Dimercaptosuccinic acid: A multifunctional cost effective agent for imaging and therapy

Jaya Shukla, Bhagwant Rai Mittal
Department of Nuclear Medicine and PET, Post Graduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT
Dimercaptosuccinic acid (DMSA) is an analog of dimercaprol used as metal chelating moiety in variety of conditions. In nuclear medicine itself two types of Tc-99m DMSA complexes are used, trivalent and pentavalent forms. In this review, we have discussed the mechanism of uptake of both complexes as well as diagnostic and therapeutic application in a clinical scenario.

Keywords: Dimercaptosuccinic acid, glucose-mediated acidosis, pentavalent, renal cortex, trivalent

INTRODUCTION
Dimercaptosuccinic acid (DMSA) contains two sulfhydryl groups, an analog of dimercaprol and is used for metal chelation. Traditionally, this has been used as an antidote to heavy metal toxicity.[1,2] It is also reported to be used for removal of heavy metals from the body of autistic children, a one major concern in autism.[3] However, its chelation property has been exploited in nuclear medicine. Tc-99m labeled DMSA shows altered organ distribution depending on methods of preparation. At acidic pH (pH 2–3), DMSA chelates with technetium in lower oxidation (III) and forms a trivalent complex Tc-99m (III) DMSA also represented as Tc-99m DMSA [Figure 1a]. Tc-99m DMSA accumulates in proximal tubular cells of kidneys and thereby used for renal cortical imaging. At alkaline pH (pH 8–9), it chelates with technetium in higher oxidation state to form a pentavalent complex Tc-99m (V) DMSA, resembles phosphate ion and is rapidly excreted in the urine[4] [Figure 1b].

MECHANISM OF UPTAKE
Trivalent Tc-99m dimercaptosuccinic acid
Trivalent Tc-99m DMSA has high binding affinity for the proximal convoluted tubules thus providing good imaging of the renal parenchyma. Two main Tc-99m DMSA tubular uptake routes have been proposed (i) peritubular extraction from plasma and (ii) tubular reabsorption.[5,6] Muller and Gutsche in 1995 proposed that after injection, Tc-99m DMSA is bound to plasma proteins in the circulating blood and penetrate the glomerular filter at very low rates. Tc-99m DMSA is completely excreted and does not reabsorbed from the tubular fluid. Peritubular excretion accounts for the Tc-99m DMSA uptake in the proximal tubular cells of the renal cortex. Tc-99m DMSA is then bound to the cell plasma protein with a high binding constant and accumulates in the kidney.[6] Burckhardt et al. proposed the role of sodium-dependent dicarboxylate transporter (NaDC-3) in the basolateral uptake of Tc-99m DMSA from peritubular capillaries into proximal tubule cells.[7] Tc-99m DMSA reabsorption from the glomerular ultra-filtrate substantially contributes to the renal uptake of the tracer.[8-10] Recently, Weyer et al. studied the role of the megalin/cubilin receptors for the accumulation of Tc-99m DMSA and proposed that Tc-99m DMSA binds to α-1 microglobulin plasma protein. Tc-99m DMSA is freely filtered by glomeruli and accumulates in renal proximal tubules by multiligand-binding mediated by megalin/cubilin receptor endocytosis. Free Tc-99m DMSA and trace amounts of microglobulin–bound Tc-99m DMSA are excreted in the urine.[11]

Pentavalent Tc-99m (V) dimercaptosuccinic acid
Tc-99m (V) DMSA localizes in a number of tumor types, most notably medullary thyroid carcinoma (MTC), bone metastases and other bone lesions. At pentavalent state, both sulfhydryl groups (-SH) of DMSA are bound with Tc-99m and no free -SH group is left for protein binding [Figure 1b]. The small Tc-99m (V) DMSA complex does not accumulate in the kidney and gets easily excreted by the kidney.[12]
Tc-99m (V) DMSA core has structural similarity with phosphate ion (PO$_4^{3-}$) and is avidly taken up by metabolic active cancer cells. In addition, Tc-99m (V) DMSA uptake by tumors is related to glucose-mediated acidosis and mitotic activity. In aggressive or malignant tumors the rate of glycolysis, so the production of lactic acid is increased that results in the acidic pH of the tumor microenvironment. Phosphate is transported via all three NaPi co-transporters, however, Tc-99m (V) DMSA is transported by NaPi Type III co-transporters and can be used as a tumor proliferation marker. Physiological uptake of Tc-99m (V) DMSA has been reported in the nasal mucosa, lacrimal glands and blood pool such as in the heart, and vessels. The excretion of Tc-99m(V)DMSA is through kidney. Uptake is also noted in pituitary and breast.

**Factors Influencing the Uptake of TC-99m (V) DMSA**

**Phosphonoformic acid**

The phosphate accumulation is linked to NaPi Type III co-transporter expression. In the presence of a specific NaPi cotransporter inhibitor, phosphonoformic acid, Tc-99m (V) DMSA accumulation decreases with the decreased phosphate accumulation.

**Extracellular sodium concentration**

Tc-99m (V) DMSA uptake is dependent on extracellular sodium concentration, in the same way as phosphate uptake, suggesting an important role of sodium-dependent transporter in Tc-99m (V) DMSA uptake and more specifically, the involvement of NaPi co-transporter, as phosphate transporters is known to be strongly dependent on extracellular sodium. In the absence of extracellular sodium only <30% Tc-99m (V) DMSA enters in cells by simple diffusion.

**pH**

Uptake of both Tc-99m (V) DMSA and phosphate is stimulated at acidic pH and inhibited at alkaline pH. The plausible reason is that at acidic pH, carboxyl groups of DMSA (V) are fully associated and impart an average global charge of -1 to the DMSA (V) complex. The activity of Type III NaPi co-transporters increases because of preference for monovalent substrates. Tumor cells over express Type III NaPi co-transporters and have more acidic extracellular pH than normal tissues.

**Applications of dimercaptosuccinic acid in nuclear medicine**

Dimercaptosuccinic acid is a very useful radiopharmaceutical and being used for the detection of many diseases such as renal disorder, MTC, brain tumor, etc. Pentavalent Re-188/Re-186 DMSA is suitable candidate for internal radiation therapy.

**Trivalent Dimercaptosuccinic Acid (Tc-99m DMSA)**

**Renal disorders**

At low pH (2–3), trivalent Tc-99m DMSA is formed and localizes in the kidney. Since it is taken up by renal cortex and retained there, according to latest EANM guidelines, trivalent Tc-99m DMSA is the agent of choice for the detection of focal renal parenchymal abnormalities, renal sequelae after acute infection, acute pyelonephritis, ectopic kidney, confirmation of nonfunctional multicystic kidney and associated abnormalities such as abnormal duplex kidney, small kidney, dysplastic tissue, horseshoe kidney etc. It is very useful in the detection of renal cortical scars. The superior renal to background ratio offered by DMSA is useful in the diagnosis of congenital renal conditions such as horseshoe kidney, ectopic kidney, crossed fused ectopic kidney. Tc-99m DMSA is also used to evaluate kidney parenchyma, functioning renal tissue and proximal tubular dysfunction. This scintigraphy has a great value in the diagnosis and evaluation of tubule-Interstitial nephropathy in diseases like Joubert syndrome.

Tc-99m DMSA renal scintigraphy can also be used to assess effects of cytotoxic drugs such as ifosfamide, cisplatin, methotrexate and cyclophosphamide on renal function in children who receive chemotherapy for various malignancies. A highly significant relationship has been reported between Tc-99m DMSA uptake and cumulative ifosfamide dose ($P < 0.001$). Tc-99m DMSA scintigraphy is a noninvasive and sensitive method for the detection of ifosfamide-induced tubular dysfunction, subclinical injury and to predict risk at retreatment.

**Pentavalent Dimercaptosuccinic Acid (Tc-99m DMSA)**

The blood pool activity of Tc-99m (V) DMSA is seen up to 3 h and is actively taken up by the growing bones. Tc-99m (V) DMSA is proved to be useful in patients with MTC, brain, and soft tissue tumors. However in lung, liver, gastrointestinal tract, malignant melanoma and lymphoma Tc-99m (V) DMSA has only limited role. The biodistribution and diagnostic value of Tc-99m (V) DMSA planar and single photon emission computed tomography (SPECT) scintigraphy had been assessed in patients with head and neck tumors. The results showed the bi-exponential blood clearance and rapid elimination from all organs except kidneys.
**Medullary carcinoma of thyroid**

Medullary carcinoma of the thyroid is an uncommon tumor and arises from the parafollicular cells of the thyroid. The early detection of tumor sites in patients with MTC is important as it tends to metastasize to regional neck lymph nodes and mediastinum. [30-32] The major distant metastasis sites are lung, liver, and bones. Tc-99m (V) DMSA has demonstrated to be taken up by the primary as well as recurrent and metastatic tumors [33-35] [Table 1]. Intense accumulation of Tc-99m (V) DMSA is found in MTC and its metastatic sites. [36] Tc-99m (V) DMSA is found to be very specific since no significant uptake is observed in other thyroid malignancies, normal thyroid, salivary glands, and bones. [37]

Tc-99m (V) DMSA has been compared to Tc-99m tetrofosmin and TI-201 in patients of MTC with variable calcitonin levels and showed superior detection of metastatic sites in patients with MTC over Tc-99m tetrofosmin and TI-201 scintigraphy. [38] Tc-99m (V) DMSA showed sensitivity similar to In-111 octreotide and I-131 MIBG in localizing primary MTC; but, these scans are unable to detect small lymph node involvement before initial surgery. [39,40] However, the sensitivity may improve with high serum calcitonin levels. [41] Tc-99m (V) DMSA demonstrated better sensitivity and specificity as compared to CT and can be used for identification of recurrence or metastasis of MTC. [42,43] In another study based on the lesion sensitivity, Tc-99m (V) DMSA has been found to be superior to Tc-99m MIBI and TI-201 in the follow-up of MTC patients. [44] Tc-99m (V) DMSA may result in early diagnosis and proper management of patients with MTC [Table 1].

**Head and neck**

The identification of primary and metastatic sites plays an important role in the treatment and management of squamous cell carcinoma (SCC). Many radiopharmaceuticals such as Ga-67 citrate, Co-57 bleomycin, In-111 bleomycin, etc. have been used in past with low sensitivity and specificity. The studies of head and neck SCC of Tc-99m DMSA showed good uptake at the primary tumor and correlated well with the results of clinical and conventional imaging findings. However, it is found to be less sensitive for metastatic cervical nodes. [45-47] Tc-99m (V) DMSA SPECT imaging demonstrated high affinity in patients with oral SCC for metastatic lymph nodes in the neck and were helpful for designing proper neck dissection. [48,49] Tc-99m (V) DMSA showed no role in detecting primary nasopharyngeal carcinoma (NPC). [48,49] However, metastatic neck lymph node lesions of NPC could be detected by Tc-99m (V) DMSA. These studies demonstrated that Tc-99m (V) DMSA imaging may be used for the detection of the primary site in SCC of head and neck, with limited utility in the evaluation of cervical nodes. [50] The role of Tc-99m (V) DMSA has been explored in other head and neck malignancies like pharyngolaryngeal carcinoma and parotid tumors and fairly good results were obtained [30,32] [Table 2].

**Ocular tumors**

Tc-99m (V) DMSA scintigraphy may play a crucial role in the detection and follow-up of retinoblastoma, uveal melanoma, and choroidal melanoma. Locally extended as well as a metastatic orbital retinoblastoma has been assessed by Tc-99m (V) DMSA. Planar and SPECT images demonstrated primary and metastatic sites which were confirmed by ultrasonography, magnetic resonance imaging, and incision biopsy. [51] Intraocular tumor of metastatic breast, lung, and rectal carcinomas can be imaged by Tc-99m (V) DMSA. The scan also detected unknown primary and other systemic lesions that may help in the diagnosis and the management of these patients [52-54] [Table 2]. This group suggested the complementary role of Tc-99m (V) DMSA on rare situations of decision making.

**Brain tumors**

Tc-99m (V) DMSA can be used as a promising agent for brain tumors. It has high specificity for differential diagnosis of benign from malignant tumors and also differentiating their histological malignancy grade, noninvasively. Approximately 95% of benign and malignant primary brain tumors are detected by Tc-99m (V) DMSA SPECT images. The vascularity could be adjudged by early uptake ratios without statistically significant difference in

---

Table 1: Studies showing role of Tc-99m (V) DMSA in MTC

| Authors year | Number of patients | Tumor | Sensitivity/specificity | Gold standard/compared with | Reference number |
|--------------|--------------------|-------|-------------------------|----------------------------|-----------------|
| Kurtaran et al., 1998 | 22 | MTC | (58%) primary (36%) metastatic | Histopathology, histochemistry | [31] |
| Clarke et al., 1987 | 10 | MTC | 80% | Biopsy (histology) | [32] |
| Clarke et al., 1988 | 9 | MTC | 95% | Histology | [33] |
| Clarke et al., 1989 | 32 | MTC | 80% | Histology | [34] |
| Adealet et al., 1999 | 24 | MTC | 88% (TP) | Ti-201, Tc-99m tetrofosmin | [35] |
| Ohta et al., 1984 | 4 | MTC | - | - | [36] |
| Berná et al., 1995 | 11 | MTC | 8 sites in 5/11 9 sites in 6/11 (ln) | In-111 octreotide | [37] |
| Guerra et al., 1989 | 26 | MTC | 84% | I-131 MIBG | [38] |
| Mojmírni ýi et al., 1991 | 10 | MTC | - | Serum calcitonin | [39] |
| Arslan et al., 2001 | 14 | MTC | 57% with octreotide 85% | CT/MRI | [40] |
| Dabiri 2006 | 15 | MTC | 91%, 75% | Serum calcitonin | [41] |
| Ugur et al., 1996 | 14 | Recurrent MTC | 95% | CT/MRI | [42] |

**DMSA:** Dimercaptosuccinic acid, **MTC:** Medullary thyroid carcinoma, **MRI:** Magnetic resonance imaging, **CT:** Computed tomography, **MIBI:** 2-methoxyisobutylisonitrile
DMSA uptake is observed in almost all sarcomas, metastatic tumors, breast cancer cells. Tc-99m (V) DMSA uptake is also found to have high diagnostic potential in the detection of breast cancer patients and also for the surgical planning of such patients.

Lung carcinoma

Role of Tc-99m (V) DMSA has been explored in scintimammography and demonstrated high sensitivity and specificity for breast cancers patients with high T/B ratios. Tc-99m (V) DMSA could detect cases of nonpalpable ductal carcinoma in situ, metastatic lymph nodes and preinvasive lesions with risk of developing malignancy. It is suitable for the assessment of primary lesions and axillary involvement in breast cancer patients and also for the surgical planning of such patients.

Soft tissue tumor

Tc-99m (V) DMSA demonstrated diagnostic potential in histological proven cases of soft tissue tumors. Tc-99m (V) DMSA uptake is observed in almost all sarcomas, metastatic carcinomas, highly recurrent benign tumors of extra-abdominal desmoids, tenosynovial giant cell tumors, hemangiomias, and granulomatous soft-tissue lesions. Low-grade malignant and highly recurrent benign lesions can be detected with Tc-99m (V) DMSA scintigraphy with no uptake in benign solid soft tissue tumors.[65-66] [Table 2].

Breast cancer

The role of Tc-99m (V) DMSA has been explored in scintimammography and demonstrated high sensitivity and specificity for breast cancers patients with high T/B ratios. Tc-99m (V) DMSA could detect cases of nonpalpable ductal carcinoma in situ, metastatic lymph nodes and preinvasive lesions with risk of developing malignancy. It is suitable for the assessment of primary lesions and axillary involvement in breast cancer patients and also for the surgical planning of such patients.[67-70] The uptake of Tc-99m (V) DMSA is found to have a positive correlation with the proliferative activity (Ki-67) of breast cancer cells. Tc-99m (V) DMSA uptake in breast cancer and Ki-67 expression suggests Tc-99m (V) DMSA as a surrogate marker of cell proliferation.[71] Tc-99m (V) DMSA correlates with tumor aggressiveness and provides important information regarding the correlation of tumor subtype with breast density.[72] [Table 4].

Skeletal metastases

Tc-99m (V) DMSA has also been evaluated in the detection of metastatic and degenerative bone lesions. The diagnostic efficacy of Tc-99m (V) DMSA in the detection of bone metastases is comparable to Tc-99m-methylene diphostonate (MDP).
However, degenerative lesions do not show the uptake of Tc-99m (V) DMSA.\[42,44-46\] Choong et al. evaluated Tc-99m (V) DMSA and Tl-201 imaging in the management of cartilaginous tumors and compared with histology.\[47\] Tc-99m (V) DMSA SPECT/CT in patients with osteosarcoma is found to be comparable with F-18 fluorodeoxyglucose (F-18 FDG) PET/CT in the evaluation of primary and metastatic lesions with size more than 1cm. However, F-18-FDG PET/CT could also detect sub-centimeter lesions.\[48\] Basu et al. studied and compared the findings of Tc-99m-MDP bone scan and Tc-99m (V) DMSA scintigraphy in the detection of osseous metastases arising from various malignancies.\[49\] [Table 4].

### Other tumors

The role of Tc-99m (V) DMSA has not been established in patients with carcinomas of the gastrointestinal tract, malignant melanoma, and lymphoma.\[50\] However, one study demonstrated approximately 90% sensitivity of Tc-99m (V) DMSA in the detection of hepatocellular carcinoma.\[51\] Pancreatic neuroendocrine tumors also demonstrated high uptake of Tc-99m (V) DMSA.\[52\] [Table 4].

#### Table 3: Studies showing role of Tc-99m (V) DMSA in lung, soft tissue and breast cancers

| Authors year | Number of patients | Tumor | Sensitivity/specificity | Gold standard/compared with | Reference number |
|--------------|--------------------|-------|-------------------------|-----------------------------|-----------------|
| Hirano et al., 1995 | 31 | Lung | 90% | - | [61] |
| Kao et al., 1992 | 50 | Lung | 43%/70% | X-ray | [62] |
| Atasever et al., 1997 | 36 | Lung | 90% | Clinical/radiological | [63] |
| Ergün et al., 2007 | 12 | Lung | 90% | Ga-67 citrate | [64] |
| Kobayashi et al., 1993 | 3 | Tenosynovial giant tumor | 100% | Histology, Ga-67 citrate | [65] |
| Kobayashi et al., 1994 | 76 | Soft tissue tumor | ~ 100% | Mammogram | [66] |
| Papantoniou et al., 2000 | 41 | Breast cancer | 88%/93% breast cancer | Sestamibi | [67] |
| Massardo et al., 2002 | 111 | Breast cancer | 78%/86% lymph node metastasis | Sestamibi | [68] |

#### Table 4: Studies showing role of Tc-99m (V) DMSA in skeletal cancers (primary and metastatic) other cancers, infections and response to therapy

| Author, year | Number of patients | Pathology | Sensitivity/specificity | Gold standard/compared with | Reference number |
|--------------|--------------------|-----------|-------------------------|-----------------------------|-----------------|
| Kobayashi et al., 1995 | 17 | Chondrogenic | 44% benign/100% malignant | Histopathology | [73] |
| Ugr et al., 1996 | 14 (MTC) | Bone metastases | 95%/100% | Tc-99m MIBI Tl-201 | [42] |
| Lam et al., 1997 | 10 | Bone metastasis | 86% | Tc-99m MDP | [43] |
| Sahin et al., 2000 | 34 | Bone metastasis | 90% | Tc-99m MDP | [44] |
| Zissimopoulos et al., 2005 | 28 | Osteosarcoma/osteomyelitis/bone fractures | 100% | FNA, Tc-99m MDP, CT | [76] |
| Choong et al., 2004 | 92 | Cartilaginous tumors | - | Histological examination, Tl-201 | [77] |
| Bandopadhyaya et al., 2012 | 22 | Osteosarcoma | 100% primary and metastatic lesions >1 cm | F-18FDG-PET | [78] |
| Basu et al., 2004 | 17 | Skeletal metastases | 88.9% | Tc-99m MDP | [79] |
| Wang et al., 1999 | 9 | HCC | 100% | X-ray/CT | [80] |
| Bani et al., 1996 | 5 | Pancreatic NET | 100% | Histologic/cytologic | [81] |
| Lee et al., 2001 | 62 | Intestinal inflammation | 95%/94% | Colonoscopy/biopsy | [82] |
| Koutroubakis et al., 2003 | 76 | IBD | 92%/86% | Endoscopic and histology | [83] |
| Javadi et al., 2013 | 54 | IBD | - | Colonoscopy | [84] |
| Lee et al., 1998 | 36 | Bone and joint infection | - | Ga-67 citrate | [85] |
| Akbunar et al., 2000 | 8 | Metabolic bone disease | 86% | Biochemical evaluation | [86] |
| Ohta et al., 1990 | 11 | Fibromatosis | 100% | Histology | [87] |
| Kobayashi et al., 1994 | 3 | Granulomatous sarcoïdosis | 100% | CT/MRI/Ga-67 citrate, histology | [88] |
| Sarikaya et al., 2002 | 11 | Renal osteodystrophy | 100% | Biochemistry | [89] |
| Koutsikos et al., 2003 | 11 | Multiple myeloma | Response to chemo-therapy | Tc-99m MIBI | [90] |

DMSA: Dimercaptosuccinic acid, MDP: Methylene diphosphonate, MIBI: 2-methoxyisobutylisonitrile.
Infection and inflammation

Te-99m (V) DMSA is also evaluated as an agent for visualization of inflammatory lesions and proven as a procedure of choice with colonoscopy for confirming the diagnosis.\(^{82-84}\) Te-99m (V) DMSA showed greater sensitivity and as well as accuracy than Ga-67 in the assessment of bone and joint infection, metabolic bone disease. However, the difference is not statistically significant.\(^{85,86}\) High uptake at the sites of fibromatosis and moderate uptake at granulomatous inflammatory lesions of sarcoidosis is shown with Te-99m (V) DMSA and could be of value in the diagnosis and in determining the appropriate site for biopsy.\(^{87,88}\) [Table 3].

Therapy and response evaluation

Re-186/188 (V) DMSA is a therapeutic analog of Te-99m (V) DMSA and may be used for therapy of soft tissue tumors and bony metastases.\(^{78}\) Basu \textit{et al.} demonstrated the role a Te-99m (V) DMSA in selection of patients for Re-188 (V) DMSA therapy and response evaluation to bisphosphonate therapy.\(^{79}\) Re-186/188 (V) DMSA offers the potential for targeted radiotherapy, the avidity of the tracer in most bone metastasis suggests that this could be applied for palliative treatment. Te-99m (V) DMSA is a noninvasive tumor cell proliferation marker and may also be used to evaluate the response to radio and chemotherapy, predict patient prognosis and help in management of various tumors and other therapies.\(^{51,56-58}\)

CONCLUSION

Trivalent Te-99m DMSA is a widely used tracer for renal cortical imaging Te-99m (V) DMSA accumulation is linked to phosphate uptake and kinase pathway activation and act as a surrogate marker of cell proliferation. It has the potential role in patient management, prognosis estimation, and therapy response monitoring. However, sensitivity is not comparable to F-18-FDG PET/CT in those centers where PET/CT offers the potential for targeted radiotherapy, the avidity of the tracer in most bone metastasis suggests that this could be applied for palliative treatment. Te-99m (V) DMSA is a noninvasive tumor cell proliferation marker and may also be used to evaluate the response to radio and chemotherapy, predict patient prognosis and help in management of various tumors and other therapies.\(^{51,56-58}\)

REFERENCES

1. Dart RC, Hartlib KM, Maiorino RM, Myersohn M, Aposhian HV, Hassen LV. Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. J Pediatr 1994;125:709-16.
2. Asiedu P, Mouton T, Blum CB, Roldan E, Loloconco NJ, Graziano JH. Metabolism of meso-2,3-dimercaptosuccinic acid in lead-poisoned children and normal adults. Environ Health Perspect 1995;103:734-9.
3. Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, et al. Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: Part A – Medical results. BMC Clin Pharmacol 2009;16.
4. Krejcarick GE, Wicks JH, Heerwald PE. The structure of stannous dimercaptosuccinic acid chelates. J Nucl Med 1976;17:565.
5. de Lange MJ, Pieris DA, Kosterink JG, van Luijk WH, Meijer S, de Zeeuw D, et al. Renal handling of technetium-99m DMSA: Evidence for glomerular filtration and peritubular uptake. J Nucl Med 1989;30:1219-23.
6. Müller-Suur R, Gutsche HU. Tubular reabsorption of technetium-99m-DMSA. J Nucl Med 1995;36:1654-8.
7. Burekhardt BC, Drinkuth B, Menzel C, König A, Steffen J, Wright SH, et al. The renal Na(+) dependent dicarboxylate transporter, NaDC-3, translocates dimethyl- and disulphhydryl-compounds and contributes to renal heavy metal detoxification. Am Soc Nephrol 2002;13:2628-38.
8. Provoost AP, Van Aken M. Renal handling of technetium-99m DMSA in rats with proximal tubular dysfunction. J Nucl Med 1985;26:1063-7.
9. Peters AM, Jones DH, Evans K, Gordon I. Two routes for 99mTc-DMSA uptake into the renal cortical cellular tube. Eur J Nucl Med 1998;24:1555-61.
10. van Luijk WH, Ensing GJ, Meijer S, Donker AJ, Piers DA. Is the relative 99mTc-DMSA clearance a useful marker of proximal tubular dysfunction? Eur J Nucl Med 1984;43:49-52.
11. Weyer K, Nielsen R, Petersen SV, Christiansen EI, Rethling M, Bier H. Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. J Nucl Med 2013;54:159-65.
12. Blower PJ, Nielsen R, Petersen SV, Christiansen EI, Rethling M, Bier H. Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. J Nucl Med 2013;54:159-65.
13. Yokoyama A, Saiji H. Tumor diagnosis using radioactive metal ions and their complexes. In: Siegel H, editor. Metal Ions in Biological Systems. New York: Marcel Dekker; 1980. p. 313-40.
14. Wulfrank DA, Schelstraete KH, Small F, Fallais CJ. Analogy between technetium-99m-dimercaptosuccinic acid. J Nucl Med 1991;32:845-9.
15. Saji H. Tumor diagnosis using radioactive metal ions and their complexes. In: Siegel H, editor. Metal Ions in Biological Systems. New York: Marcel Dekker; 1980. p. 313-40.
16. Wulfrank DA, Schelstraete KH, Small F, Fallais CJ. Analogy between technetium-99m (V) DMSA and technetium-99m-MDP Clin Nucl Med 1989;14:588-93.
17. Horiiuchi K, Saiji H, Yokoyama A. (Te)-DMSA tumor localization mechanism: A pH-sensitive Te(-V) DMSA-enhanced target/nontarget ratio by glucose-mediated acidosis. Nuel Med Biol 1998;25:549-55.
18. Papanontiou V, Nakopoulou L, Christodoulidou J, Papadaki E, Sourvatzoglou M, Stipsanis A, et al. Correlation and multivariate regression analysis between Te-99m (V) DMSA and Te-99m MIBI uptake and steroid receptors, proliferation index, tumor size, age, malignant grade, p53, and c-erbB-2 in primary breast cancer [abstract]. Eur J Nucl Med 2001;28:1120.
19. Tannock IF, Rotin D. Acid pH in tumors and its potential for therapeutic exploitation. Cancer Res 1989;49:4737-84.
20. Werner A, Dehmlit M, Nalbant P, Na-pentavalent phosphate cotransporters: The NaPi protein families. J Exp Biol 1998;201:3135-42.
21. Dehmlit M, Nalbant P, Na-pentavalent phosphate cotransporters: The NaPi protein families. J Exp Biol 1998;201:3135-42.
22. Denoyer D, Perek N, Le Jeune N, Furet D, Dubois F. Evidence that 99mTc-(V) DMSA uptake is mediated by NaPi cotransporter type III in tumour cell lines. Eur J Nucl Med Mol Imaging 2004;31:77-84.
23. Watkinson JC, Lazarus CR, Mistry R, Maisie MN, Clarke SE. 99mTc-DMSA: A clinical, planar and SPECT study to evaluate patients with head and neck squamous carcinoma. Nucl Med Commun 1990;11:111-20.
24. Nakamoto Y, Sakahara H, Kobayashi H, Saga T, Tsuboyama N, Nakamura T, et al. Technetium-99m (V) dimercaptosuccinic acid: Normal accumulation in the breasts. Eur J Nucl Med 1997;24:1146-8.
25. Fernandez I, Berleveau E, Friedlander G, Silve C, Na, PO(cotransport type III (PiT1) expression in human embryonic kidney cells and regulation by PTH. Am J Physiol Renal Physiol 1999;277:F543-51.
26. Kavanagh MP, Karab D. Identification and characterization of a widely expressed phosphate transporter/retnovirus receptor family. Kidney Int 1996;49:59-63.
27. Piepsz A, Colarinha P, Gordon I, Hahn K, Olivier P, Roca I, et al. Guidelines for 99mTc-DMSA scintigraphy in children. Eur J Nucl Med 2001;28:BP17-41.
28. Gedik GК, Lay Ergin F, Fani Bozkurt M. The role of 99mTc DMSA renal scintigraphy in joubert syndrome. Rev Esp Med Nucl 2006;25:258-62.
29. Annings JK, Valdes Olmos RA, de Kraker J, van Tinteren H, Hoefnagel CA, van Rosyn EA. Technetium-99m dimercaptosuccinic acid and ifosfamide tubular dysfunction in children with cancer. Eur J Nucl Med 1994;21:658-62.
30. Rossleigh MA, Farnsworth RH, Leighton DM, Yong JL, Rose M, Christian CL. Technetium-99m-dimercaptosuccinic acid scintigraphy studies of renal cortical scarring and renal length. J Nucl Med 1998;39:1280-5.
31. Caglar M, Yarıs N, Akyuz C. The utility of 99mTc-DMSA and Te(99m)-EC scintigraphy for early diagnosis of ifosfamide induced nephropathy. Nucl Med Commum 2001;22:1325-32.
29. Ohita H, Endo K, Fujita T, Konishi J, Totsuka K, Horiiuchi K, et al. Clinical evaluation of tumour imaging using 99mTc(V) dimercaptosuccinic acid, a new tumour-seeking agent. Nucl Med Commun 1988;9:105-16.

30. An R, Bender H, Gubike S, Biersack HJ. Diagnostic value of pentavalent 99mTc-dimercaptosuccinic acid ([V]-DMSA) in head and neck tumors. J Tongji Med Univ 2000;20:303-7.

31. Kurutan A, Scheuba C, Kaserer K, Schima W, Czerny C, Angelberger P, et al. Indium-111-DTPA-D-Phe1-octreotide and technetium-99m-(V)-dimercaptosuccinic acid scanning in the preoperative staging of medullary thyroid carcinoma. J Nucl Med 1998;39:1007-9.

32. Clarke SE, Lazarus C, Mistry R, Maisey MN. The role of technetium-99m pentavalent DMSA in the management of patients with medullary carcinoma of the thyroid. Br J Radiol 1987;60:1089-92.

33. Clarke SE, Lazarus CR, Wraith P, Sampson C, Maisey MN. Pentavalent [99mTc]DMSA, [131I]MBG, and [99mTc]MDP – An evaluation of three imaging techniques in patients with medullary carcinoma of the thyroid. J Nucl Med 1988;29:33-8.

34. Clarke S, Lazarus C, Maisey M. Experience in imaging medullary thyroid carcinoma using 99mTc(V) dimercaptosuccinic acid (DMSA). Henry Ford Hosp Med J 1989;37:167-8.

35. Adalat I, Demirkale P, Unal S, Ouz H, Alagöl F, Cantez S. Disappointing results with 99mTc tetrofosmin for detecting medullary thyroid carcinoma metastases comparison with 99mTc-VDMSA and TI-201. Clin Nucl Med 1999;24:678-83.

36. Ohita H, Yamamoto K, Endo K, Mori T, Hamanaka D, Shimazu A, et al. Scintigraphic imaging of head and neck cancers with 99m technetium (v) dimercaptosuccinic acid using CT and SPECT. Br J Radiol 1991;64:909-14.

37. Ohta H, Endo K, Fujita T, Konishi J, Torizuka K, Horiuchi K, et al. Technetium-99m pentavalent DMSA in the management of patients with medullary carcinoma of the thyroid. Ke Za Zhi 2004;39:425-8.

38. Guerra UP, Pizzocaro C, Terzi A, Giubbini R, Maira G, Pagliaini R, et al. Evaluation of pentavalent Tc-99m-DMSA scintigraphy in small cell and nonsmall cell lung cancers. Nucl Med Commun 1992;13:1111-1116.

39. Ohta H, Endo K, Fujita T, Konishi J, Torizuka K, Horiuchi K, et al. Technetium-99m pentavalent DMSA imaging in patients with pituitary adenomas. Eur J Endocrinol 1995;133:38-47.

40. Yamamura K, Suzuki S, Yamamoto I. Differentiation of pituitary adenomas from other sellar and parasellar tumors by 99mTc(V)-DMSA scintigraphy. Neurol Med Chir (Tokyo) 2003;43:181-6.

41. Colao A, Ferone D, Lombardi G, Lastoria S, 99mTc Technetium pentavalent dimercaptosuccinic acid scintigraphy in the follow-up of clinically nonfunctioning pituitary adenomas after radiotherapy. Clin Endocrinol (Oxf) 2002;56:713-21.

42. Atasever T, Gündoğdu C, Vural G, Kapucu IO, Karalezli U, Unli M. Evaluation of pentavalent Tc-99m DMSA scintigraphy in small cell and nonsmall cell lung cancers. Nuklearmedizin 1997;36:223-7.

43. Engin EK, Kara PO, Gedik GK, Kara A, Türker A, Caner B. The role of Tc-99m(V) DMSA scintigraphy in the diagnosis and follow-up of lung cancer lesions. Ann Nucl Med 2007;21:275-83.

44. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komishi J, Kotoura Y, et al. Scintigraphic evaluation of tenosynovial giant-cell tumor using technetium-99m(V)-dimercaptosuccinic acid. J Nucl Med 1995;36:202-7.

45. Eto H, Watanabe T, Kadowaki T, Kusumoto T, Nakamura K, et al. Pneumococcal infection in patients with medullary thyroid carcinoma. Intern Med 2001;40:816-20.

46. Hirano T, Otake H, Shibasaki T, Tamura M, Endo K. Differentiating histologic malignancy of primary brain tumors: Pentavalent technetium-99m-DMSA. J Nucl Med 1997;38:20-6.

47. Hirano T, Otake H, Kazama K, Wakabayashi K, Zama A, Shibasaki T, et al. Technetium-99m(V)-DMSA and thallium-201 in brain tumor imaging: Correlation with histology and malignant grade. J Nucl Med 1997;38:1741-9.

48. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komishi J, Kotoura Y, et al. Scintigraphic evaluation of tenosynovial giant-cell tumor using technetium-99m(V)-dimercaptosuccinic acid. J Nucl Med 1993;34:1745-7.

49. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komishi J, Kotoura Y, et al. Soft-tissue tumors: Diagnosis with Tc-99m (V) dimercaptosuccinic acid scintigraphy. Radiology 1994;190:277-80.

50. Papantoniou V, Sourtopoulos M, Stipsantie P, Louvrou A, Feda H, Chondros G, et al. Pentavalent technetium-99m dimercaptosuccinic acid [99mTc-(V)DMSA] brain scintimorphography—a plausible non-invasive depleter of glioblastoma proliferation and therapy response. J Neurooncol 2007;85:291-5.

51. Hirano T, Otake H, Yoshiida I, Endo K. Primary lung cancer SPECT imaging with pentavalent technetium-99m-DMSA. J Nucl Med 1995;36:202-7.

52. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komish J, Kotoura Y, et al. Scintigraphic evaluation of tenosynovial giant-cell tumor using technetium-99m(V)-dimercaptosuccinic acid. J Nucl Med 1993;34:1745-7.

53. Papantoniou V, Sourtopoulos M, Stipsantie P, Louvrou A, Feda H, Chondros G, et al. Pentavalent technetium-99m dimercaptosuccinic acid [99mTc-(V)DMSA] brain scintimorphography—a plausible non-invasive depleter of glioblastoma proliferation and therapy response. J Neurooncol 2007;85:291-5.

54. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komishi J, Kotoura Y, et al. Soft-tissue tumors: Diagnosis with Tc-99m (V) dimercaptosuccinic acid scintigraphy. Radiology 1994;190:277-80.

55. Papantoniou V, Sourtopoulos M, Stipsantie P, Louvrou A, Feda H, Chondros G, et al. Pentavalent technetium-99m dimercaptosuccinic acid [99mTc-(V)DMSA] brain scintimorphography—a plausible non-invasive depleter of glioblastoma proliferation and therapy response. J Neurooncol 2007;85:291-5.

56. Massardo T, Alonso O, Kabasakal L, Llamas-Olier A, Shankar UR, Zhu H, et al. Pentavalent technetium-99m dimercaptosuccinic acid [99mTc-(V)DMSA] brain scintimorphography—a plausible non-invasive depleter of glioblastoma proliferation and therapy response. J Neurooncol 2007;85:291-5.

57. Koyabashi H, Sakahara H, Hosono M, Shirato M, Komishi J, Kotoura Y, et al. Soft-tissue tumors: Diagnosis with Tc-99m (V) dimercaptosuccinic acid scintigraphy. Radiology 1994;190:277-80.
71. Papantoniou VJ, Sourvatzoglou MA, Valotassiou VJ, Louvrou AN, Anhela C, Koutsikos J, et al. Relationship of cell proliferation (Ki-67) to 99mTc-(V)DMSA uptake in breast cancer. Breast Cancer Res 2004;6:R56-62.

72. Papantoniou V, Valsamaki P, Sotropoulou E, Tsroucha A, Tsiruris S, Sotropoulou M, et al. Increased breast density correlates with the proliferation-seeking radiotracer (99m)Tc(V)-DMSA uptake in florid epithelial hyperplasia and in mixed ductal carcinoma in situ with invasive ductal carcinoma but not in pure invasive ductal carcinoma or in mild epithelial hyperplasia. Mol Imaging 2011;10:370-6.

73. Kobayashi H, Kotoura Y, Hosono M, Tsuhyama T, Nishiijima N, Sakahara H, et al. Uptake of pentavalent technetium-99m dimercaptosuccinic acid in idiopathic synovial chondromatosis. Ann Nucl Med 1995;9:153-5.

74. Lam AS, Kettle AG, O’Doherty MJ, Coakley AJ, Barrington SF, Blower PJ. Pentavalent 99Tcm-DMSA imaging in patients with bone metastases. Nucl Med Commun 1997;18:907-14.

75. Sahin M, Basoglu T, Bemay I, Yapici O, Canbaz F, Yalin T. Evaluation of metastatic bone disease with pentavalent 99Tc(m)-dimercaptosuccinic acid: A comparison with whole-body scanning and 4/24 hour quantitation of vertebral lesions. Nucl Med Commun 2000;21:251-8.

76. Zissimopoulos A, Zanglis A, Andropoulos D, Bezioti N. The role of 99mTc(V)-DMSA scan as compared to 99mTc-MDP and CT scans in imaging the primary tumor and metastases of osteosarcoma. Hell J Nuel Med 2005;8:162-4.

77. Choong PF, Kunisada T, Slavin J, Schlicht R, Hicks R. The role of thallium-201 and pentavalent dimercaptosuccinic acid for staging cartilaginous tumours. Int Semin Surg Oncol 2004;1:10.

78. Bandopadhyaya GP, Gupta P, Singh A, Shukla J, Rastogi S, Kumar R, et al. (99m)Tc-(V)DMPSA in Evaluation of Osteosarcoma: Comparative Studies with (18)F-FDG PET/CT in Detection of Primary and Malignant Lesions. ISRN Oncol 2012;2012:371830.

79. Basu S, Nair N, Awasare S, Tiwari BP, Aparna R, Nair C. 99mTc-(V)DMSA scintigraphy in monitoring the response of bone disease to vitamin D3 therapy in renal osteodystrophy. Ann Nucl Med 2002;16:19-23.

80. Kobayashi H, Kotoura Y, Sakahara H, Yamamuro T, et al. Scintigraphic evaluation of aggressive fibroblastosis. J Nucl Med 1990;31:1632-4.

81. How to cite this article: Shukla J, Mittal BR. Dimercaptosuccinic acid: A multifunctional cost effective agent for imaging and therapy. Indian J Nucl Med 2015;30:295-302.

Source of Support: Nil. Conflict of Interest: None declared.