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Imaging Techniques for Metastatic Thyroid Medullary Cancer

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Postoperatively elevated calcitonin levels strongly suggest the presence of residual or recurrent medullary thyroid carcinoma (MTC). Several imaging modalities including radiological and radionuclide techniques are often performed in patients with an elevated calcitonin levels until the tumor is localized. In this review, the major noninvasive imaging techniques and the advantages and disadvantages of each modality are discussed for metastatic MTC.

Key words: Medullary Thyroid Carcinoma, metastases, imaging techniques

Introduction

Medullary thyroid carcinoma (MTC) originating from the calcitonin- secreting parafollicular cells is a relatively uncommon disease. It constitutes 3% to 10% of all thyroid malignancies (1). MTC may occur in sporadic or rarely familial form as a part of multiple endocrine neoplasia syndrome type 2A and 2B. The sporadic MTC is mostly detected on the basis of clinical symptoms. Calcitonin that is secreted from the parafollicular C cells is a useful marker for initial diagnosis and follow-up (2). Carcinoembryonic antigen (CEA) can also be used as a tumor marker for MTC (3). Total thyroidectomy with cervical lymph node dissection is the primary therapeutic option for MTC because of the high incidence of lymphatic metastasis (4). At the time of initial diagnosis cervical lymph node metastases have been detected in 71- 80% of the patients, and mediastinal involvement and distant metastases have been reported in 36- 20% (5-8) of the patients with MTC, respectively.

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Management of MTC patients with an increased calcitonin level after thyroid surgery is difficult. Postoperative elevated calcitonin levels strongly suggest residual, recurrent or metastatic MTC. Several imaging modalities including radiological [ultrasonography (USG), computerized tomography (CT) or magnetic resonance imaging (MRI)]and radionuclide techniques [^{201}Thallium Chloride ^{123}Iodine or ^{131}Iodine Metaiodobenzylguanidine (MIBG), ^{99m}Technetium Sestamibi (MIBI), Pentavalent ^{99m}Technetium Dimercaptosuccinic Acid (V-DMSA), Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG- PET), ^{111}Indium-labeled Pentetreotide or Octerotide and Radio-labeled anti-CEA Monoclonal Antibodies] have been performed according to availability of these methods and the experience of the team.

In this review, the major noninvasive imaging techniques and the advantages and disadvantages of each modality are discussed for metastatic MTC.

Nonisotopic Imaging

Ultrasonography (USG)

USG is a useful method for the detection of residual or recurrent thyroid cancer in local lymph nodes and in the thyroid bed (9,10). USG was reported as

the most sensitive imaging modality for localization of a recurrent tumor mass or lymph node metastases in the neck (sensitivity 96%, specificity 83%) (9). In this study, 17 of 25 patients with non-palpable metastatic node involvement had positive sonograms. Lymph node metastases were found in 28%-78% (11,12) of the MTC patients with USG postoperatively, in two different studies. In addition, USG has the advantage of allowing fine-needle aspiration but this is limited to cervical lesions (13).

Computed Tomography (CT)

CT scan is a useful method for the detection of thyroid cancer recurrence, especially in the retrosternal and peritracheal areas (10,14) and also helpful for the evaluation of distant metastases (10,15). In a multi-center study, the sensitivity and specificity of CT were reported as 50% and 67%, respectively (16). In other studies, the lymph node detection rate of CT was reported as 38-70%(11,12). CT is better for detecting calcification than MRI imaging and is also less expensive and more accessible (10,17). Helical CT employs rapid data collection to virtually eliminate motion artifacts and significantly improve the detection and characterization of the lung nodules (18).

Magnetic Resonance Imaging (MRI)

MRI is another useful method for the evaluation of recurrent or residual cancer as well as distant metastases (10). The accuracy of MRI in the diagnosis of MTC was investigated in a small number of studies (19-21). In a study including 14 patients, a sensitivity and specificity of 74% and 98% were reported respectively in the detection of lymph node metastases (21).

In a multicentiric study, the authors found a higher sensitivity (82%) but a lower specificity (67%) (16).

Morphologic imaging techniques can confirm the involvement of lymph nodes on the basis of their size, but these investigations are often insufficient because of the smallness of the tumor (19-22). In addition, distortion of normal anatomy after surgery can affect the interpretation of the images of USG, CT or MRI (23). Thus, these methods frequently fail to reveal the recurrent or metastatic tumor. However, CT and MRI are useful in the majority of pulmonary and hepatic metastases (24).

Radionuclide techniques may play a complementary role in tumor or lymph node detection for MTC, especially in the mediastinum(25).

Isotopic Imaging

^{201}Thallium Chloride

Tl^{201} is a nonspecific isotopic agent (10). Tl uptake in MTC was investigated in several studies (26-29) Koizumi et al. reported that Tl^{201} showed rapid washout in MTC, and was often seen only in the early scans (28). Montravers et al. found a sensitivity of 83% and believed that Tl^{201} was superior to MIBG in MTC (29). Adalet et al. and Rainers et al. reported 72% and 63% sensitivity respectively in detecting metastases (30,31).

^{123}Iodine or ^{131}Iodine Metaiodobenzylguanidine (MIBG)

Both ^{123}I and ^{131}I- MIBG are useful imaging techniques in many neuroendocrine tumors (pheochromocytoma, neuroblastoma) (10,23). However, it has a low uptake in MTC. Rainers et al. reported a sensitivity of 31% for metastatic disease (31). Skowsky et al. reported a true-positive rate of 30% (slightly higher in familial than sporadic form) and false-negative rate of 52% (32). Szakall et al. found positive scan findings in only 3 of the 40 patients with ^{131}I- MIBG scintigraphy (24). MIBG does not seem to be an ideal agent for imaging MTC. However, it may be used for imaging of pheochromocytoma in MEN kindred and therapy (10,33).

^{99m}Technetium Sestamibi (MIBI)

Another radiotracer, ^{99m}Tc- MIBI provides some advantages (low radiation exposure, inexpensive) when compared with other isotopic methods, but it appears to have low sensitivity and specificity in the detection of recurrent or metastatic disease in MTC (34). In earlier studies, sensitivity of MIBI was reported as 59%(30) and 25% (16). MIBI accumulates in the mitochondria, and the uptake depends on the membrane and mitochondrial potential (10,16). In a study, ^{99m}Tc- MIBI was shown to be more sensitive than CT in the assessment of recurrent MTC in the neck and the chest, particularly in patients with very high calcitonin levels (>6000 pg/ml) (35).

Pentavalent ^{99m}Technetium Dimercaptosuccinic Acid (V-DMSA)

Several investigators believe that this is the most suitable imaging technique for MTC (36-38). Guerra et al. reported an overall sensitivity of 68% and specificity of 100% for metastatic disease in their review (36). A review of five small series led to a similar sensitivity and confirmed the excellent uptake in metastatic disease of both bone and soft tissue (32). In the other studies, the reported sensitivities of V-DMSA vary between 33% and 95% (24, 30,39). V-DMSA is inexpensive and can be easily prepared before use (10).

Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG- PET)

^{18}F-FDG- PET is a new isotopic method for the detection of metastases in patients with MTC. The sensitivity of ^{18}F-FDG- PET is independent from the calcitonin level. This makes ^{18}F-FDG- PET superior to other radionuclide techniques. Brandt-Mainz et al. reported that the sensitivity of ^{18}F-FDG-PET was 76% for the detection of metastases (16). In a multi-center study, radiologic imaging techniques and functional imaging methods with single-photon emitters were compared and ^{18}F-FDG- PET was found as the most accurate method for detecting recurrent or metastatic MTC with a high sensitivity and specificity (78% and 79%, respectively) (15). Szakall et al. reported that ^{18}F-FDG- PET was a highly sensitive method for the detection of metastases in MTC patients with elevated tumor marker levels, and its sensitivity was superior to other imaging procedures, especially in the localization of cervical and mediastinal lymph node involvement (13).

^{111}Indium-labeled Pentetreotide or Octerotide

As a neuroendocrine tumor, MTC may express high-affinity to somatostatin receptor scintigraphy (41,42). In the literature, the sensitivity of somatostatin receptor imaging methods in a large patient population was reported between 17% and 72% (43-47). Furthermore, Frank-Raue et al. reported low sensitivity in patients with minimal disease in the neck and low calcitonin levels (47). The method, although excellent for imaging pulmonary metastases (48), is insensitive in liver metastases (47,48). In addition, false-positive uptake in areas of inflammation, granulomatous disease and neuroma was reported (48). However, this method also can be used as a guide for the treatment with somatostatin analogues (49).

Radio-labeled anti-CEA Monoclonal Antibodies

Most of the MTC express CEA. Anti CEA antibody binds to CEA expressed on C cell surface (25). Thus, CEA antibodies labelled with ^{111} In or ^{99m}Tc may be used for scintigraphy, and have a sensitivity of 60% (31,50,51). Juweid et al. reported that MTC imaging with anti- CEA monoclonal antibodies could be very useful in determining the ideal candidates for re-exploration of the neck, and the sensitivity of the method was 81% (52). However, nonspecific liver uptake makes imaging of liver metastases difficult (10). In addition, Anti CEA antibodies may be used for metabolic radiotherapy.

Comment

When the specifities and sensitivities of different imaging techniques are taken into consideration, USG and CT should be the first step for the evaluation of an MTC patient with an elevated calcitonin level postoperatively. But if they fail to localize the tumor or metastatic lesion one of the V-DMSA, Tl^{201} or ^{99m}Tc MIBI isotopic imaging techniques can be performed as the second diagnostic step according to the availability of the method and experience of the center. If all these modalities fail to localize the tumor or metastatic lesion ^{18}F-FDG-PET can be preferred for the last step in the evaluation of the tumor site instead of other imaging techniques to save time and money.

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