Technetium-99m (v) Dimercaptosuccinic Acid Uptake in Patients with Head and Neck Squamous Carcinoma: Experience in Imaging

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A recently developed imaging agent, technetium-99m (v) dimercaptosuccinic acid (^{99m}Tc (v) DMSA), has been used to assess head and neck squamous carcinoma (SCC). We have prospectively studied 62 patients of whom 53 had a histologically proven head and neck SCC. The remaining nine had benign lesions. The results of planar imaging in patients with primary disease yielded an 85% sensitivity and 78% specificity. Planar imaging in patients with cervical lymphadenopathy revealed a 59% sensitivity. Nineteen patients also had single photon emission computed tomography imaging which improved the image quality, spatial resolution and sensitivity of the investigation. Twenty-seven patients were scanned before and after radiotherapy and, of these, 96% showed positive uptake in the salivary glands with no evidence of tumor recurrence. This study has shown ^{99m}Tc (v) DMSA imaging provides a cheap and rapid method of investigating head and neck SCC and further studies are necessary to evaluate its role in the management of patients with this disease.

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In 1965, Johnston, Larson, and McCurdy (*1*) reported the accumulation of mercury-197 chlormerodrin at sites of head and neck squamous cell carcinoma (SCC). Since then, both physicians and surgeons have been attracted by the use of radionuclide scanning techniques in head and neck SCC in an attempt to identify primary and occult tumor with cervical metastases together with residual or recurrent disease following surgery and irradiation. They have, however, been frustrated in their efforts using gallium-67 (^{67}Ga) citrate (*2–12*), cobalt-57 (^{57}Co) bleomycin (*13–15*), indium-111 (^{111}In) bleomycin (*16–17*), and technetium-99m (^{99m}Tc) bleomycin (*18–19*) due to low sensitivity and specificity, considerable cost, and prolonged blood clearance which delays the scanning time up to 48 hr. Indium-111 transferrin (*20*), [^{99m}Tc]sodium pertechnetate (*21*), [^{99m}Tc]sulfur colloid (*22–23*), many of the radiolanthanides (*24*), and radiolabeled monoclonal antibodies (*25–26*) have also been evaluated with similar limited success.

Recently, a new imaging agent technetium-99m (v) dimercaptosuccinic acid (^{99m}Tc (v) DMSA) has been developed (*27–28*) with the same ligand but different characteristics to the well-established renal imaging agent ^{99m}Tc (III) DMSA and which now occupies a distinct role in the management of patients with medullary carcinoma of the thyroid (MCT) (*29–31*). Recent reports have described its use in the detection of head and neck tumors and, in particular, SCC and rhabdomyosarcoma (*32–34*). The aim of this study was to evaluate the uptake of ^{99m}Tc (v) DMSA in patients with head and neck SCC using both planar imaging and single photon emission computed tomography (SPECT) and to assess salivary gland uptake before and after radiotherapy.

MATERIALS AND METHODS

DMSA is a low molecular weight organic acid which forms the ligand for the static renal imaging agent ^{99m}Tc (III) DMSA. Under alkaline conditions with a low stannous chloride concentration, DMSA forms polymeric complexes with ^{99m}Tc to form a pentavalent core. In this study a standard DMSA kit (Amersham International plc, Buckinghamshire, UK) was employed using a modification (*35*) of the technique described by Ohta et al. (*32*). This modification method was chosen since it produces pentavalent DMSA which is identical to that produced using the technique described by Ohta et al. (*32*).

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TABLE 1
^{99m}Tc (v) DMSA Imaging—Primary Site

Tongue	9
Floor of mouth	4
Larynx	11
Hypopharynx	13
Ear	3
Nasopharynx	3
Others	8
Unknown	2
Total	53 (80 scans)

The purity of the complex was analyzed by thin layer chromatography (TLC) [Merck silica gel, developed with n-butanol/acetic acid/H_2O (3:2:3)], and no free pertechnetate or other ^{99m}Tc derivative was detected; 10 mCi (370 MBq) of the prepared radiopharmaceutical was injected intravenously and patients imaged at 2 hr using a large field-of-view gamma camera interfaced to a data processor to obtain standard planar views.

A prospective study was carried out from December 1985 to September 1987 on patients with suspected head and neck cancer referred to a "tertiary referral" specialist head and neck unit. Sixty-two patients were imaged (89 scans), age range 28–82 yr (mean 60 yr), 15 females and 47 males, and of these, 53 had had a histologically proven head and neck SCC (Table 1), the remaining nine having benign lesions (Table 2). Of the 53, two patients had an occult primary, one had a second occult primary, 24 patients had cervical lymphadenopathy and of these, 22 had palpable disease. Twenty-seven patients were imaged before and after radiotherapy and, of these, four were followed up with scans at 6 mo and 1 yr.

In 19 patients, SPECT imaging was also performed using elliptical orbits (where possible) and a parzen filter 1.5 to perform the tomographic reconstructions. All scans were reviewed blind by two of the authors (SEC and JCW) without prior knowledge (where possible) of the patient's history, histology, or surgical management.

RESULTS

The results of planar imaging patients with primary disease yielded an 85% sensitivity and 78% specificity. The positive and negative predictive accuracies were 79% and 84%, respectively, (Table 3). There were 33 true positives (Fig. 1), all proven histologically, and 32 true negatives. There were six false negatives, all of whom had mucosal exophytic lesions of the tonsil (*1*), floor of mouth (*2*), and supraglottis (*3*), respectively, with a high surface area-to-bulk ratio which was assessed visually and at subsequent surgery. There were nine false positives, who had all had recent surgery or radiotherapy. Two patients had occult primaries which remained undetected despite ^{99m}Tc (v) DMSA planar whole-body imaging, head and neck SPECT evaluation, and computerized axial tomography (CAT). In one patient a histologically proven occult second primary was discovered in the apex of the right lung using planar ^{99m}Tc (v) DMSA imaging despite a normal chest radiograph.

TABLE 2
^{99m}Tc (V) DMSA Imaging—Benign Lesions

Branchial cysts	2
Inflammatory neck masses	1
Chronic laryngitis	1
Squamous papilloma of the oropharynx (pre- and post-operation)	2
Nasopharyngeal abscess	1
Hypophysectomy (pre- and post-operation)	2
Total	9 scans

TABLE 3
^{99m}Tc (v) DMSA Imaging—Primary Site

True positives	33
True negatives	32
False positives	9
False negatives	6
Sensitivity	85%
Specificity	78%
Positive predictive accuaracy	79%
Negative predictive accuracy	84%

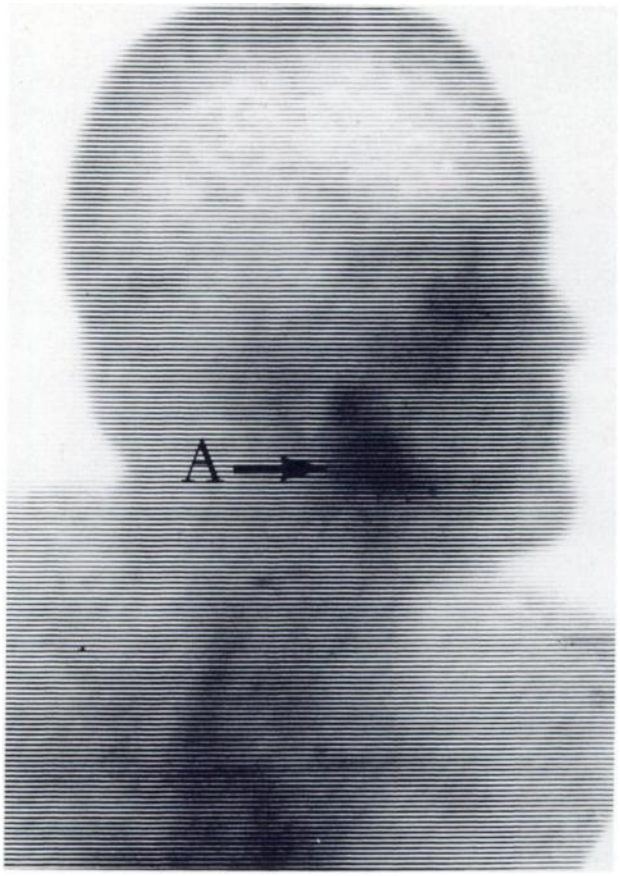

FIGURE 1
Two-hour right lateral planar ^{99m}Tc (v) DMSA head and neck image in a patient with a T_4 squamous carcinoma of the right retromolar trigone. Uptake is seen at the primary site (A).

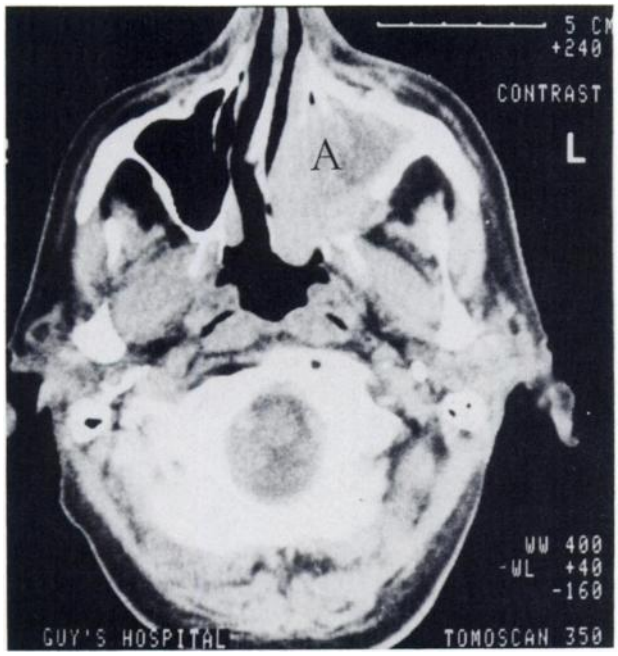

FIGURE 2
Transaxial CAT scan of a patient with an SCC of the left maxillary sinus (A).

The results of planar imaging patients with cervical metastases yielded a 59% sensitivity and 100% specificity. Twenty-four patients were imaged and, of these, there were 13 true positives, all of whom were proven histologically, and had palpable disease with nodes measuring more than 2 cm in size. There were two true negatives, one of whom had an obstructed submandibular gland due to a floor of mouth tumor; the other had reactive lymphadenopathy secondary to oral sepsis. The 100% specificity reflects the small number of patients scanned with benign disease. There were nine false negatives with a lesion size ranging from 1.5 cm to 6 cm and of these, seven had palpable disease.

In ten patients with no tumor, the normal biodistribution at 2 hr was defined with tracer visualized in the nasal mucosa, lacrimal glands, blood pool, breast tissue, testes, kidney, and bladder. All patients with benign lesions were negative on imaging except one, who had equivocal uptake in the larynx which disappeared following removal of a squamous papilloma from his oropharynx.

In addition to planar scintigraphy, 19 patients also had SPECT imaging performed which improved not only the image quality and spatial resolution (Figs. 2 and 3) but also the sensitivity of the investigation (Fig. 4 and Table 4). The observed sensitivity for planar imaging in Table 4 is lower than that previously described for primary disease and metastatic lymphadenopathy since this table contains a subgroup with false negatives from both those groups.

In 27 patients treated primarily by radiotherapy, images were obtained in all patients before and after treatment and, of these, 26 (96%) showed positive uptake in the salivary glands with no sign of tumor recurrence (Fig. 5). All patients were followed up clinically to 1 yr and, of these, four were followed up sequentially with planar ^{99m}Tc (v) DMSA imaging. All four showed a marked reduction in salivary gland uptake at 6 mo which had completely disappeared by 1 yr (Fig. 6).

There was 95% agreement between the authors (SEC and JCW) on reporting the scintigraphic studies. A decision on the remaining 5% was reached by joint discussion.

DISCUSSION

Although many radiopharmaceuticals have been investigated as possible tumor imaging agents in head and neck SCC, [^{67}Ga]citrate remains the one extensively evaluated. It is now 19 yr since Edwards and Hayes (*36*) investigated its potential as a bone scanning agent and noted its concentration in the cervical lymph nodes of a patient with Hodgkins disease. Following this early work [^{67}Ga]citrate was enthusiastically described as "tumor-seeking" and a number of early reports evaluated its uptake, not only for head and neck malignancy but

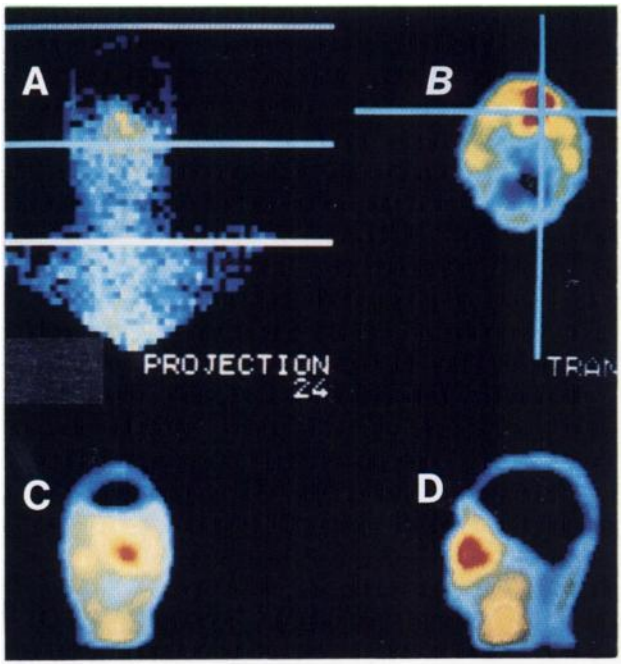

FIGURE 3
Two-hour anterior head and neck planar and SPECT ^{99m}Tc (v) DMSA images in the same patient as Figure 2. There is minimal uptake observed in the region of the left maxillary sinus on the planar image (A) but the subsequent transaxial (B), coronal (C) and sagittal (D) SPECT images show asymmetric accumulation (in red) of ^{99m}Tc (v) DMSA at the site of known tumor within the left maxillary sinus.

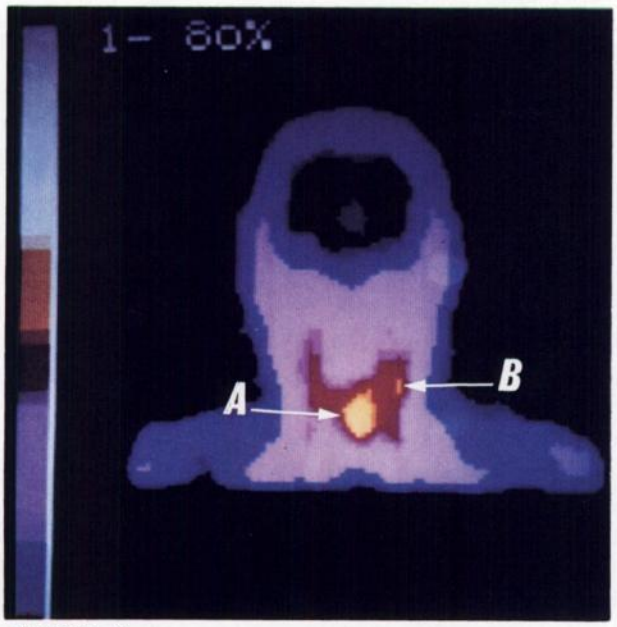

FIGURE 4
Two-hour anterior head and neck coronal SPECT ^{99m}Tc (v) DMSA image in a patient with a laryngeal SCC. No cervical lymphadenopathy was demonstrated, either by palpation or CAT evaluation. Uptake is seen at the primary site (A) and at the site of a left cervical lymph node (B) which contained histologically proven metastatic SCC and which measured < 2 cm.

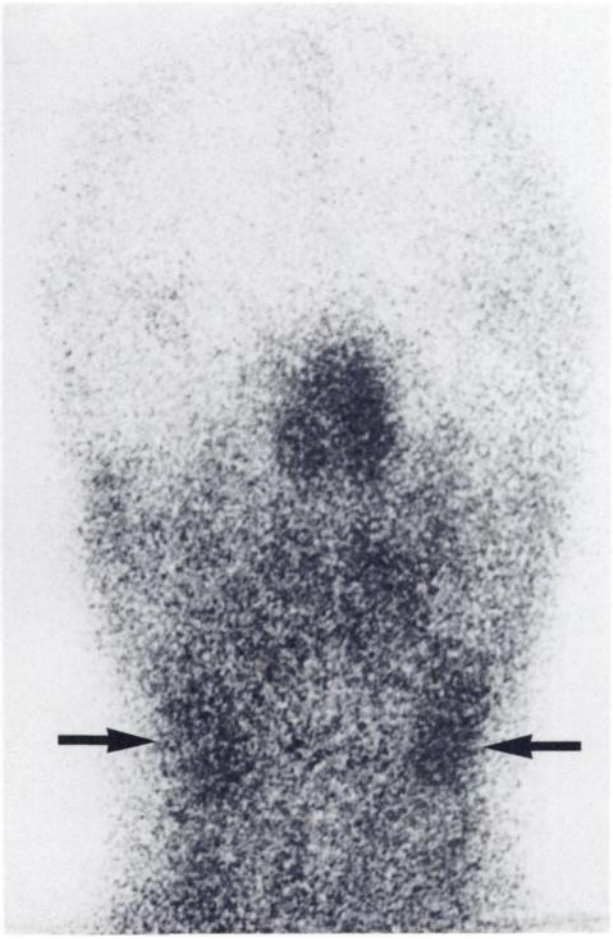

FIGURE 5
Two-hour anterior head and neck planar ^{99m}Tc (v) DMSA image in a patient with a laryngeal SCC treated with radiotherapy 3 wk previously. Accumulation of ^{99m}Tc (v) DMSA is seen at the site of the submandibular salivary glands (arrowed) which were included within the irradiation field.

for tumors in general (*37–39*). However, it is expensive, images are acquired at 48 hr, and its well-recognized distribution in bone, liver, bowel, and inflammatory tissue contributes to both a low sensitivity and specificity. Such "tumor-seeking" claims have since been disregarded and although its current clinical use in tumor imaging is confined to the evaluation of lymphoma, bronchial carcinoma, hepatoma, and seminoma (*40–41*), reports continue to be published describing its value in the investigation of patients with head and neck SCC (*12*). Technetium-99m (v) DMSA is a new imaging agent which has been used to evaluate head and neck malignancy and, in particular, SCC. It is as sensitive and more specific than [^{67}Ga]citrate (*28*) and has the distinct advantage that patients can be imaged 2 hr after injection. We have shown that ^{99m}Tc (v) DMSA is undoubtedly taken up at the sites of head and neck SCC. The sensitivity of the investigation correlates well with other series (*28*) but the high specificity for primary and secondary cervical disease reflects the small number of patients scanned with benign conditions. The 100% specificity for planar imaging cervical nodes reflects the highly selective nature of the group. Patients were only imaged prior to treatment and that following surgery and/or radiotherapy, the false-positive rate would have been increased. Patients with head and neck cancer have a high incidence of inflammatory neck nodes and the high specificity in this group suggests ^{99m}Tc (v) DMSA is not avidly accumulated by inflammatory tissue. Technetium-99m (v) DMSA is not 100% sensitive for head and neck SCC and uptake has been reported in inflammatory masses, soft-tissue, and benign tumors (*42*), together with MCT (*28–31*).

TABLE 4
^{99m}Tc (v) DMSA Imaging: Planar vs. SPECT (19 Patients)

	Planar	SPECT
True positives	10	14
True negatives	1	1
False negatives	8	4
Sensitivity	55%	78%

Using planar imaging in patients with primary disease there were six false negatives, all of whom had superficial mucosal exophytic lesions with a large surface area-to-bulk ratio and this may well be an important factor in controlling ^{99m}Tc (v) DMSA uptake. In this series, the sensitivity increased to 100% for solid infil-

FIGURE 6
Two-hour anterior planar head and neck ^{99m}Tc (v) DMSA image in the same patient as in Figure 5, performed 1 yr later. Uptake is seen at the site of clinically recurrent SCC (A). The previously noted accumulation of ^{99m}Tc (v) DMSA within the submandibular salivary glands has now disappeared.

trative lesions. There were nine false positives, all of whom had recently had surgery and radiotherapy and both these modalities can modify the uptake of radiopharmaceuticals into human tissue (*5,43*). Of those patients with benign disease, there was one false positive who had a squamous papilloma of the anterior faucial pillar. There was unexplained equivocal uptake in the larynx which was not present on the postoperative scan following surgical removal of the lesion. The explanation for this is unclear although uptake into the thyroid cartilage is recognized with [^{57}Co]bleomycin (*15*) and many metal chelates are taken up into immature bone (*44*) which may be present in varying amounts in the adult larynx during the normal process of ossification that occurs with aging. Similar mechanisms may affect ^{99m}Tc (v) DMSA uptake. The increased sensitivity with SPECT is encouraging. Of the four patients imaged that were converted from false negatives to true positives, two had mucosal exophytic lesions of the supraglottic larynx and two had cervical lymphadenopathy. While the increased sensitivity for primary lesions may be of interest, it is of little value to the surgeon since most head and neck SCCs can be diagnosed under direct or indirect vision with the naked eye.

Using ^{99m}Tc (v) DMSA planar scanning, no lymph nodes were detected that measured < 2 cm in size. One patient, however, had a laryngeal tumor with no detectable lymphadenopathy on clinical examination, CAT, or planar ^{99m}Tc (v) DMSA imaging. SPECT imaging showed uptake in the primary tumor and also at the site of a cervical lymph node (Fig. 4), which was confirmed at operation, and one node measuring < 2 cm in size was subsequently found to contain metastatic tumor on histologic examination. Other workers have confirmed increased sensitivity, image quality, and spatial resolution with SPECT (*28,32,45*). These results are encouraging since an early criticism of both [^{67}Ga]citrate and [^{57}Co]bleomycin planar imaging of cervical nodes was their inability to detect lesions < 2 cm in size by which time they were usually clinically palpable (*15*).

In the management of head and neck SCC the most important prognostic factor at the time of initial presentation is the presence or absence, level, and size of metastatic cervical lymphadenopathy (*46–47*). There is a large observer error when palpating the neck (*48*) and although CAT scanning has added a new dimension to its evaluation, it is expensive, nodes detected < 1.5 cm in size are regarded as clinically nonsignificant, and groupings of three or more 8–15 mm contiguous nodes contribute to a possible source of false-positive results (*49*).

Of those patients with primary disease, all the false positives had had previous surgery or radiotherapy. While further work is underway to assess the effect these modalities have on ^{99m}Tc (v) DMSA uptake, these preliminary results suggest SPECT imaging may be of value in the pre-operative evaluation of patients with the N_0 neck (no palpable lymphadenopathy). This would be an important contribution since should tumor upstaging take place it would directly affect the way patients are initially treated and, ultimately, their prognosis.

Uptake in the salivary glands of [^{67}Ga]citrate following radiotherapy is well recognized and is thought to be a result of interstitial edema, perivascular inflammation, and subsequent interstitial fibrosis (*50*). We have confirmed uptake of ^{99m}Tc (v) DMSA in the salivary glands of 96% of patients following radiotherapy, a finding not observed, to our knowledge, by other workers (*28,32*). In four patients followed up to 12 mo, the uptake gradually subsided in a similar manner to that observed with [^{67}Ga]citrate (*49*) and similar mechanisms probably operate with both radiopharmaceuticals to explain this phenomenon. Uptake of ^{99m}Tc (v) DMSA in the normal breast and nasal mucosa has been confirmed by others (*45*), and ^{99m}Tc (v) DMSA is currently being evaluated as an imaging agent in breast carcinoma (*30*). The inclusion of the nasal mucosa in the normal biodistribution of ^{99m}Tc (v) DMSA reflects, in part, the rich blood supply which this organ receives and, because of this, it is included in the biodistribution of other radiopharmaceuticals such as [^{67}Ga]citrate (*2–5*). This uptake of ^{99m}Tc (v) DMSA in the region of the

nasopharynx and paranasal sinuses is well recognized (*45*) and may lead to reduced sensitivity and specificity necessitating caution in the interpretation of images of this area.

The biologic tumor uptake of ^{99m}Tc (v) DMSA varies from moderate to intense. The uptake mechanism is poorly understood although it has been suggested that it is partly a result of the similarity of the TcO_4 pentavalent core to the phosphate molecule which is avidly taken up by some tumor cells (*28*). This cannot be the only mode of uptake, however, since bony accumulation would be more prominent than is currently seen with ^{99m}Tc (v) DMSA, although high bone uptake has been demonstrated in both rodents and rabbits, species characterized by incomplete bone maturation (*27*). Further work is underway to investigate the uptake mechanism in SCC using cellular subfractionation techniques in an animal model, and also to assess the uptake in inflammatory tissue which surrounds tumor cells as well as other factors such as radiotherapy and surgery, which are both known to modify radiopharmaceutical behavior.

CONCLUSION

Technetium-99m (v) DMSA has many attractive advantages as a tumor imaging agent. It is ideally suited for imaging with the gamma camera, a cheap radiopharmaceutical with an apparent high sensitivity and specificity, minimal patient irradiation (*30*), and is ideally suited for SPECT. Monoclonal antibodies offer a potential answer to SCC tumor imaging (*25–26*) but there are, however, many theoretic and practical problems associated with their use. Technetium-99m (v) DMSA provides a rapid method of investigating head and neck SCC. Further studies are underway to evaluate its role in the detection of the occult primary and cervical metastases together with late recurrence following surgery and irradiation. SPECT imaging using ^{99m}Tc (v) DMSA may be of value in the assessment of the N_0 neck, but follow-up scans in patients who have had radiotherapy should be interpreted with caution.

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