# A patient with medullary thyroid carcinoma and right ventricular cardiac metastasis treated by $^{90}$Y-Dotatoc

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## Abstract

Medullary thyroid carcinoma (MTC) is rare derived from C cells of the thyroid gland and represents approximately 5% of all thyroid carcinomas. We report a case of a 74 years old male with MTC, diagnosed in 2002 and treated with total thyroidectomy and lymphadenectomy. A metastatic lesion was diagnosed on the right ventricle by indium-111-octreoscan, fluorine-18-fluorodeoxyglucose-positron emission tomography/computerized tomography, echocardiography, magnetic resonance imaging, high resolution computed tomography and was confirmed by histopathology. We present the results of treatment of this patient with yttrium-90-DOTA-tyr$^3$ –octreotide.

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## Detailed case report

We report a case of a 74 years old male with a history of medullary thyroid carcinoma (MTC), first diagnosed in 2002, having massive lymph node metastases and treated with total thyroidectomy and lymphadenectomy. Rearranged during transfection (RET) gene analysis and carcino-embryonic antigen (CEA) were negative and no relatives of the patient had any similar disease. Calcitonin (Ct) levels remained low and $^{111}$In-Octreoscan ($^{111}$In-OC) was negative for many years until the end of 2007, when Ct progressively increased. The patient underwent neck echography, which was negative and a new $^{111}$In-OC revealed light right cardiac uptake with negative chest computed tomography (CT) and echocardiography. The patient also underwent fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT) imaging that showed a lesion with increased uptake located at the fourth thoracic vertebra (D4), presumably metastatic that was confirmed by magnetic resonance imaging (MRI) and CT and matched the previous finding of $^{111}$In-OC showing increased uptake at the right ventricle. The patient underwent radiofrequency treatment as follows: in a sterile setting, after administration of local anaesthesia and conscious sedation, using a 13-gauge needle under fluoroscopic guidance, the lesion was ablated using 150W of energy at a temperature of 100°C for 5min, followed by cement injection and vertebroplasty on the 4th thoracic vertebra. Clinical results were satisfactory as confirmed by PET, MRI, CT and a reduction of Ct levels, from 1100pg/mL to 580pg/mL.

After few months, there was a Ct relapse to 1977pg/mL, while neck echography remained negative. The patient underwent another $^{18}$F-FDG-PET/CT scan revealing pathological uptake at the 7$^{th}$ right rib, left pulmonary hilar lymph nodes, the D4 near the site of previous vertebroplasty and increased right cardiac ventricle uptake. The presence of a cardiac mass of 8x7cm in diameter was confirmed by MRI (Fig. 1). Another echocardiography re-

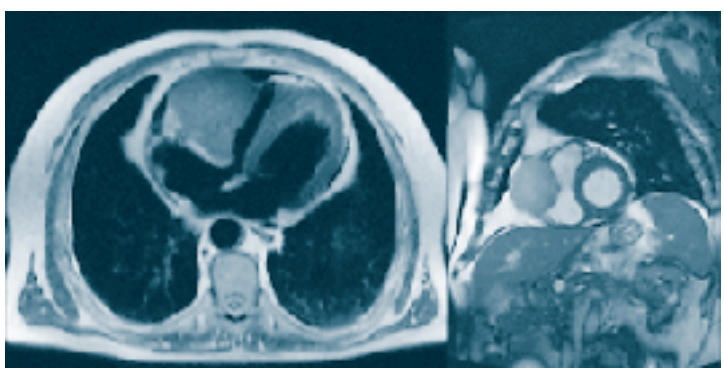

**Figure 1.** MRI of 1.5 Tesla. Cine MRI sequences were performed along the three axis. Four cameras view and short axis view are shown. Metastatic mass is visible in the right ventricle.

vealed infiltration of the free right ventricular wall, and severe compression of the right ventricular cavity and the right atrium. Coronary angiography showed normal coronary arteries. After right anterior mini-thoracotomy, a biopsy was performed. The patient developed complete right bundle branch block (RBBB) and hypertension treated with calcium-antagonists and beta-blockers and remained asymptomatic. Histology revealed a metastatic neuroendocrine carcinoma due to the primary MTC lesion, cytokeratin 7 positive (CK7+), thyroid transcription factor-1 positive (TTF-1+), synaptophysin positive, chromogranin postive, CEA+/-, glycoprotein receptor CD5+/-, cytokeratin CK20-, Ct+ and proliferative index MIB-1: 15%. The cardiac lesion was judged inoperable by the surgeon.

The patient then underwent both iodine-123 metaiodobenzylguanidine ($^{123}$I-MIBG) scan that revealed a slight uptake in the heart, and $^{111}$In-OC scintigraphy to assess the feasibility of systemic treatment as reported by other studies [1]. The $^{111}$In-OC scan revealed high uptake in all metastases (Fig. 2) and the patient was subsequently scheduled for yttrium-90-DOTA$^{0}$ tyr$^{3}$-octreotide ($^{90}$Y-Dotatoc, $^{90}$Y-D) treatment. A phase II-A experimental protocol i.e. 4 cycles of 2.56GBq $^{90}$Y-D every 2 months, approved by the Ethics Committee of our hospital, was applied for treatment after informed consent of the patient (Fig. 3). The patient was treated by intravenous (i.v.) infusion of $^{90}$Y-D with renal aminoacid infusion protection by i.v. administration of 10g of lysine chlorhydrate in 500mL of saline solution plus 20g of arginine chlorhydrate in 500mL of saline solution 1-2h before the $^{90}$Y-D administration followed by another 10g of lysine chlorhydrate in 500mL of saline after treatment. At the time of his first hospital admission, the patient was slightly symptomatic reporting light dyspnea and fatigue. A slight bilateral pleural effusion was present. The first cycle of treatment was performed with half standard activity (1.33GBq) in order to preserve cardiac function of a possible post-actinic oedema. Bremsstrahlung planar total body images (Fig. 4) were acquired after 24h and Ct levels were measured at 3700pg/mL. A contextual dosimetric evaluation was performed using $^{111}$In-OC [2] and the estimated effective dose was 10Gy to the cardiac metastasis. Ten days after hospital admission, the patient did not show any sign of haematological or renal toxicity, whereas Ct increased again to 5360pg/mL, perhaps due to a cytolytic phenomenon like degeneration or dissolution of cells after disruption of cell membrane because of radiation resulting to release of protein and of intracellular components. A new cardiac MRI revealed a light dimensional increase of the mass with a significant worsening of right and left ventricles kinetics (right EF=35% and left EF=35%). It also confirmed the presence of disease relapse at the D4 location.

The patient was readmitted to hospital 1 month later to perform a second cycle of treatment. He had still dyspnea and fatigue and increased bilateral pleural effusion, atrial fibrillation, (RBBB) and echocardiographic signs of cardiac failure. In order to administer 25Gy to the cardiac mass, a provisional dosimetry based on $^{111}$In-OC imaging was performed and an activity of 2.701GBq of $^{90}$Y-D was administered i.v. In order to determine the biodistribution of the radiopharmaceutical before each administration, a set of scintigraphic images using $^{111}$In-DTPA-OC as a surrogate tracer were obtained. By a dual-head hybrid system (GE Infinia II Hawkeye™, USA equipped with 1" Starbrite detectors and medium energy general purpose collimators), 4 total body images (256×1024 pixels) were acquired at 30min, 2h, 6h and 24h after the administration of 220MBq of $^{111}$In-DTPA-OC [3-8]. To measure the tumor mass and determine attenuation characteristics of the patient, a single photon emission tomography (SPET)/CT scintigraphy of the chest region was performed at 24h. In order to determine the activity retained in the tumor and critical organs and the time-activity curves, the conjugated view method, described in Medical Internal Radiation Dose (MIRD) Pamphlet n.16-1999 [9] was applied and all imag-

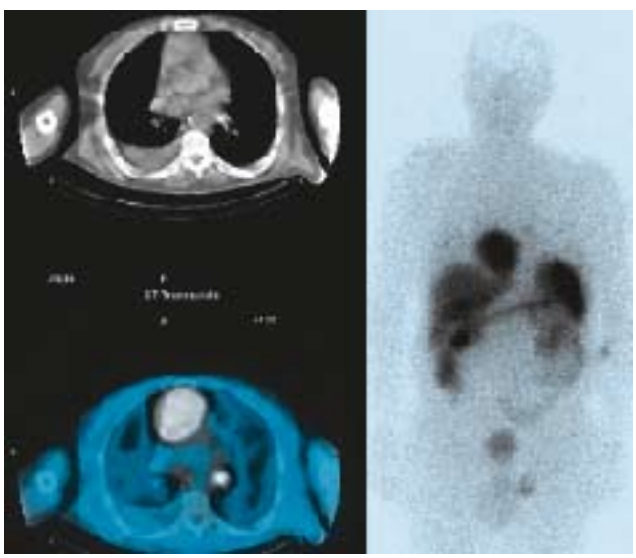

**Figure 2.** Images after $^{111}$In-octreoscan SPET/CT showing high uptake at the right ventricular mass and one hilar lymph node.

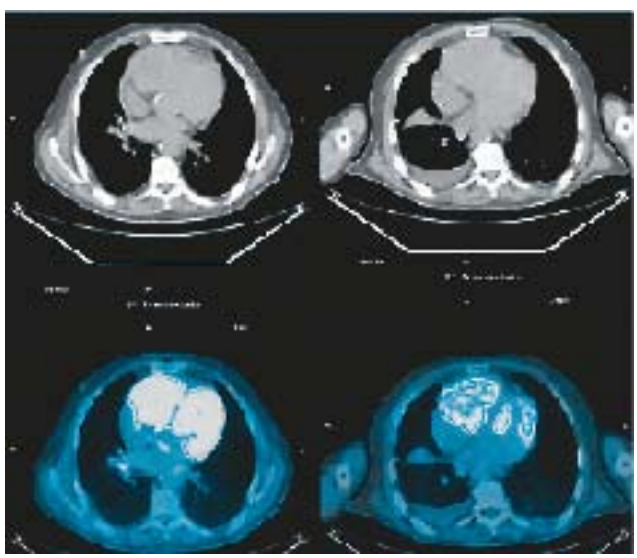

**Figure 3.** The $^{18}$F-FDG-PET/CT scan shows high uptake at the right ventricular mass before treatment and after 4 cycles of $^{90}$Y-Dotatoc.

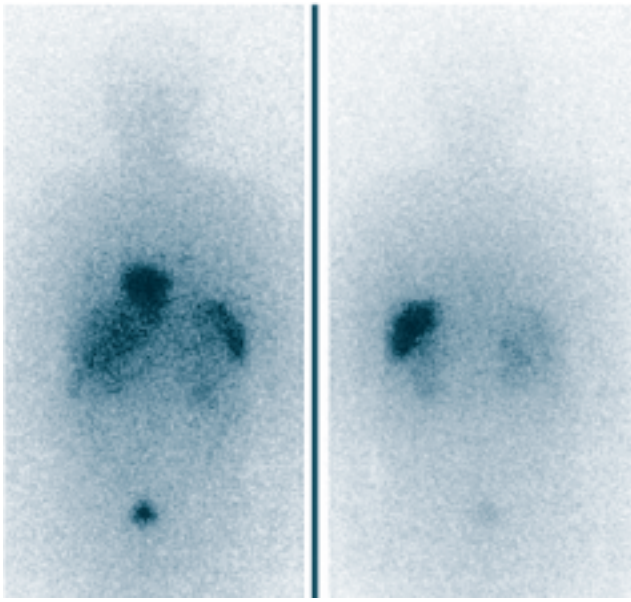

**Figure 4.** Bremsstrahlung images, 24h after $^{90}$Y-Dotatoc administration. ECT H-Mode, 30sec/projection, 4mm pixel size, MEGP collimator, 50-200keV window.

es were corrected for background, scatter, attenuation and physical decay. Dose calculation was performed by the Organ Level Internal Dose Assessment/EX-ponential Modeling (OLINDA/EXM) software by Stabin GM, Vanderbilt University, Nashville, Tennessee [10] for the adult male phantom and the patient specific total and organ mass corrections [11-17]. After the second cycle of treatment, a pacemaker was implanted due to the patient's cardiologic clinical condition.

The patient underwent the remaining 2 cycles of standard activity (2.56GBq) of $^{90}$Y-D. Thirty days after the fourth cycle, Ct levels progressively dropped to 4700pg/mL. Because of the implanted pacemaker, a 64slice-CT was performed to assess the cardiac mass dimensions after the last cycle which revealed an unchanged cardiac lesion. A new $^{18}$F-FDG-PET/CT scan was performed revealing a reduction of maximum standardised uptake value, SUVmax of all lesions. In particular, the SUVmax of the cardiac mass declined from 10.8 at the first PET evaluation to 7.0 (-35%) at the last one (Fig. 3). The SUVmax of the pulmonary hilar lymph nodes decreased from 4.5 to 3.2 (-29%), the SUVmax of the D4 lesion decreased from 4.1 to 3.8 (-7.3%) and the SUVmax of the 7$^{th}$ right rib lesion decreased from 3.5 to 2 (-43%).

According to the *European Organisation for Research and Treatment of Cancer* (EORTC) PET response criteria [18], a partial response to treatment was reached and according to *response evaluation criteria in solid tumours,* (*RECIST*) and World Health Organization (WHO) response criteria in solid tumours, a stable disease was reached, although the analysis was performed with different techniques due to the specific clinical situation of the patient characterised by mild progressive deterioration. The patient died in April 2008, after seven years from the diagnosis of MTC and after two years from his clinical relapse showing a good quality of life, considering that his particular oncologic situation, also during radionuclide treatment that was well tolerated.

## Discussion

MTC in the USA has a prevalence of 37,340 cases per year. It occurs 25% in a hereditary form rearranged during RET gene related and 75% in sporadic forms which frequently metastasize to the cervical lymph nodes. Approximately 30% of the cases are correlated with multiple endocrine neoplasia type 2 (MEN 2), an autosomal dominant syndrome. Surgical extirpation of the primary tumour and of nodal metastases is the treatment of choice, because radioactive iodine, external beam radiation treatment, and conventional chemotherapy are not effective [19, 20].

Myocardial metastases from any tumour, in particular from neuroendocrine tumours, are relatively uncommon with a highly variable incidence ranging from 2% to 20% for patients with metastatic cancer [21-23]. A study of 7,289 post mortem examinations, reported an incidence of 9.1% of cardiac metastases in patients with primary cancer not known to have metastases and an incidence of 14% in patients with metastatic cancer [23]. Myocardial metastases are usually associated with wide spread dissemination and aggressive histological types [24], lymphatic system involvement, and may involve the pericardium, epicardium or myocardium [23] with various clinical and electrocardiographic findings like shortness of breath, tachycardia, heart tamponade, atrial flutter or fibrillation, premature beats, atrioventricular blocks and when the size is large, increased central venous pressure, paradoxical pulse, right atrioventricular diastolic collapse and systolodiastolic dysfunction [23]. There are reports of cardiac metastases from pleural mesothelioma [23], melanoma [25-29], lung adenocarcinoma [30], kidney clear cell carcinoma [31], hypopharyngeal carcinoma [32], large-cell neuroendocrine carcinoma [33], Merkel cell skin carcinoma [24-26, 32-36] and more frequently from carcinoid tumors [21, 24, 35, 36, 38-43]. Up to now, no data are available about cardiac metastases from neuroendocrine MTC treated by $^{90}$Y-D.

If $^{90}$Y-D started earlier, it would be better for the patient although in this case the patient was 74 years old and referred to us in a progressive phase of the disease.

Comparing the findings from the multiple imaging procedures performed to the patient, the CT scan was the same or less effective than MRI and could have been replaced by MRI, the $^{99m}$Tc-MIBG scan was no better than the $^{111}$In-OC scan and both $^{111}$In-OC and $^{18}$F-FDG scans were well diagnostic although the $^{111}$In-OC scan was more specific.

*In conclusion,* $^{90}$Y-D treatment as a well established treatment for gastro-entero-pancreatic neuroendocrine tumours could also be useful in patients with metastatic MTC with cardiac metastases, showing low toxicity and being well tolerated.

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