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Current Investigations on Early Diagnosis and Treatment on Medullary Carcinoma of Thyroid Gland

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Abstract

Thyroid cancers are most commonly hit endocrine disease in general population. They are categorized as benign and malignant types. Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy associated with a higher incidence of distant metastasis and poorer prognosis compared with the more frequently encountered well-differentiated papillary and follicular thyroid carcinomas. MTC is characterized by a sheet like growth pattern and is composed of round polygonal or spindle shaped tumor cells. Elevated serum levels of Calcitonin or CEA are indication of metastases. Cervical ultrasound is considered to be essential in the diagnosis of lymph node metastasis. CT and MRI scanning are involved in more accurate assessment of infiltration of neighboring structures. FNAB with calcitonin concentration measurement in biopsy needle washout fluid demonstrates to be supportive in diagnosis. The radiophar4maceuticals 131I or 123I-labelled metaiodobenzylguanidine (MIBG) 99mTc(V)-DMSA (five value 99m Tc-labeled dimercaptosuccinic acid), 111In-pentetreotide and 99m Tc-EDDA/HYNIC- tyr3-octreotide are used in Plannar scintigraphy and single-photon emission computed tomography (SPECT). Total thyroidectomy is a surgical procedure which is performed to treat various thyroid diseases. Sunitinib, lenvatinib and vandetanib are under investigation treatment options for MTC. Total thyroidectomy provides little significant advantage of being safer procedure compared to subtotal thyroidectomy.

Keywords: Medullary thyroid carcinoma; Thyroid cancers; Thyroidectomy; Metastases

Introduction

Thyroid disorders are most commonly hit endocrine disease in general population [1]. The thyroid is a small endocrine gland which produces hormones that regulate various metabolic activities of the body [2]. Thyroid diseases can be grouped into benign and malignant types. In benign cases, the common diseases encountered are thyroiditis (mostly Hashimoto thyroiditis), goiter, thyroid adenoma, and so forth [3]. Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy associated with a higher incidence of distant metastasis and poorer prognosis compared with the more frequently encountered well-differentiated papillary and follicular thyroid carcinomas [4,5].

Pathology

MTC is a type of neuroendocrine tumor which is categorized as part of apudoma ("apud" denotes to amine precursor uptake and decarboxylation. In thyroid gland, parafollicular cells derived from neural crest, are duly responsible for occurrence of medullary thyroid carcinoma. MTCs are generally well-defined tumors of variable size [6-8]. Hereditary MTCs are often bilateral and multifocal; these features are less common in sporadic MTC [9–12]. Microscopically, the classic MTC is characterized by a sheet like growth pattern and is composed of round polygonal or spindle shaped tumor cells. The nuclei are fairly uniform in shape and have coarsely clumped chromatin and inconspicuous nucleoli. The cytoplasm may have a granular appearance and can be either eosinophilic or basophilic. Necrosis and hemorrhage appear more often in larger tumors. Stromal amyloid deposits may be seen in up to 80%, a unique feature not seen in other thyroid tumors [12,13]. Although the diagnosis of MTC is usually straightforward on standard histopathology, diagnostic dilemmas can occur [13]. For example, MTC may represents some features of papillary carcinoma like pseudo inclusions or psammoma bodies or follicular thyroid carcinoma by imitating follicular pattern or undifferentiated thyroid cells by signifying

spindle cells or giant cells. In such cases, positive immune-histochemical staining for calcitonin and other neuroendocrine markers, such as chromogranin and synaptophysin, is usually diagnostic.

How does medullary carcinoma present?

Early detection of this tumor may significantly improve chances of survival [6].

How should a thyroid lump be investigated?

Elevated serum levels of Calcitonin or CEA are indication of metastases. But these tumor markers are not sufficient to start therapies. Elevated tumor markers and especially a low doubling time of serum calcitonin and CEA are rather considered risk factors for the presence and development of metastases and a poor prognosis. Those patients are being followed with serum tumor marker measurements and regular imaging, the interval depending on the serum marker level and doubling time [5,14]. Imaging procedures in metastatic MTC include conventional contrast-enhanced spiral CT scan or MRI of the brain, neck, chest and liver and bone scintigraphy [3]. Ultrasonography, computed tomography (CT) and Magnetic resonance imaging (MRI) are different diagnostic techniques to measure tumor invasion of surrounding muscles, trachea, larynx, esophagus. Retro-esophageal space and mediastinum. Medullary thyroid carcinoma (MTC) is insignificantly different from other thyroid carcinomas when observed in ultrasonography imaging. Parafollicular C cells are the area from where tumor originates, these areas are mainly located in the upper and central parts of the lobes. In heritable cases, lesions are basically multifocal, and may be located in both lobes [1]. In Ultrasonography, the malignancy of thyroid tumor represents as solid structure, hypo echogenicity, with improved central flow, uneven margin, its anterior-posterior dimensions greater than the transverse one and internal calcifications [12,13]. As compared to the papillary cancer, however, medullary thyroid carcinoma more often shows the features of benign lesions including oval shape, homogenous structure, cystic degenerative lesions or smooth well-defined margins [14]. Medullary thyroid carcinoma often does not show the characteristics for cancer [15]. As, calcitonin is considered to be a biological marker for MTC, therefore many experts used calcitonin determination in the diagnostic procedure for thyroid focal lesions. Ultrasound guided Fine needle aspiration biopsy (FNAB) is considered a standard in the diagnosis for thyroid. The sensitivity value of FNAB in the case of MTC is 44-63% [16,17]. Immunocytochemical detection of concentration of calcitonin, calcitonin gene-related peptide (CGRP), neuron specific enolase (NSE) as well as calcitonin measurement in FNAB washout fluid, increase the diagnostic value of FNAB [1].

Monitoring of Patients

To monitor the recurrence of medullary thyroid carcinoma, evaluating the tumor location is most essential prognostic element. After surgery, a patient is periodically monitored for serum concentration of calcitonin and CEA. The first test is usually recommended after 3 months of surgery, probably due to high level of calcitonin during wound healing and long half-life of calcitonin and CEA [1]. Depending upon the results, more measurements should be made. If the concentration of calcitonin and CEA are undetectable, then test should be suggested every 6 months in the first year and then every 12 months; but if the concentrations are detectable, at least every 6 months [1]. If calcitonin and CEA arte lying in undetectable or normal concentrations, then ultrasound of neck should be performed [18].

Diagnosis of local Recurrence and Lymph Node Metastasis

The most common site of medullary thyroid carcinoma (MTC) metastasis is lymph node. At diagnosis time, metastasis of lymph nodes ranges between 75-81% and distant ones present up to 13% [9-11]. When the concentration of calcitonin is upto 150 pg/ml then the ultrasound of neck is performed as first line medical examination to assess the metastasis or local recurrence to the neck lymph node [19]. Shape of lymph nodes with metastatic lesions are normally round or oval in shape, with obscure hilum, raised heterogeneous echogenicity, contain cystic degenerative lesions or calcification and have chaotic blood flow in Doppler imaging. These nodes are found in retro-tracheal and para-and retro-esophageal space. These nodes are undetectable by ultrasound technique which sensitivity is about 46 – 88% but CT scan (sensitivity about 42-86%) and MRI of neck (sensitivity about 38-91%) are complementary techniques helpful in visualizing these nodes. [17-20].

FNAB plays a vital role in the diagnosis of nodal metastasis, especially in the case when small nodes were found without significant morphological change. Calcitonin concentration can also be assessed in biopsy needle wash-out fluid in FNAB [18]. Local recurrence is often difficult to detect because of small size and problem associated with differentiating it from scar changes in tumor. Cervical ultrasound is considered to be essential in the diagnosis of lymph node metastasis. CT and MRI scanning are involved in more accurate assessment of infiltration of neighboring structures. FNAB with calcitonin concentration measurement in biopsy needle washout fluid demonstrates to be supportive in diagnosis [18].

Diagnosis of Distant Metastasis

When concentration of calcitonin exceeds 150 pg/ml then computed tomography, magnetic resonance imaging or positron emission tomography are recommended to diagnose distant metastasis. if calcitonin value is less than 150 pg/ml, then these methods cannot detect tumor foci. Diagnostic tests for distant metastasis, including computed tomography, magnetic resonance imaging or positron emission tomography are only recommended when concentration of calcium exceeds 150 pg/ml, because below this value, tumor foci cannot be detected

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by these methods [1,19]. Another important point should be remembered that at high concentration of up to 1000 pg/ml, risk of false negative imaging results remain high [19]. Most probable cause of false negative imaging are micro-metastasis to the liver, which can be detectable by laparoscopy [20]. Medullary thyroid carcinoma (MTC) is one of the cancer in which liver metastasis are hyper echogenic on ultrasound [21]. Occasionally, in the ultrasound low or mixed echogenicity is possessed by metastasis due to the presence of fluid and calcification. In such cases CT and MRI are recommended tests to make a difference from haemagioma [11,21, 22]. Their vascularization is very well developed. The most sensitive diagnostic imaging technique for MTC metastasis to liver is dynamic MRI [16].

Medullary thyroid carcinoma metastasis in lungs may be micro or macro-nodular [11]. These are small and in the form of multiple lesions in majority of cases [1,11]. Sometimes these lesions appear in the form of miliary spread, perihilar fibro-nodular lesions or calcified masses [23,24]. CT scan provides maximum sensitivity in detection of metastasis to lungs and mediastinum [1,16]. Metastasis of MTC to bones are predominantly osteolytic and less often osteoblastic, however both forms of metastasis coexist [25]. Classis bone scinitigraphy with hydroxyl methylene diphosphonate or 99m Tc labeled methylene diphosphonate are responsible to detect osteoblastic lesions which are highly prone to capturing radioisotopes, in the case of medullary thyroid carcinoma provides the sensitivity of about 58-73% [16,26]. MRI technique is responsible to provide higher sensitivity in the detection of MTC metastasis approximately about 61-100% [16,26]. In T1-weighted sequence, metastasis is less intensive, but may be enhanced after administration of gadolinium. MRI technique has more sensitivity in detection of lesions in the axial skeleton, while classic scintigraphy considered to be more sensitive in detection of lesions in long bones metastasis [16]. In diagnostic measures of MTC metastasis toward bones, both MRI and scintography are equally complementary so when they are used in combination the sensitivity can be boosted up to 61-94% [16].

Nuclear Medicine Imaging in the diagnosis of Medullary Thyroid Carcinoma (MTC)

Plannar scintigraphy and single-photon emission computed tomography (SPECT). The radiopharmaceuticals emitting γ radiation used for Medullary Thyroid Carcinoma (MTC) scintigraphic diagnosis include:

131I or 123I-labelled metaiodobenzylguanidine (MIBG) 99mTc(V)-DMSA (five value 99m Tc-labeled dimercaptosuccinic acid), 111In-pentetreotide and 99m Tc-EDDA/HYNIC- tyr3-octreotide. MIBG is a noradrenalin analog specific for tumors developing from neural crest [27]. Primarily used in the diagnosis of neuroblastoma and Pheochromocytoma, it may also be useful for MTC foci imaging [27]. The available preprations are 131I and 123I-labelled, and due to enhanced dosimetric characteristics of 123I, the scintigraphy by the use of 123I-MIBI results in improved imaging sensitivity enhanced quality [28]. On contrary, 131I-MIBI due to α radiation may be used in the case of palliative treatment of MTC, although this treatment option often considered as ineffective [1,29]. In the case of MTC, the Specificity of MIBG scintigraphy is greater up to 95%, but its sensitivity is fewer about 25-30% only, and majorly it is based on the level & degree of differentiation of the tumor. It is larger in patients with MEN 2A syndrome than in sporadic Medullary Thyroid Carcinoma [30,31]. Greater sensitivity of MIBG scintigraphy was observed in the case of localization of persistent tumor cells and localized MTC recurrence, as compared with distant metastasis, which is explained by progressive differentiation of metastatic lesions [28,30].

Scintigraphy along with 99m Tc(V)-DMSA can be used both in the diagnosis of the primary foci and the recurrence of MTC [31,32]. Its sensitivity value fluctuates in different studies is about 50-80% [31,33]. Depending on the type of tissue, 99mTc (V)-DMSA uptake is significantly high in soft tissues as compare to bone [28]. Somatostatin receptor scintigraphy with the use of 111In-pentetreotide or 99m Tc-EDDA/ HYNIC-Tyr3-octreotide is also a helpful tool for MTC diagnosis [33-40]. Along with imaging of tumor foci, it is essential in the selection of patients with unrespectable MTC to be treated with hot and cold Somatostatin analogues [35, 36]. There is great variation in the results of the evaluation of octreScan sensitivity in the detection of MTC ranges from 20 to 78.5% [27,28,33]. According to numerous studies, this value is measured to be lesser than that of the conventional imaging including X-rays, ultrasound, bone scintigraphy or CT scan [34]. The studies of comparison of 111In-pentetreotide scintigraphy with 99mTc(V)-DMSA and MIBG, defines that its sensitivity is greater than that of MIBG and comparable to or more than 99mTc(V)-DMSA [33,35].

In well differentiated tumors the uptake of 111In-pentetreotide is higher, but observed significantly less in tumors undergo rapid progression and distant metastasis, that is because of decreased expression of Somatostatin receptors in less differentiated tumors [36]. The sensitivity of 99m Tc-EDDA/HYNIC-Tyr3-octreotide scintigraphy, compared to 111In-pentetreotide is greater [37,38]. This value is evaluated as 56.2-79.5% [39,40]. It has been found that results of 99mTc-EDDA/HYNIC Tyr3-octreotide scintigraphy were little worse than 18F-FDG PET, while better than 99mTc-MIBI scintigraphy [40]. By using scintigraphy, good results were obtained based upon monoclonal antibodies against carcino-embryonic antigen (CEA) labeled with isotopes 99m Tc, 123I, 131I and 111In [36]. The anti-CEA antibodies scintigraphy indicates sensitivity 50-78%, somewhat less or comparable with 99m Tc (V)-DMSA, and higher than 131I-MIBG [36,41,42]. Contrary to Somatostatin receptor scintigraphy, this diagnostic technique proved to be beneficial for extremely aggressive MTC [36]. 131I-labeled anti-CEA antibodies show effectiveness in palliative treatment [36]. The effectiveness of 201Tl, 99mTc-MIBI and 111In-labeled

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calcitonin antibodies scintigraphy was also evaluated, but the studies evaluating those methods in the diagnostic procedures of MTC indicate, that these methods have less sensitivity as compared to other procedures [40,41,43].

Positron Emission Tomography (PET)

18F-fluorodeoxyglucose(18F-FDG) was 1st radiopharmaceutical emitting β+, that is used for neoplasm as diagnostic radiopharmaceutical by positron emission tomography [44]. Studies have shown in less differentiated and rapid growing tumors there is more uptake of 18F-FDG, which rapidly metabolize glucose [44]. Sensitivity of 18F-FDG PET ranges from 17 to 95% in diagnosis of recurrence of MTC [45-49]. It has been found that it is greater in patients having larger tumors (calcitonin is greater than 1000 pg/ml), as well as in patients with quickly proliferating (with calcitonin concentration doubling time less than 2 years) and less differentiated tumors [16,45,50].

In patients of MTC, Positive result of 18F-FDG PET is related to worse prognosis. Patients having calcitonin level less than 1000 pg/ml has a limited use of 18F-FDG PET, as in that situation the range of sensitivity is from 20-37% [16,50]. In patients with MEN 2A, Sensitivity of 18F-FDG PET is significantly less due to less aggressive course of MTC in such patients [50]. Major advantage of 18-FDG PET is entire body imaging capability as compare to conventional diagnostic imaging. Although this is not considered to be a radiopharmaceutical of choice in well differential tumors, including MTC, it has been found that 18-FDG PET has more sensitivity as compare to SPECT [40,44,47]. The sensitivity of 18F-FDG PET depends on the size and location of lesions [16, 46]. Studies showed that this is valuable in detection of the neck and mediastinum lymph node metastasis and local recurrence, defines more sensitivity compared to MRI or CT scan [16,46,47]. In detection of small metastasis which are located in the liver and lungs, 18F-FDG PET is less sensitive as compare with CT scan, and worse sensitive than MRI or scintigraphy in the bone metastasis imaging [16,46,47].

Another radiopharmaceutical, 18F-DOPA, is effectively used in MTC PET collected by the cells liable for decarboxylation and up taking catecholamine precursors [48]. 18F-FDG PET estimated about 47-83% is less than the sensitivity of 18F-DOPA PET [17,25,48-52]. These two diagnostic examinations are considered to be complement for each other, as 18F-DOPA can be used for the detection of MTC having less proliferation capacity, and 18F-FDG can be used for more aggressive tumors with doubling time of calcitonin less than 12 months [25]. 18F-DOPA PET/CT is specifically useful in detection metastatic lymph nodes and also allow to detect those tumor foci which are at calcitonin concentration greater than 150 pg/ml [52]. In the PET diagnosis of MTC, 68Ga-labeled Somatostatin analogs (68Ga-DOTA-NOC, 68Ga-DOTA-TOC, 68Ga-DOTA-TATE) all are important radiopharmaceuticals [49,53,54]. In detection of MTC recurrences, sensitivity of 68Ga-DOTA-TATE PET/CT is 72% compare to 18F-FDG PET/CT which is 78% [53]. By means of PET/CT, evaluation of somatostatin receptor expression can be helpful in selection of patients for treatment with "hot" (177Lu- or 90Y-DOTA-TATE) or "cold" (pasireotide) somatostatin analogues [54]. After comparing the results of PET/CT in those patients having persistent and recurrent MTC, it has been found that 18F-DOPA has more sensitivity for cancer foci detection when compared with 18F-FDG and Somatostatin analogues[49]. Expansiveness and least availability are disadvantages of this method, as well 68Ga-DOTA-TATE PET/CT and 18F-FDG PET/CT found to have no significant differences in sensitivity in result evaluation of these two diagnostic examinations [49,53]

How is the diagnosis of medullary carcinoma confirmed?

Imaging plays a critical role in both early detection and accurate staging of MTC, which dictates surgical management. Furthermore, MTC may recur even after radical surgical resection, and imaging plays a crucial role in follow-up to detect early recurrence. In addition, 25% of MTCs occur as hereditary forms, the majority of which occur as part of the multiple endocrine neoplasia (MEN) 2 syndromes [7,8]

What needs to be discussed before thyroidectomy?

Treatment goals in advanced MTC are ultimately related to promoting the quality of life. It is important to explicitly discuss with the patient the expectations and goals with respect to quality of life in the individual context and to agree on a personalized treatment plan. In general, it is important to document the sites of metastases and the tumor volume as well as tumor progression to get an estimate of total tumor burden and prognosis. In addition, it is necessary to document signs and symptoms and estimate imminent problems. A satisfactory quality of life can usually be maintained, in patient with recurrent disease, for months or even years. Treatment choices must stabilize the typically slow progression rate and the rational life expectancy against the efficacy and side effects of treatments [52-54]. A vital step is to choose whether any therapy be palliative or curative, because the risk-benefit ratio of palliative and curative treatments is different. Curative treatments are defined as improved as well as disease-free survival. The main objective of palliative therapies is to improve quality of life by relief of symptoms. When recurrent local disease is present or distant metastases are limited to a single organ curative surgical resection may be considered. Unfortunately, in advanced MTC, curative options are limited as both local recurrent disease and metastases are seldom amenable to curative surgery. Brain metastases, airway obstruction, threatening spinal cord compression, impending, bleeding or active fracture or hormonal secretion are critical locations for lesions and require an active treatment [9,54].

Treatment under Investigation

i. Sunitinib showed remarkable decrease in calcitonin levels in MTC patients but under investigation due to some cardiac toxicities [55,56].

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ii. Lenvatinib showed promising antitumor activity in various human thyroid cancer xenograft models derived from DTC, MTC, and ATC cell lines [57].

iii. Vandetanib has shown efficacy in patients with locally advanced or metastatic MTC [58,59].

Treatment

Total thyroidectomy is a surgical procedure which is performed to treat various thyroid diseases wherein the thyroid gland is removed. But the use of total thyroidectomy procedure is considered not to be safe for thyroid carcinomas and also for treatment of few benign diseases because of the risks involved [53]. Total thyroidectomy is a safe and effective procedure for most of the thyroid diseases in the hands of an expert surgeon. Subtotal thyroidectomy is similarly effective, but it is associated with significant recurrence rate and may leave few traces of inadequately treated thyroid cancers. Thus, total thyroidectomy provides little significant advantage of being safer procedure compared to subtotal thyroidectomy.

Concluding Remarks

To cope with different thyroid cancers especially medullary thyroid carcinoma proper diagnosis in early stages helps in the treatment and better prognosis of disease.

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