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Diagnostic imaging of medullary thyroid cancer

Diagnostyka obrazowa raka rdzeniastego tarczycy

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S u m m a r y

Medullary thyroid cancer (MTC) is an uncommon malignancy with a high tendency to metastasize both to lymph nodes and distant localizations. In recurrent disease the most important prognostic factors are the early diagnosis, localization of the recurrent lesions and adequate patient selection for further treatment. An important role in monitoring of patients with medullary thyroid cancer plays periodical measurement of calcitonin concentration, which allows to detect the recurrence early. There is no single universal diagnostic method to localize all medullary thyroid cancer recurrence lesions, however, the development of positron emission tomography (PET) methods observed in recent years led to an important progress in this field. Conventional diagnostic methods (ultasonography, computed tomography, magnetic resonance) currently play the basic role in the diagnosis of the medullary thyroid carcinoma. In this article we also described nuclear medicine imaging, both convencional scintigraphy and positron emission tomography methods, used in diagnosing of this neoplasm. Particular attention was paid to the use of each method depending on the clinical situation and the suspected location of tumor foci.

S t r e s z c z e n i e

Rak rdzeniasty (MTC) jest rzadko występującym nowotworem tarczycy o dużej skłonności do tworzenia przerzutów zarówno do węzłów chłonnych, jak i odległych. W przypadku wznowy raka rdzeniastego tarczycy najistotniejsze znaczenie dla rokowania mają: wczesne rozpoznanie, lokalizacja ognisk nowotworu i właściwa kwalifikacja chorych do dalszego leczenia. W monitorowaniu chorych z tym nowotworem powszechnie uznaną rolę odgrywa okresowa ocena stężenia kalcytoniny, pozwalająca na wczesne wykrycie wznowy. Nie ma jednak jednej uniwersalnej metody diagnostycznej pozwalającej wykryć wszystkie ogniska nawrotu tego nowotworu, choć obserwowany w ostatnich latach rozwój pozytonowej tomografii emisyjnej (PET) przyniósł istotny postęp w tej dziedzinie. Podstawową rolę w diagnostyce raka rdzeniastego tarczycy odgrywają obecnie metody diagnostyki konwencjonalnej (ultrasonografia, tomografia komputerowa, rezonans magnetyczny). W artykule omówiono również wykorzystywane w diagnostyce tego nowotworu metody medycyny nuklearnej, zarówno oparte na klasycznej scyntygrafii, jak i wykorzystujące technikę pozytonowej tomografii emisyjnej. Szczególną uwagę zwrócono na zastosowanie poszczególnych metod w zależności od sytuacji klinicznej i przewidywanej lokalizacji ognisk nowotworu.

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INTRODUCTION

Medullary thyroid cancer (MTC) is a malignancy that originates from the neuroendocrine calcitonin-secreting parafolicullar C cells. According to the latest data it represents only about 1-2% of the thyroid cancers (1). Due to another origin than differentiated thyroid cancers groving from thyrocytes it has different biology and worse prognosis, accounting for 13.4% of deaths caused by thyroid cancers (2). Approximately 25% of the MTC are the forms of hereditary syndromes associated with type 2 multiple endocrine neoplasia (MEN 2) (1). MTC has a high tendency to metastasize both by lymphatic system (to the cervical lymph nodes, mediastinum and pulmonary hila) and by blood (most often to the liver, lungs, bones, rarely to the brain, breast and skin). In 81% of palpable tumours lymph node matastasis is found on the side of the tumour, and in 44% – at the opposite side (3).

Even if at the time of diagnosis the distant metastases are not found, the recurrence rate after total thyroidectomy with lymphadenectomy is 50% (4).

BIOCHEMICAL MARKERS OF MTC

The main markers of MTC are calcitonin and carcinoembryonic antigen (CEA). Serum calcitonin concentration correlates well with the tumour mass – for example, when the tumour diameter is approximately 3 mm serum calcitonin is below 100 pg/ml, and when the diameter is 25 mm – it exceeds 1000 pg/ml (5). Usually, when calcitonin is above 200 pg/ml, there are already metastases to the cervical lymph nodes on the side opposite to the tumour (6). The American Thyroid Association recommends preoperative diagnostic imaging oriented on searching for distant metastases in patients with calcitonin levels greater than 500 pg/ml or with lymph node metastasis (1). Increased calcitonin concentration in the patient after total thyroidectomy indicates incomplete tumour excision or recurrence. If serum calcitonin concentration after the surgery normalizes, pentagastrin-stimulation test (not available in Poland currently) or calcium gluconate-stimulation test may be considered. A 10-year survival rate for patients with biochemical remission (calcitonin undetectable under baseline conditions or after stimulation) is 97.7% (7). **Evaluation of CEA level is important especially in patients with poorly differentiated MTC, in whom the neoplastic cells in the process of dedifferentiation lose their ability to synthesize and secrete calcitonin** (1). **The time that is needed to double the calcitonin and CEA concentrations plays an important prognostic role in patients with MTC** (1).

CONVENTIONAL DIAGNOSTIC IMAGING

Primary tumour diagnosis

Ultrasonography of the neck plays a fundamental role in the diagnosis of the primary tumour. Computed tomography (CT) and magnetic resonance imaging (MRI) are used mainly to assess tumour infiltration of the surrounding muscles, trachea, larynx, oesophagus, retro-oesophageal space and mediastinum.

Medullary cancer observed in ultrasonographic imaging is not significantly different from other thyroid cancers. As the tumour originates from parafollicular C cells, which are mainly located in the upper and central parts of the lobes, it is often found there. In heritable forms, the lesions are frequently multifocal, and may be present in both lobes (1). Ultrasound features indicating the malignancy of the thyroid tumour is a solid structure, hypoechogenicity, enhanced central flow, irregular margin, anterior-posterior dimension greater than the transverse one and internal calcifications (especially microcalcifications) (fig. 1A) (8, 9). Compared to the papillary cancer, however, MTC more often exhibitis the characteristics of benign lesions such as oval shape, homogeneous structure, cystic degenerative lesions or smooth well-defined margins (fig. 1B) (10). According to some authors, the morphology of up to 1/3 of the medullary cancers is not suspected in ultrasound imaging (9, 10). In the elastographic examination, MTC often does not have a typical for cancer "hard" character also (11). Hence, many experts call for the introduction of routine calcitonin determination in the diagnosis of thyroid focal lesions.

Ultrasound imaging is the basis for the classification of thyroid tumours for fine needle aspiration biopsy (FNAB), which is the golden standard in the diagnosis of thyroid cancer. FNAB sensitivity in the diagnosis of MTC is about 44-63% (12, 13). Medullary thyroid cancer may be misdiagnosed as follicular tumour, parathyroid tumour, poorly differentiated cancer of unknown aetiology or (rarely) anaplastic cancer. Immunocytochemical detection of calcitonin, calcitonin gene-related peptide (CGRP), chromogranin A, CEA or neuron-specific enolase (NSE), as well as calcitonin measurement in fine-needle aspiration biopsy washout fluid, significantly increase the diagnostic value of FNAB (1).

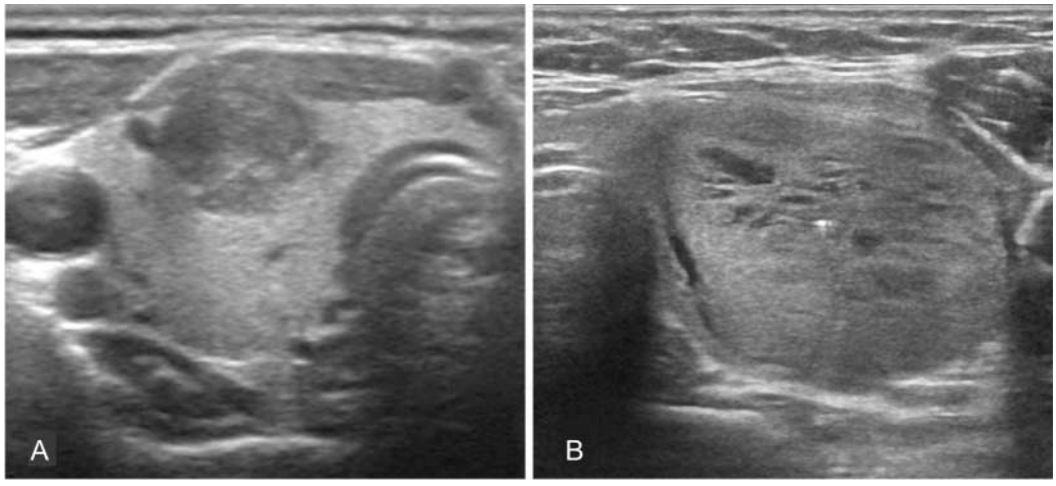

Fig. 1. A – thyroid tumor with characteristics suggestive of malignancy (solid structure, markedly reduced heterogeneous echogenicity, microcalcifications, irregular margins, infiltration of surrounding tissues); B – medullary thyroid cancer showing no typical ultrasound features of malignancy (solid with cystic areas, isoechogenic, homogenous, oval, smooth well-defined margins).

The size and morphology of the primary lesion significantly correlate both with lymph node and distant metastases. Metastases to cervical lymph nodes are found in 20-30% of tumours less than 1 cm in diameter and in more than 90% of lesions over 4 cm (14). **In MTC it was also shown, that the presence of ultrasonographic features of tumour malignancy (solid, hypoechoic nodule with irregular margins) is associated with greater local advancement, higher incidence of lymph node and distant metastases and significantly poorer prognosis compared to benign ultrasound morphology** (10).

Monitoring of patients

In the recurrence of MTC, the most important prognostic factors are early diagnosis, location of the tumour foci and proper qualification of patients for further treatment. In monitoring a patient after the surgery, it is essential to determine the concentrations of calcitonin and CEA periodically. The first test is recommended after 3 months (1). It shall not be performed earlier than 2-3 months after the surgery, due to the possibility of increased levels of calcitonin during wound healing and long half-life of calcitonin and CEA. Further measurements should be made depending on the results: if the concentrations are undetectable – every 6 months in the first year and then every 12 months; if they are detectable – at least every 6 months (1). In the case of undetectable or normal basal concentrations of calcitonin, the ultrasound of the neck should be performed and the stimulation test with pentagastrin or calcium (15) shall be considered.

In the case of local recurrence, reoperation is the only treatment that gives a chance for long-term remission or even curing the patient (16).

Imagining of both local recurrence as well as distant metastases of MTC is often a big challenge for the clinician. None of the currently available methods is sufficiently sensitive in the detection of local recurrence or metastatic lesions to be used alone. Even the combination of various diagnostic procedures allows for location of the recurrent tumour in approximately 40% of patients only (17).

Diagnosis of local recurrence and lymph node metastases

The lymph nodes are the most common site of MTC metastasis. At the time of diagnosis lymph node metastases are found in 75-81% of patients and the distant ones – in up to 13% (3, 18, 19).

In patients with calcitonin concentration of up to 150 pg/ml, the first-line examination is the ultrasound of the neck, since in these cases local recurrence or metastasis to the neck lymph nodes are most common (1). The lymph nodes with metastatic lesions are usually oval or round in shape (the ratio of the long to short axis of node is < 1.5), with blurred hilum, increased heterogeneous echogenicity, contain cystic degenerative lesions or calcifications and have chaotic blood flow in Doppler imaging. The sensitivity of ultrasound is 46-88%, similar to CT (42-86%) and MRI of the neck (38-91%), which are, however, complementary, as they allow to visualize the nodes inaccessible by ultrasound, located in the retro-tracheal as well as in the para- and retro-oesophageal space (20-25). An important role in the diagnosis of nodal metastases, especially when small nodes with no obvious morphological changes are found, plays the FNAB with the assessment of calcitonin concentration in the biopsy needle wash-out fluid (26).

Local recurrence is often difficult to detect due to small size and problems with differentiating it from scar changes in the tumour bed. Similarly to the diagnosis of lymph node metastasis, the cervical ultrasound is essential. CT and MRI scanning allow for more accurate assessment of the possible infiltration of neighbouring structures. In the final diagnosis, FNAB with calcitonin concentration measurement in biopsy needle wash-out fluid often proves to be helpful (26).

Diagnosis of distant metastases

Distant metastases are the main cause of death of patients with MTC. The most frequent are the metastases to liver, mediastinum, lungs and bones, less often to brain, and sporadic to breast and skin (1, 19, 24, 27, 28). **They are often multifocal and affect several organs at the same time** (1, 19, 24). The tests focused on the search for distant metastases, such as computed tomography, magnetic resonance imaging or positron emission tomography are recommended only when the concentration of calcitonin exceeds 150 pg/ml, because these methods are usually not able to detect the tumour foci below this value (1, 15). It should be remembered that the risk of false negative imaging results remains high at the concentrations of up to 1000 pg/ml (15). A frequent cause of false negative imaging are micro-metastases to the liver, detectable only by laparoscopy (29).

MTC is one of the few cancers which liver metastases are often hyperechogenic on ultrasound (30). In these cases CT and MRI allow to differentiate them from haemangioma. Sometimes, metastases may also have low or mixed echogenicity in ultrasound, contain fluid or calcifications (19, 30, 31). Their vascularisation is usually very well developed (19). Small calcified metastases may imitate mild granulomas (31). The most sensitive imaging technique for MTC metastases to liver is dynamic MRI with contrast agent administration (24). Giraudet et al. assessed its sensitivity at 49%, while the sensitivity of CT was 44%, USG – 41% and FDG PET – only 27% (24).

Lung metastases tend to be micro or macronodular (19). In the majority of cases, they are small size, multiple lesions (1, 19). Sometimes they appear in the form of miliary spread, perihilar fibro-nodular lesions or calcified masses (32, 33). The highest sensitivity in detecting metastases to lungs and mediastinum is provided by CT (1, 24).

Metastases to bones are predominantly osteolytic, less frequently – osteoblastic, however both types of metastases may coexist (59). Classic bone scintigraphy with hydroxy methylene diphosphonate or ^{99m}Tc-labeled methylene diphosphonate, focused mainly on detecting osteoblastic lesions that are highly prone to capturing radioisotope, in MTC provides the sensitivity of approximately 58-73% (24, 34). Slightly higher sensitivity in detecting MTC metastases to bones, estimated at 61-100%, is provided by MRI (24, 34). In T1-weighted sequences, metastases are hypointensive and are enhanced after the administration of gadolinium. MRI is more sensitive in detecting lesions in the axial skeleton, while classic scintigraphy – in the long bones metastases (24). In the diagnosis of MTC metastases to bones, scintigraphy and MRI are therefore mutually complementary, and their combined use increases the sensitivity from 61 to 94% (24).

NUCLEAR MEDICINE IMAGING IN THE DIAGNOSIS OF MTC

Planar scintigraphy and single-photon emission computed tomography (SPECT)

The radiopharmaceuticals emitting γ radiation used for MTC scintigraphic diagnosing include: ^{131}I- or ^{123}I-labeled metaiodobenzylguanidine (MIBG), ^{99m}Tc(V)-DMSA (five-value ^{99m}Tc-labeled dimercaptosuccinic acid), ^{111}In-pentetreotide and ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (tectrotid).

MIBG is a noradrenalin analog specific for tumours developing from neural crest (17). Mainly used in the diagnosis of pheochromocytoma and neuroblastoma, it may also be useful for MTC foci imaging (17). Currently the ^{131}I and ^{123}I-labeled preparations are available, wherein due to better dosimetric properties of ^{123}I, the scintigraphy with the use of ^{123}I-MIBI provides better quality and higher imaging sensitivity (35). In contrast, ^{131}I-MIBG due to α radiation may be used in the palliative treatment of MTC, although this therapy is generally regarded as ineffective (1, 36). Specificity of MIBG scintigraphy in MTC reaches 95%, but its sensitivity is about 25-30% only, and largely depends on the degree of differentiation of the tumour – it is higher in patients with MEN 2A syndrome than in sporadic MTC (37, 38). Higher sensitivity of MIBG scintigraphy was also observe in the localization of persistent tumour and local MTC recurrence, compared with distant metastases, which is explained by progressive de-differentiation of metastatic lesions (35, 37).

Scintigraphy with the use of ^{99m}Tc(V)-DMSA can be used both in the diagnosis of the primary foci and the recurrence of MTC (38, 39). Its sensitivity in different studies was estimated at 50-80% (38-40). ^{99m}Tc(V)-DMSA uptake varies considerably depending on the type of tissue – from significant in soft tissue to minimal within bones (35). Today, due to increasing prevalence of other techniques, this method is used less frequently and it is unavailable in many countries (35).

In the diagnosis of MTC, somatostatin receptor scintigraphy with the use of ^{111}In-pentetreotide (OctreoScan) or ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (tectrotid) (40-47) is also used. In addition to imaging of tumour foci, it is important in the selection of patients with unresectable MTC to be treated with the "cold" and "hot" somatostatin analogues (42, 43). The results of the evaluation of OctreoScan sensitivity in the detection of MTC vary a lot (from 20 to 78.5%) (17, 35, 40). According to some authors, it is lower than this of the conventional imaging (X-ray, ultrasound, CT or bone scintigraphy) (41). The studies comparing ^{111}In-pentetreotide scintigraphy with MIBG and ^{99m}Tc(V)-DMSA, indicate that its sensitivity is higher than that of MIBG and comparable to or higher than ^{99m}Tc(V)-DMSA (40, 42). The uptake of ^{111}In-pentetreotide is greater in differentiated tumours, but significantly lower in rapidly progressing tumours and distant metastasis, which is due to the reduced expression of somatostatin receptors in less differentiated tumours (43). The sensitivity of ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide scintigraphy, compared to ^{111}In-pentetreotide is higher (44, 45). In the studies concerning MTC, it was evaluated at 56.2-79.5% (46, 47). The results of ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide scintigraphy were slightly worse than of ^{18}F-FDG PET, while still better than ^{99m}Tc-MIBI scintigraphy (47).

Relatively good results were also obtained using scintigraphy based on the use of monoclonal antibodies against carcino-embryonic antigen (CEA) labelled with isotopes ^{99m}Tc, ^{123}I, ^{131}I and ^{111}In (43). The sensitivity of anti-CEA antibodies scintigraphy is 50-78% – slightly lower or comparable with ^{99m}Tc(V)-DMSA, and higher than ^{131}I-MIBG (43, 48, 49). In contrast to somatostatin receptor scintigraphy, this method proved to be particularly useful in the diagnosis of highly aggressive MTC with worse prognosis (43). Attempts were made in palliative treatment of ^{131}I-labeled anti-CEA antibodies (43).

The usefulness of ^{201}Tl, ^{99m}Tc-MIBI and ^{111}In-labeled calcitonin antibodies scintigraphy was also evaluated, but the studies assessing those methods in the diagnosis of MTC indicate their relatively low sensitivity compared to the previously described ones (35, 47, 48).

Positron emission tomography (PET)

The first radiopharmaceutical emitting β +, used in the diagnosis of neplasms by positron emission tomography (PET) was ^{18}F-fluorodeoxyglucose (^{18}F-FDG) (50). Numerous studies have shown that the uptake of ^{18}F-FDG is higher in poorly differentiated and fast-growing tumours, which quickly metabolize glucose (50). In the diagnosis of recurrence of MTC, the sensitivity of ^{18}F-FDG PET in the various examinations was highly variable and ranged from 17 to 95% (51-55). It has been shown that it is higher in patients with a larger tumour mass (calcitonin level > 1000 pg/ml), as well as in quickly proliferating (with calcitonin concentration doubling time

< 2 years) and less differentiated tumours (24, 51, 56). It was also found that the positive result of ^{18}F-FDG PET in patients with MTC is associated with worse prognosis. In patients with calcitonin level < 1000 pg/ml, ^{18}F-FDG PET is of a limited use because of the sensitivity of only 20-37% (24, 56). In patients with MEN 2A the sensitivity of ^{18}F-FDG PET is also significantly lower, which is probably due to the less aggressive course of MTC in those patients (56). The whole body imaging capability is a definite advantage of ^{18}F-FDG PET in comparison with the conventional diagnostic imaging. Although ^{18}F-FDG is not the radiopharmaceutical of choice in well differentiated tumours, including MTC, it was shown that ^{18}F-FDG PET is characterized by a higher sensitivity compared to SPECT scans employing markers dedicated to neuroendocrine tumours (47, 50, 53). The sensitivity of ^{18}F-FDG PET varies depending on the size and location of the lesions (24, 52). Some of the studies showed that it is especially useful in detecting local recurrence and the neck and mediastinum lymph node metastases, demonstrating higher sensitivity than CT or MRI, but others have not confirmed these findings (24, 52, 53). ^{18}F-FDG PET is much less sensitive than CT in detecting small metastases located in the liver and lungs, and it is worse than MRI and scintigraphy in the bone metastases imaging (24, 52, 53). Another radiopharmaceutical used in MTC PET imaging is ^{18}F-DOPA, accumulated by the cells uptaking and decarboxylating catecholamine precursors (54). ^{18}F-DOPA PET, compared with ^{18}F-FDG PET has a significantly higher sensitivity, estimated at 47-83% (54-60). It has also been shown, that these two examinations can complement each other, because ^{18}F-DOPA can detect MTCs of a low proliferative capacity, and ^{18}F FDG – the tumours more biologically aggressive, with the doubling time of calcitonin < 12 months or CEA < 24 months (59). ^{18}F-DOPA PET/CT is particularly effective in the detection of metastatic lymph nodes and allows to detect tumour foci already at calcitonin concentration > 150 pg/ml, thereby enables efficient selection of patients for reoperation with the intention to treat (60). ^{68}Ga-labeled somatostatin analogs (^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE) are another radiopharmaceuticals successfully used in the PET diagnosis of MTC (55, 61, 62). The advantage of these radiofarmaceuticals is, that in contrast to the previously discussed cyclotron markers, ^{68}Ga is an isotope obtained in a generator. Conry et al. demonstrated that the sensitivity in detecting MTC recurrences by ^{68}Ga-DOTA-TATE PET/CT is 72% – comparable with ^{18}F-FDG PET/CT (78%) (61). Evaluation of somatostatin receptor expression by PET/CT can be helpful in selection of patients for treatment with "cold" (pasireotide) or "hot" (^{177}Lu- or ^{90}Y-DOTA-TATE) somatostatin analogues (62).

In a study comparing the results of PET/CT in patients with persistent and recurrent MTC, it has been shown that the test using ^{18}F-DOPA has the highest sensitivity for detection of cancer foci compared with ^{18}F-FDG and somatostatin analogues (55). Unfortunately, that this is also the most expensive and the least available method. The authors evaluating the results obtained with ^{18}F-FDG PET/CT and ^{68}Ga-DOTA-TATE PET/CT found no significant differences in sensitivity of these two examinations, while in some studies it was demonstrated that they can be complementary (55, 61).

CONCLUSIONS

Localisation diagnostics of MTC remains a challenge for clinicians and requires combining a number of different diagnostic methods. The conventional imaging, however, still plays the leading role. The basic role in detecting lesions located in the neck plays the ultrasound imaging, in the diagnosis of metastases in the chest – CT, in the evaluation of the abdominal cavity – ultrasound scan and CT, while MRI is considered to be the best method for diagnosis of metastases in the liver. Bone metastases are best evaluated by the classical scintigraphy, possibly complemented by MRI. These methods, however, can not visualize all of the tumour foci. The attempts to use scintigraphy with a variety of radiopharmaceuticals, including MIBG and somatostatin receptor analogs, have not resulted in the selection of one sufficiently sensitive diagnostic method. The scintigraphic methods have recently been displaced to a great extend by the development of positron emission tomography. It has been proved that ^{18}F-FDG PET has a higher sensitivity in the diagnosis of postoperative recurrence of MTC than SPECT using neuroendocrine tumours dedicated markers. It seems that ^{18}F-FDG PET may play an important role, especially in aggressive, poorly differentiated MTCs. At present, the most sensitive PET radioisotope used in the diagnosis of MTC seems to be ^{18}F-DOPA PET. Thus far, however, there is no data supporting the assumption that PET imaging is the primary diagnostic method of recurrence of MTC. Therefore, PET still remains only complementary method to the conventional imaging methods.

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