Chapter 5

# Medullary Thyroid Carcinoma: Recent Updates on the Diagnosis and Management

Andrei Cismaru, Iulia Coroian, Gabriel Cismaru and Adrian Udrea

Additional information is available at the end of the chapter

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**Abstract**

Medullary thyroid carcinoma is a hormone-producing malignant tumor that synthesizes calcitonin. MTC can be sporadic or familial. It has a malignant behavior. Our chapter has 3 parts: *1.Updates on the diagnosis of MTC* -in this part we review the clinical findings in MTC: isolated thyroid nodule, palpable cervical lymph nodes and systemic manifestations. Fine needle aspiration, serum calcitonin, computed tomography (CT) and fludeoxyglucose - positron emission tomograpyh (FDG-PET) are summarized. Biomarkers with prognostic value are be described in detail: plasma calcitonin, carcino-embryonic antigen, germ-line RET mutation and matrix metalloproteinase. *2. Updates on the management and treatment of MTC* -we discuss the surgical treatment, radiation therapy, systemic therapy with angiogenesis inhibitors and transcatheter arterial embolization to prevent extension of the tumor. Based on the characteristics of MTC a new approach using gene therapy has been developed to obtain complete remission of the carcinoma. *3. We describe a typical case of MTC* from the oncology department, with cervical lymph nodes and a thyroid nodule. Immunohistochemistry staining showed *calcitonin* in the tumor cells. Thyroid ultrasound with fine needle aspiration biopsy confirmed the MTC. CT images of the cervical lymph nodes and thyroid nodule as well as microscopy images are presented. Chemotherapy with Dacarbazine was initiated with favorable outcome.

**Keywords:** thyroid, carcinoma, neck, calcitonin, lymph nodes, medullary, chemotherapy

## 1. Introduction

Medullary thyroid carcinoma (MTC) is a tumor that is derived from the calcitonin-producing cells, which can be either sporadic or hereditary like in MEN2 neoplasia [1]. MTC is suspected after physical examination by measuring plasma calcitonin. For a positive

diagnosis, histological confirmation is needed. The tumor extent and presence of metastases are determined using ultrasonography, computed tomography, and magnetic resonance imaging (MRI).

## 2. Updates on the diagnosis of medullary thyroid carcinoma

### 2.1. Clinical findings: when should we suspect MTC?

#### *2.1.1. Isolated thyroid nodule*

At presentation, most of the time, patients have an isolated thyroid nodule [2], and the diagnosis needs fine needle biopsy with elevated serum calcitonin. An isolated thyroid nodule can be incidentally detected during a carotid ultrasound or a chest CT scan with neck images [3]. Sometimes malignant thyroid nodules might appear in the context of a multinodular goiter.

#### *2.1.2. Palpable cervical lymph nodes*

Usually patients with MTC present with a painless thyroid nodule with cervical adenopathies. They are fast growing and fixed to the adjacent structures [4]. Sometimes, the lymph node can be incidentally detected during a carotid ultrasound or a chest or neck computed tomography. Cervical lymph nodes appear early in the course of a MTC and can be found in more than three-fourths of patients. Most of the time, the involvement is ipsilateral and also of the central lymph nodes [5].

#### *2.1.3. Systemic manifestations*

A minority of patients present with diarrhea, painful bone metastasis, flushing, or symptoms related to hypercorticism when the adrenocorticotropic hormone (ACTH) production is increased. Typically, MTC metastases occur in the liver, lung bones, lymph nodes, and mediastinum [6].

### 2.2. Paraclinical examinations: what test should we perform to confirm diagnosis?

#### *2.2.1. Fine needle aspiration (FNA)*

It is one of the most important tools for the diagnosis of MTC. The cytological characteristics include isolated cells or cells arranged in isolated groups with two or more round nuclei with eccentric position [7] and presence of fusiform cells and comet-like projections [8]. The sensitivity of FNA is between 46 and 63% with the most frequent negative results given by inadequate function in case of a multinodular goiter or a too small sample for analysis. The washout fluid can be used for calcitonin sampling which increases the sensitivity of the diagnosis. In the doubtful cases, immunohistochemical staining for calcitonin helps the correct diagnosis [9].

*2.2.2. Ultrasonography*

It is the most commonly used method for lesion assessment and is followed by fine needle biopsy in case of abnormal results. Ultrasonography permits an accurate assessment of the size and characteristics of the nodule, as well as identification of additional abnormal nodules inside the thyroid gland. The most common sonographic features of MTCs are solid composition, hypoechogenicity, and the absence of halo [10]. Calcifications are frequent in MTCs either in the form of macro or microcalcifications. When a lesion with the above characteristics is found, calcitonin should be measured and FNA is performed [11].

*2.2.3. Computed tomography (CT) and magnetic resonance imaging (RMI)*

These are important for both preoperative and postoperative assessment of MTC. In one of six CTs of the neck, an incidentaloma of the thyroid can be found. But in routine CT and MRI, there is no specific sign to differentiate between malignant and benign thyroid tumor [12]. In patients presenting with cervical lymph nodes, a primary thyroid origin is suggested by the presence of cystic components, calcifications, or hemorrhage appearing as hyperdensity in CT or hyperintensity in MRI. CT and MRI cannot distinguish between different histological types of thyroid cancer and also cannot diagnose multifocal tumors. MRI and CT have a good accuracy for predicting invasion of the trachea [13], larynx, or esophagus [14].

*2.2.4. FDG-PET*

It is used in the imaging of carcinoids and MTCs. It has a high sensitivity and specificity for MTC and can be used after a successful surgery to detect occult tumor fragments [15]. It has the disadvantage of being positive also in case of infection, inflammation, or other types of thyroid cancers. FDG-PET sensitivity increases with high levels of plasma calcitonin [16] or in case of a short doubling time. It can also be a marker of prognosis of MTC [17].

**2.3. Biomarkers with prognostic value**

Biomarkers are used in the clinical management of patients with MTC. Some of them are already implemented in the daily management of the disease: plasma calcitonin and CEA are easy to determine but further studies are needed to establish the prognostic of high values. Germline RET mutations are used for the timing of MTC treatment matrix metalloproteinase (MMP)-2 may have a prognostic value.

*2.3.1. Plasma calcitonin*

Calcitonin is secreted by the thyroid C-cells and is a highly specific marker for MTC. Sometimes, for an unknown reason, MTCs do not secrete calcitonin. The secretion of calcitonin from the C-cells can be increased by pentagastrin or calcium. This test can differentiate between elevated calcitonin from MTC and elevated calcitonin of other causes (smoking, nonC-cell thyroid carcinoma). The doubling time of plasma calcitonin is a good marker for MTC recurrence and survival of patients [18]. A more specific and sensitive method to

measure calcitonin is selective venous catheterization of the neck veins and taking a blood sample from near the thyroid nodule. It can exclude other sources of calcitonin rising outside the neck. After surgery, calcitonin is deferred for 6 weeks to allow the postsurgery nadir. A good marker of complete remission is a negative calcitonin after pentagastrin stimulation at 6 weeks after surgery.

#### *2.3.2. Carcinoembryonic antigen (CEA)*

It is not specific for MTC but used for prognostic purposes. An elevated CEA levels before surgery are associated with tumor size and recurrences [19]. MTCs that do not secrete calcitonin can be followed by measuring CEA [20].

#### *2.3.3. Germline RET mutation*

Germline RET mutation is a well-known MTC biomarker, present in 98% of MEN 2. The presence of RET mutation indicated a familial MTC and the risk of developing MTC is close to 100%. It is used for the follow-up of metastatic and recurrent MTC [21].

#### *2.3.4. Matrix metalloproteinase-2*

It participates in angiogenesis and carcinogenesis. In the study of Calvalheiro et al., it was demonstrated a correlation between MMP-2 and the persistence of MTC after a successful treatment [22].

## 3. Updates on the management and treatment of medullary thyroid carcinoma

### 3.1. Surgical treatment

MTC has a malignant behavior. There is a general agreement that operation for MTC should obtain complete removal of the neck tumor because adjuvant therapy in MTC has not been proved to be effective. Cervical lymph nodes metastases are often present in initial stages [23]. The appropriate initial treatment is total thyroidectomy with lymph node dissection. Lymphadenectomy comprises central compartment with ipsilateral node dissection, but some centers also perform contralateral lymph node dissection [24]. Where there is a suspicion of mediastinal disease, median sternotomy may be required with mediastinal dissection. Distant metastases can also be treated with surgery such as bone excision and lung resection for metastases.

The parathyroid glands should be preserved during thyroid surgery. In case they are normal, they can be left in place or transplanted in a sternocleidomastoidian muscle [25].

After surgery, plasma calcitonin levels can detect the presence of occult tumor fragments. Elevated calcitonin levels are a sign of persistent MTC after surgery, which can be the case in almost 50% of patients. Furthermore, in a small percentage of patients, several years

after thyroidectomy, the plasma calcitonin can increase indicating a recurrent MTC [26]. Measurements should be performed after surgery at 6, 12, 18, 24, 30, 34, and 40 months due to the risk of relapse [27].

### 3.2. Radiation therapy

In contrast to other forms of thyroid carcinoma, MTC is not sensitive to radioactive iodine or levothyroxine suppressive therapy. External beam radiotherapy is used in an adjuvant therapy in patients with a high risk of local recurrence after surgery. It is also used in palliative therapy in case of bone metastasis [28]. The most important application of radiotherapy is used for painful bone metastases [29].

### 3.3. Systemic therapy angiogenesis inhibitors

Axitinib, which is a tyrosine kinases inhibitor targeting Vascular endothelial growth factor (VEGF) receptor, was used for MTC treatment. It is associated with a partial response rate of nearly 20% with moderate side effects such as fatigue, proteinuria, and high blood pressure [30]. A second angiogenesis inhibitor AMG-706 was also used in MTC patients, which is an inhibitor of VEGFR [31].

### 3.4. Transcatheter arterial embolization

Transcatheter arterial embolization can prevent extension of the tumor outside the thyroid gland. However, the method is restricted to visualized primary or metastatic tumors [32]. The small, unvisualized tumors cannot be cured by transcatheter arterial embolization. Another indication of Transcatheter arterial embolization (TAE) is liver metastases with or without adjunction of ethanol injection.

### 3.5. Percutaneous ethanol injection

It is also able to prevent the extracapsular extension of MTC. The small metastatic tumors that cannot be visualized with recent techniques and have the potential of tissue invasion are not prone to ethanol injection. A combination between transcatheter arterial embolization with ethanol injection and gene therapy could be used in the near future to obtain complete remission [33].

### 3.6. Gene therapy

Trials of genetic cytokine emerged for treating MTC. Gene therapy using calcitonin gene and adenovirus vector is available; however, the technique is not fully accessible in humans [34]. There are four approaches for gene therapy in MTC: (1) corrective gene therapy to inhibit the RET oncogene; (2) cytoreductive gene therapy using toxin genes to permit $^{131}I$ uptake; (3) immunomodulatory gene therapy using cytokines; and (4) combined approach [35]. With some improvements for the vector design in terms of efficacy and safety, gene therapy for MTC may soon help to overcome obstacles in the treatment of this type of cancer [36].

### 3.7. Treatment for MTC metastases

In the case of isolated metastases of the brain, surgical resection should be proposed. If surgery is not possible, radiotherapy should be considered [3].

The liver is the most frequent site of metastases. The liver lesions are multiple and disseminated. Treatment is indicated in the case of large hepatic tumor or rapidly progressive lesions, as well as intense pain or intractable diarrhea [37].

Bone metastasis leads to pain, hypercalcemia, spinal cord compression, and pathological fractures. They associate low survival. Spinal cord compression is treated with emergency surgery and systemic corticoids. Radiotherapy can be used in case of painful metastases or when complete resection cannot be achieved. Intravenous bisphosphonates can be effective to prevent bone fractures, spinal cord compression, and hypercalcemia [38].

Lung metastases that associate hemoptysis or obstruction of the airwaves should be treated with radiotherapy.

## 4. A case of medullary thyroid carcinoma

We present a case of metastasis to the lung, adrenal glands, and cervical lymphnodes of a medullary thyroid carcinoma. Informed consent was obtained from the patient before the case report submission. A 54-year-old male presented with cervical adenopathies. Computed tomography of the neck and chest showed enlarged laterocervical lymph nodes (**Figure 1**), a left inferior lobe thyroid nodule (**Figure 2**), a tumor of the right pulmonary hilum (**Figure 3**), and bilateral nodules of malignant appearance of adrenal glands (**Figure 4**). Biopsy from the laterocervical lymph nodes was done at first presentation (**Figure 5**).

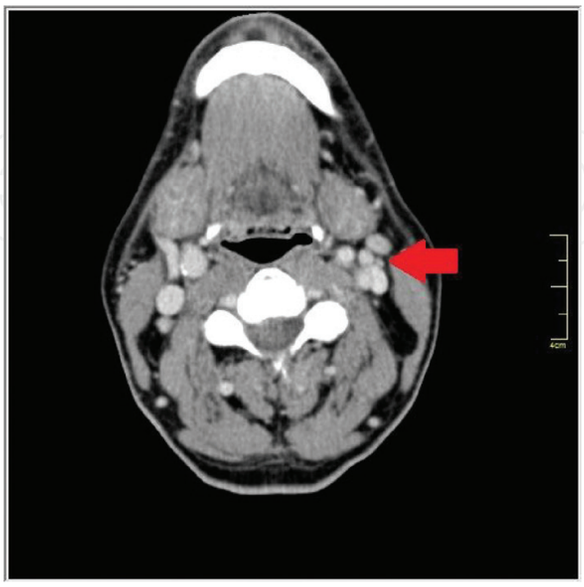

**Figure 1.** Computer tomography at the level of the neck reveals enlarged laterocervical lymph nodes on the left side.

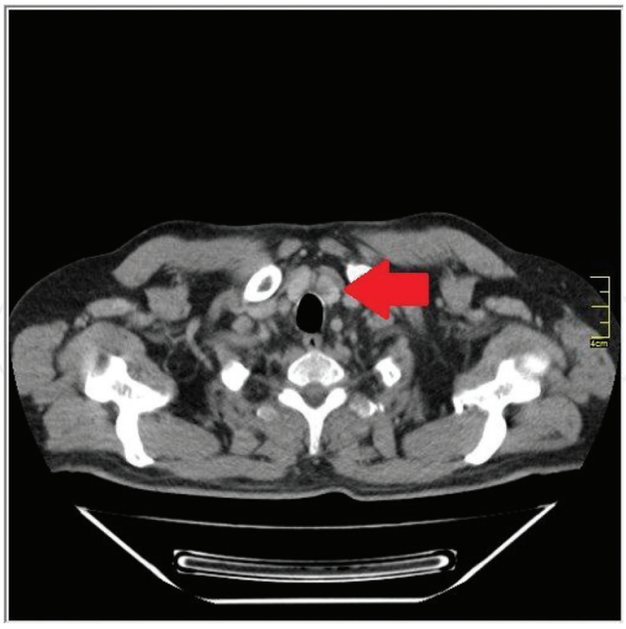

**Figure 2.** Computer tomography at the level of thyroid gland. On the left side in the inferior lobe, 8, 6/4, 8/7, and 6 mm nodule can be distinguished.

Chemotherapy with taxol + carboplatin-AUC5 (TC) was initiated concomitantly with other diagnostic tools evaluating other sites of the disease. Biopsy of the lung nodule showed neuroendocrine differentiation cancer with negative CK7 staining. Aspiration biopsy of the thyroid nodule showed MTC. All the three biopsies were reassessed and further immunohistochemical staining showed calcitonin in the tumor cells [39], in favor of lung metastases from MTC [40, 41].

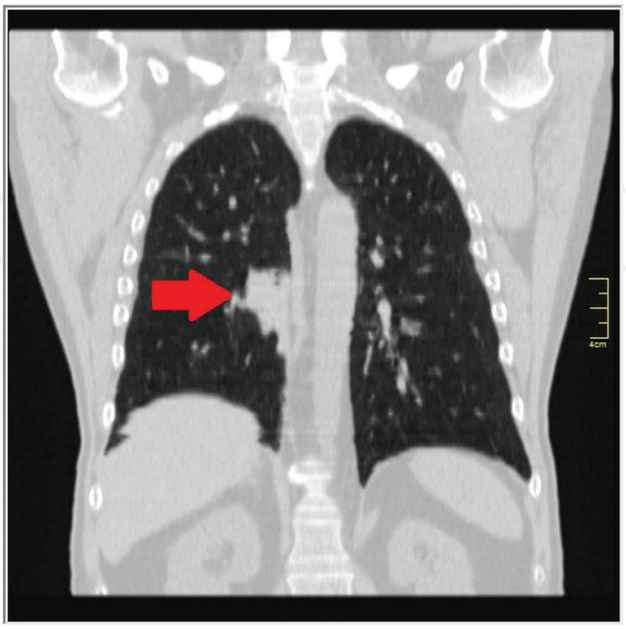

**Figure 3.** Computer tomography of the chest. On the right lung, a hilar tumor of 4.85 cm can be identified.

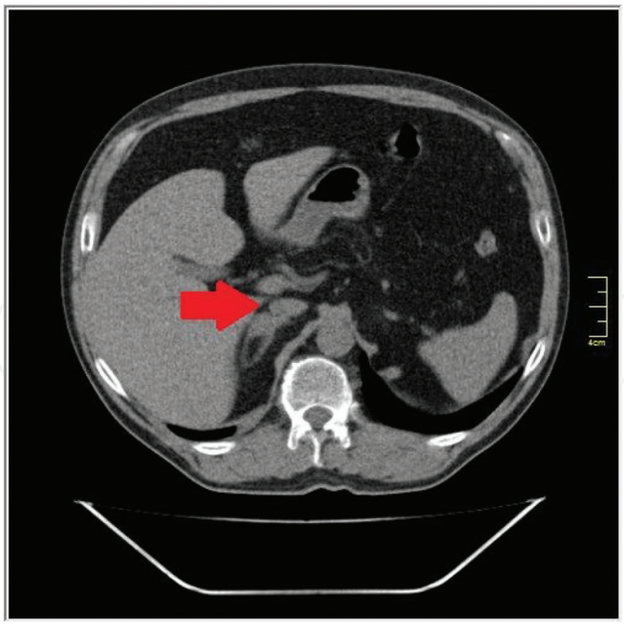

**Figure 4.** Computer tomography of the abdomen. The scan reveals on the right side an adrenal tumor of 2.8 cm.

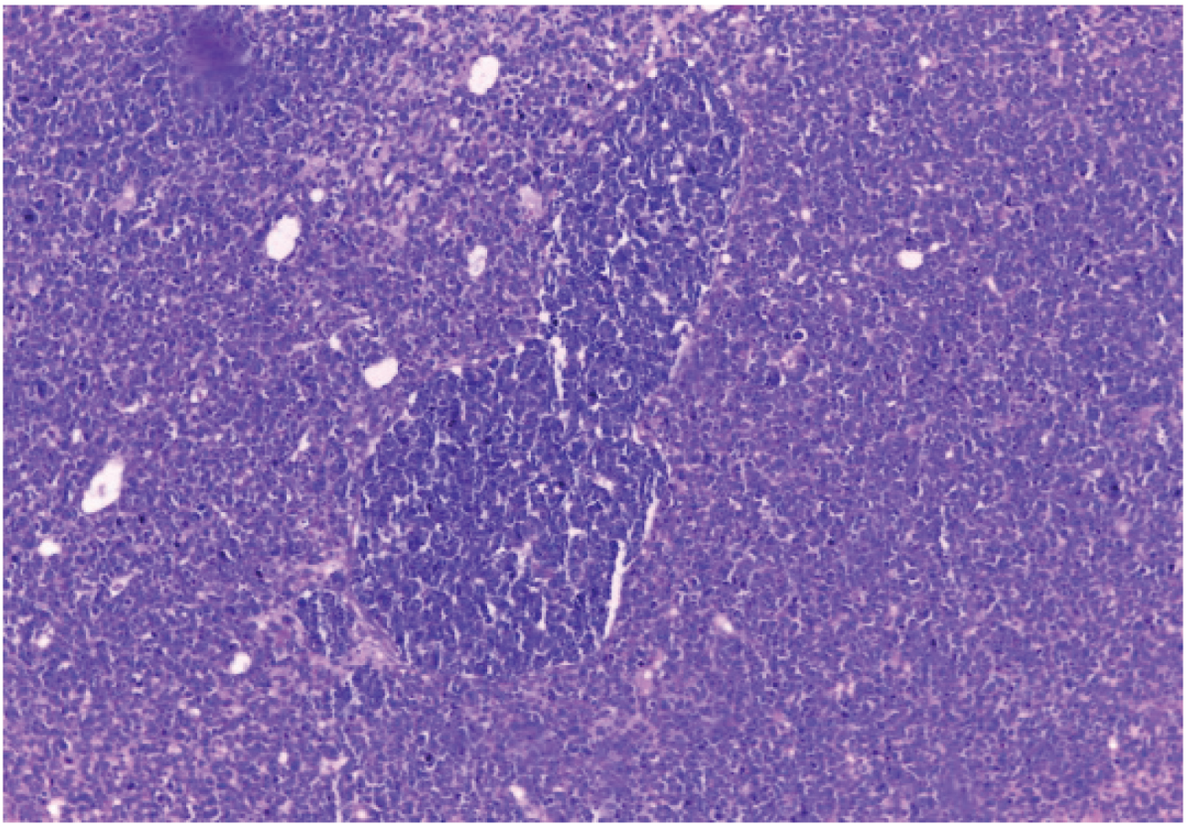

**Figure 5.** Microscopic examination from adenopathies reveals: lymph nodes occupied by a proliferation of malignant cells, with round/oval nuclei with atypia. The cells are arranged in nests, with fine beads or individual, separated by a fine stroma rich in capillaries. There are areas in which the stroma is rich, loose, myxoid, fibrous, or dense. In some areas, the cells are arranged in palisades with fibrous septa at the interface; the surface looks detached from the basal layer, giving impression of glandular structures.

### 4.1. Histological examination

The histological examination showed the following:

**Lung tumor:** *Microscopic examination* reveals fragments of respiratory mucosa with massive infiltration of poorly differentiated tumor cells. *Immunohistochemistry*: Positive; TTF1, CEA, CD56, and calcitonin.

**Laterocervical adenopathies:** *Microscopic examination reveals* highly malignant tumor cell proliferation, predominantly solid (80% from surface). *Immunohistochemistry*: TTF1 and CEA-positive; S100 and p63 negative; CD30 negative; and Ki-67 present up to 50% in solid areas.

**Thyroid nodule:** Groups of cells of medium size with immunpositivity for calcitonin in all tumor cells.

### 4.2. Differential diagnosis

A tongue tumor affecting the salivary glands was excluded through a biopsy from the base of the tongue that found no sign of malignancy. S100, si, and p63 were also negative.

CD30 negative in the laterocervical adenopathy excludes an embryonic carcinoma.

Lung adenocarcinoma with secondary thyroid metastasis is the most important differential diagnosis. Serum calcitonin levels were normal: 3.6/pg/ml ($N$ = 1–11.8/pg/ml), but the thyroid biopsy confirms MTC. Some MTCs may remain within normal ranges of calcitonin. Lung biopsy and immunohistochemistry are in favor of MTC metastases and not adenocarcinoma [42].

### 4.3. Treatment

Therapy with taxol 175 mg/m$^2$ + carboplatine-AUC5 (TC) was administered after initial assessment of the biopsies with favorable response (stable disease at thyroid site and partial response at the lung and adrenal glands) after the first three cycles. Three more cycles were delivered, and at relapse, a second-line chemotherapy with dacarbazine 1 g/m$^2$ was initiated.

Five cycles of paclitaxel and carboplatin (TC) were administrated with a consecutive computer tomography follow-up. The pulmonary tumor showed partial regression and the suprarenal nodule's dimensions decreased.

Chemotherapy had favorable results but showed relapse after sixth cycle of TC.

After dacarbazine three cycles, the dimensions of the thyroid nodule further decreased.

## 5. Conclusion

The clinical picture of medullary thyroid carcinoma (MTC) is variable and distant metastases are often present at diagnosis. It is essential to know if such is the case as different therapies

apply. High calcitonin serum levels provide valuable diagnostic data in MTC with distant metastases but may remain within normal ranges in some cases raising diagnosis difficulties.

Histology with immunohistochemistry can distinguish between primary carcinoma and metastasis.

## Author details

Andrei Cismaru[1,2], Iulia Coroian[1,2], Gabriel Cismaru[3]* and Adrian Udrea[2]

*Address all correspondence to: gabi_cismaru@yahoo.com

1 Oncology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

2 Medisprof Oncology Clinic, Cluj-Napoca, Romania

3 5th Department of Internal Medicine, Cardiac Rehabilitation, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

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