Imaging head and neck cancer using radioisotopes: a review

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Introduction
The accumulation of radioactive iodine in metastatic thyroid cancer was reported in 1942, and iodine isotope (131I) thyroid scanning was introduced into clinical practice 9 years later. The discovery that the isotope of technetium (99mTc) pertechnate (TcO4) was trapped by the thyroid gland led to its routine use in imaging. Together with 123I and 131I, it is the current agent of choice to diagnose and treat differentiated thyroid malignancy. Other radiopharmaceuticals may be used to image both thyroid cancer and other head and neck malignancies, and with the wider availability of radioisotopes, together with improved technology, there has been a renewed interest in imaging head and neck cancers. This paper reviews the clinical use of radiopharmaceuticals currently available to image head and neck cancer.

Tumour localizing radiopharmaceuticals for imaging head and neck cancer may be divided into specific and non-specific agents. Tumour-specific agents localize only within one specific tumour, or follow one specific metabolic pathway and include 131I for differentiated thyroid cancer, 99mTc(V) dimercaptosuccinic acid for medullary thyroid cancer, and iodine isotope (123I) monoclonal antibodies for squamous cell carcinoma (SCC). Tumour-nonspecific agents localise not only in a number of histologically different malignant tumours, but also in benign tumours and inflammatory lesions. Examples within the head and neck include gallium (67Ga)-citrate for lymphoma, and thallium (201Tl)-chloride for differentiated thyroid cancer.

Thyroid cancer
The investigation of differentiated (papillary, follicular and medullary) thyroid cancer involves preoperative diagnosis, usually the investigation of a solitary thyroid nodule, and the postoperative assessment of residual thyroid tissue together with the detection of residual recurrent tumour.

Clinical situations in which the possibility of differentiated thyroid malignancy arises include a solitary thyroid nodule found on palpation; a multinodular goitre with suspicious features; local symptoms such as hoarseness, dysphagia and pain, with or without a thyroid gland on palpation; exposure of the head, neck and upper thorax to previous irradiation; and, lastly, cervical lymphadenopathy or distant metastases with an unknown primary. By far the commonest way for thyroid cancer to present is as a solitary nodule when the incidence of malignancy is between 5 and 10%. The choice of radiopharmaceuticals for imaging differentiated thyroid cancer has been reviewed elsewhere. 99mTc-TcO4 is the agent used most often for routine thyroid imaging, although 123I with physical imaging characteristics similar to 99mTc is now being used more widely. However, availability and expense remain limiting factors for the more widespread use of 123I. With either 99mTc or 123I the majority of nodules greater than 5 mm in diameter can be identified7 and the use of oblique views greatly increases accuracy5. False-negative results are often associated with smaller lesions in the isthmus, but these are usually easy to palpate8 and therefore do not cause a real problem. The function of all preoperative imaging of the thyroid gland is to increase the likelihood of malignancy at operation by improving the positive predictive accuracy without any loss in sensitivity.

When a clinically solitary thyroid nodule is investigated the scan may show a solitary non-functioning or hypofunctioning area (i.e. a 'cold' nodule); a functioning area (i.e. a 'hot' nodule) or a multinodular goitre. The probability of malignancy is increased if the scan demonstrates a solitary 'cold' nodule, but decreased to less than 1% if it shows a 'hot' nodule or a multinodular goitre10. A solitary 'cold' nodule should be investigated further by ultrasound and by fine needle aspiration cytology.11 There are occasional nodules which function on the pertechnetate scan but are non-functioning on the iodine scan12. These probably reflect an ability to trap iodine but not to organise it, and problems from such rare discrepancies between pertechnetate and iodine studies can be avoided by performing 123I scans on any nodule which concentrates pertechnetate or, if 123I is not available, a TRH test should be carried out since an absent TSH response to TRH confirms a truly functioning autonomous nodule.

In an attempt to increase the pathologic specificity without any loss in sensitivity, many other radiopharmaceuticals have been used to investigate the solitary thyroid nodule. 67Ga-citrate13, 99mTc-bleomycin14, 27P15, 131C16, 75selenomethione17,18 and more recently 201Tl-chloride19,20 have been evaluated and all exhibit variable uptake in malignant lesions. At the present time (for malignancy) the false-negative rate is too high for them to have a place in the routine investigation of thyroid nodules. The 67Ga-citrate scan may be of diagnostic value in patients with longstanding Hashimoto's disease who develop a solitary thyroid nodule since this may be a lymphoma which shows avid accumulation of 67Ga.
Figure 1. Anterior head and neck 67Ga-citrate image in a patient with longstanding Hashimoto's disease. Acid uptake of 67Ga is seen at the site of known lymphoma within the thyroid gland.

(Figure 1). Imaging undifferentiated thyroid cancer is unrewarding since it does not usually accumulate iodine. Some studies have described the uptake of 67Ga-citrate within such tumours and observed an increase in sensitivity when a positive 67Ga scan is obtained with a negative 201T1-chloride scan21.

Radionuclide imaging techniques for the post-operative assessment of differentiated thyroid cancer serve to establish the completeness or otherwise of the initial surgical treatment and to detect residual or recurrent tumour. Currently the most widely used and accepted method of follow-up is regular total-body scanning using 131I combined with serial serum thyroglobulin measurements22. This is because although differentiated thyroid cancers show little or no iodine uptake in the presence of normal thyroid tissue, after ablation of normal thyroid tissue which results in high serum TSH levels, 131I will accumulate in residual or metastatic tumour which can subsequently be detected as hot lesions on a whole-body scan (Figure 2). This method permits the sensitive detection and localization of residual tumour in the neck or distant metastases and assesses the potential for radiiodine treatment1.

The localization of thyroid metastases in thyroidectomized patients using whole body 131I scans has the disadvantage of requiring the patient to be rendered hypothyroid and not all differentiated metastatic thyroid carcinomas take up 131I. Attempts to circumvent these problems have included the use of 123I-anti-human thyroglobulin monoclonal antibody23 and recently, 201T1-chloride scintigraphy has been used to detect such deposits (Figure 3) which in combination with 131I, has an increased sensitivity for the detection of metastatic disease24.

Patients with medullary carcinoma of the thyroid (MCT) have been investigated with a variety of radionuclide techniques. Primary tumours can be identified as cold areas on 99mTc-TcO4 or 123I thyroid scans with the classical pattern of bilateral symmetrical non-functioning nodules occurring in the familial type25. Since these tumours commonly metastasize to bone, 99mTc-methylene diphosphonate (MDP) bone scanning in combination with serum

Figure 2. Anterior head and neck 123I scan in a patient with recurrent papillary carcinoma of the thyroid. Uptake is seen at the site of known residual disease in the neck (arrowed). A cobalt marker has been placed on the suprasternal notch.

Figure 3. Anterior head and neck 201T1-chloride scan in a patient with recurrent papillary carcinoma of the thyroid. Uptake is seen at the site of known residual disease in the neck and upper mediastinum.

Figure 4. Anterior head and neck 99mTc(V) DMSA scan in a patient with medullary carcinoma of the thyroid. Uptake is seen at the site of known disease.
calcitonin levels has been used for the routine follow up of patients with MCT.  

201Tl-chloride has been shown to accumulate in MCT and two new radiopharmaceuticals have been developed recently which localize in MCT tumours. 113I-metaiodobenzyl guanidine (MIBG) was developed for imaging phaeochromocytoma and subsequently shown to be taken up into primary and metastatic MCT. More recently, pentavalent 99mTc (V) dimercaptosuccinic acid (DMSA) has been developed which is related to the well established renal imaging agent 99mTc (III) DMSA and its uptake has been described in MCT (Figure 4). Recent reports have confirmed uptake of both 131I-MIBG and 99mTc (V) DMSA in both primary and recurrent MCT but have shown 99mTc (V) DMSA to have distinct advantages over 131I-MIBG. It is an easily prepared, low cost radiopharmaceutical with a short imaging time, and as a technetium labelled compound, the whole body radiation dose is markedly less than a 131I MIBG scan. The main role of 99mTc (V) DMSA is in the investigation of primary and recurrent MCT and the possible advantages of 131I MIBG scanning is to assess its therapeutic potential in an individual patient.

Parathyroid tumours

Carcinoma of the parathyroid gland is uncommon. The majority of patients present with severe hyperparathyroidism and markedly elevated serum calcium and parathormone (PTH) levels and approximately 50% have a palpable neck mass. Non-invasive pre-operative localization may be facilitated by a positive 67Ga-citrate scan although, usually, the diagnosis is made at operation. Recurrent disease should be suspected when the serum calcium or PTH levels remain elevated; localization should begin with cervical examination since 45% of recurrences are palpable. 201Tl-chloride-99mTc-TcO4 subtraction scanning for the localization of parathyroid adenomas has been successfully used to locate recurrent tumour within the neck and mediastinum. However, the thyroid lobe is usually totally excised along with the parathyroid carcinoma, so local recurrence may be demonstrated by the accumulation of 201Tl-chloride alone. Suspected localization should be confirmed by CT scanning which may provide additional information.

Squamous cell carcinoma

In the management of head and neck SCC, the most important prognostic factor at the time of initial presentation is the presence or absence, and level and size of metastatic cervical lymphadenopathy. There is a large observer error rate when palpating the neck, and although X-ray CT scanning has added a new dimension to the evaluation of SCC, it is expensive. In addition, nodes detected less than 15 mm in size are regarded as clinically non-significant, and groupings of three or more 8–15 mm contiguous nodes contribute to a possible source of false-positive results. The accumulation of 197Hg chlormerodrin at sites of head and neck SCC was first reported over 30 years ago. Since then physicians and surgeons have used a variety of radiopharmaceuticals in head and neck SCC in an attempt to identify primary and occult tumour with cervical metastases together with residual or recurrent disease following surgery and irradiation. 67Ga-citrate, cobalt (67Co)-bleomycin, 131I-bleomycin, 99mTc-bleomycin, 99mTc-TcO4 and many of the radioanathanes have all been tried, but with limited success due to low sensitivity and specificity, considerable cost, and prolonged blood clearance which may delay the scanning time up to 48 h.

A criticism of both 67Ga-citrate and 67Co-bleomycin imaging of cervical nodes is their inability to detect lesions less than 20 mm in size, by which time they were usually clinically palpable. Recent attempts to image cervical nodes using 99mTc-sulphur colloid lymphoscintigraphy and 111In monoclonal antibody against the epidermal growth factor receptor have proved similarly unsuccessful due to an unacceptable false-negative rate and the inability to detect nodes less than 20 mm in size. Encouraging reports have described the uptake of 99mTc (V) DMSA within primary and metastatic head and neck SCC and (Figure 5). It is as sensitive, but more specific than 67Ga-citrate, and being a technetium labelled compound is more suitable for single photon emission computed tomography (SPECT). The use of SPECT improves the sensitivity of the investigation, so that it is now possible to detect nodes less than 20 mm which were neither palpable nor visible on CT evaluation.

Lymph glands

Almost 20 years ago Edwards and Hayes investigated the potential of 67Ga-citrate as a bone scanning agent and noted its concentration in the cervical glands of a patient with Hodgkin’s disease. 67Ga was subsequently described as ‘tumour seeking’, not only for head and neck malignancy, but for tumours in general. Its current clinical use in head and neck tumour imaging is now largely confined to the evaluation of lymphoma. 67Ga-citrate scanning may be applied to the evaluation of patients with head and neck lymphoma before a histological diagnosis is obtained, and during initial staging. It is, however, of particular value in the evaluation and restaging of residual and recurrent disease, although bilateral symmetrical accumulation within the salivary glands following radiotherapy is a normal phenomenon which may cause difficulty when interpreting images.

Bone

The clinical use of bone scanning using 99mTc-MDP in head and neck tumours has been reported to be of value in the pretreatment evaluation of bony
involvement from primary carcinoma, in the diagnosis of residual and recurrent disease, and to detect bony metastases to, and from, the head and neck. Distant metastases from head and neck carcinoma (excluding the thyroid) are uncommon, and although bone scanning is highly sensitive, it is non-specific so that bony extension within the mandible from oral cancer may not be reliably distinguished from benign dental disease. Primary bone tumours of the head and neck all accumulate 99mTc-MDP but these are all much better evaluated using other imaging modalities such as CT scanning.

Miscellaneous
Many other head and neck tumours have been evaluated using radioisotopes. Both primary and metastatic melanoma have been visualized using 131I-monoclonal antibodies and early reports are encouraging. Similarly, the localization of 131I-MIBG within thymoma and malignant parangangioma has recently been described, and further studies are underway to assess both the diagnostic and therapeutic implications of such uptake within these tumours.

Conclusion
The role of radioisotopes in the management of both differentiated and medullary carcinoma of the thyroid is now well established. Although there are many other radiopharmaceuticals available to image head and neck cancer, few can actually achieve the required diagnostic sensitivity and specificity. The search is for more sensitive and specific diagnostic and therapeutic agents. Although the introduction of monoclonal antibodies into routine imaging has been hampered by distinct practical problems, it is now possible to properly assess the use of monoclonal antibodies, their Fab or F(ab)2 fragments and to evaluate new 99mTc-labelled tumour imaging agents, using animal tumour model systems. The continued use of SPECT together with the introduction of positron emission tomography (PET) can only lead to an increase in diagnostic sensitivity and specificity and subsequently to an overall improvement in the way we diagnose, stage and treat head and neck cancer.

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