; 9: 568-573.

Kobayashi H, Kotoura Y, Hosono M, Sakahara H, Hosono M, Yao ZS, Tsuboyama T, Yamamuro T, Endo K, Konishi J. Diagnostic value of Tc-99m (V) DMSA for chondrogenic lesions with positive Tc-99m HMDP uptake on bone scintigraphy. Clin Nucl Med 1995; 20: 361-364.

Banci M, Bianchi PL, Gianni W, Romani AM, De Vincenzi G, Ieraardi M, Scopinaro F. Preliminary evaluation of the usefulness of Tc-99m (V) DMSA in pancreatic neuroendocrine tumors. Clin Nucl Med 1996; 21: 122-124.

Kobayashi H, Sakahara H, Hosono M, Shirato M, Endo K, Kotoura Y, Yamamuro T, Konishi J. Soft-tissue tumors: diagnosis with Tc-99m (V) dimercaptosuccinic acid scintigraphy. Radiology 1994; 190: 277-280.

Lee BF, Chiu NT, Chang JK, Liu GC, Yu HS. Technetium-99m(V)-DMSA and gallium-67 in the assessment of bone and joint infection. J Nucl Med 1988; 29: 2128-2131.

Ercan MT, Gulalci NC, Unsal IS, Aydin M, Peksoy I, Hasçelik Z. Evaluation of Tc-99m(V) DMSA for imaging inflammatory lesions: an experimental study. Ann Nucl Med 1996; 10: 419-423.

Miral L, de Lima PA, Martin-Comin J, Ballellas C, Xiol X, Roca M, Ricart Y, Ramos M. Simultaneous administration of 111In-human immunoglobulin and 99mTc-HMPAO labeled leucocytes in inflammatory bowel disease. Eur J Nucl Med 1995; 22: 664-670.

Delgado Castro M, Lancha C, Prats E, Mitjavila M, Abós D, Martín-Campos LM, Creepo J, Barrio J. The diagnostic value of Tc-99m human polyclonal immunoglobulin imaging compared to Tc-99m HMPAO labeled leukocytes in inflammatory bowel disease. Clin Nucl Med 1997; 22: 17-20.

Papou M, Nagy F, Narai G, Rajtar M, Szanto I, Lang J, Csernay L. Anti-granulocyte immunoscintigraphy and [99mTc]hexamethylpropyleneamine-oxime-labeled leukocyte scintigraphy in inflammatory bowel disease. Dig Dis Sci 1996; 41: 412-420.