Relevance of Calcitonin Cut-off in the Follow-up of Medullary Thyroid Carcinoma for Conventional Imaging and 18-Fluorine-Fluorodihydroxyphenylalanine PET

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Abstract. *Aim: The American thyroid association (ATA) recommends that additional imaging procedures supplement cervical ultrasonography (US) in any patient with a basal calcitonin value above 150 pg/ml in the follow-up of medullary thyroid carcinoma (MTC). The aim of the present study was to reaffirm or challenge this cut-off for 18-Fluorine-Fluorodihydroxyphenylalanine positron emission tomography (18F-DOPA PET) and conventional imaging ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI)). Materials and Methods: Thirty-nine patients (18 females, 21 males), mean age 62 years, range from 35 to 86, followed-up for MTC were included in the present retrospective study. In our patients 64 18F-DOPA scans, 28 neck US, 28 CT and 8 MRI were performed. For all cases basal calcitonin values were available. Sensitivity and specificity of 18F-DOPA PET and conventional imaging (US, CT, MRI) related to calcitonin values were calculated. Results: According to the calcitonin cut-off of 150 pg/ml, we found the following sensitivities and specificities: 79% and 80% for 18F-DOPA PET, 75% and 92% for US, 80% and 25% for CT, 50% and 75% for MRI. Taking the level of detectable calcitonin, we calculated the following sensitivities: 52% for 18F-DOPA PET, 46% for US, 79% for CT and 38% for MRI. Conclusion: We cannot confirm the calcitonin cut-off proposed by the ATA for the detection of MTC recurrences and contemporaneously we cannot state that 18F-DOPA PET has a very high sensitivity. For the neck region 18F-DOPA PET and US showed similar results. 18F-DOPA PET/CT seems to be the best imaging modality for whole-body tumor detection. Bone metastases are best detected by MRI.*

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Medullary thyroid carcinoma (MTC) arises from parafollicular C cells that produce calcitonin and, thus, it forms part of neuroendocrine tumors (1). Despite the recent promising results with systemic therapy (2-5), surgery remains the only curative therapy until now (2, 3, 6).

According to the American thyroid association (ATA) (6) follow-up after thyroidectomy is based on the sensitive tumor markers calcitonin and carcinoembryonic antigen (CEA) and on neck ultrasonography (US). The key point in this recommendation is that every rise in calcitonin levels means presence of disease, be it a local relapse, persistency, new or old (known) distant metastases. Calcitonin typically increases long before neck US or computed tomography (CT) demonstrates pathologic lymph nodes or distant metastases (7).

The ATA MTC management guidelines recommend that additional imaging procedures supplement neck US in any patient with a post-surgical calcitonin cut-off of >150 pg/ml. The recommended procedures are chest CT, 3-phase contrast-enhanced multi-detector liver CT or contrast-enhanced magnetic resonance imaging (MRI), bone MRI of the spine and pelvis and a bone scan.

18-Fluorine-Fluorodihydroxyphenylalanine positron emission tomography (18F-DOPA PET) shows a high sensitivity and specificity for MTC because of the tumor's ability to take up, store and decarboxylate dopamine (8). Various studies underline the clinical value of the tracer in the follow-up of MTC (8-10) and in the case of integrated 18F-DOPA PET/CT it appears to have 100% sensitivity in patients exceeding the basal calcitonin cut-off of 150 pg/ml (8).

Between the range of detectable calcitonin and the cut-off of 150 pg/ml, no real guidelines exist; in these cases further imaging –additionally to neck US- *may* be considered (ATA) (6). In this context is has to be emphasized that in these

patients residual or recurrent disease is present. Early and precise localization plays a key role in planning the subsequent therapy (11).

Up to now, most published studies showed that conventional imaging proved to be useful above the cut-off proposed by the ATA. However, in our hospital many patients in the follow-up for MTC underwent 18F-DOPA PET as well as conventional imaging partially following the recommendation of the ATA. The aim of the present study is to affirm or challenge the recommendation proposed by the ATA regarding the suggested calcitonin cut-off of 150 pg/ml for conventional imaging (US, CT, MRI) and 18F-DOPA PET.

Materials and Methods

Study design and patients. This was a retrospective study which comprised of 39 consecutive patients: 18 females and 21 males, median age 62 years (mean±standard deviation (SD) 62±12.2 range from 35 to 86 years) with histologically proven MTC, without separating the patient population into sporadic and hereditary MTC. The patients were referred to the Centre of Diagnostic Imaging of the Medical University of Vienna for postoperative follow-up of MTC in the timeframe from February 2003 to October 2009. The study was approved by the Ethics Committee of the Medical University of Vienna.

Laboratory work-up and imaging. All included patients had laboratory work-up for basal calcitonin levels. The imaging analyzed in this study was conducted in the timeframe of 3 months around the laboratory report. Seventeen out of 39 patients had more than one 18F-DOPA PET scan (in total 64 scans: 42 PET scans and 22 PET/CTs). Additionally, 28 neck US, 6 CTs and 8 MRI were performed. The PET/CTs were separately analyzed: this results in a total of 28 CTs.

A positive 18F-DOPA PET scan corresponds to any tracer uptake that diverges from the normal tracer distribution in the basal ganglia, gallbladder, pancreas, kidneys and urinary bladder. 18F-DOPA was supplied by the Austria Institute of Technology, AIT (Austrian Research centers Seibersdorf, ARCS, city, Austria) and ARGOS, Linz, Austria.

All patient data were consecutively numbered: in the cases where a patient underwent more than one 18F-DOPA scan, a decimal number was added to the actual number of the patient (i.e. patient no. 28 had 3 scans, so ".1, .2, .3" was added to the actual patient number).

Data evaluation. Sensitivity and specificity are calculated in relation to the calcitonin cut-off of 150 pg/ml for 18F-DOPA PET, CT, US and MRI. Additionally, the sensitivity was analyzed for a cut-off of >2 pg/ml (detectable calcitonin) for the above mentioned imaging/metabolic modalities.

A case-by-case and a lesion-by-lesion analysis is primarily performed, comparing the imaging methods with each other. Any discrepancy between the lesion-numbers found by 18F-DOPA PET with the other analytical methods is subsequently analyzed. We then analyze the overlap between 18F-DOPA PET and the other imaging modalities with regard to positive and negative results on a per case analysis. Imaging results are considered "true positive" if the lesion was confirmed with further two imaging procedures (PET, US, CT and/or MRI) or by histological findings; on the other hand, imaging results are regarded as "true negative" again if confirmed with two additional negative scans (PET, US, CT and/or MRI); in the other cases the results are considered not verified (lost to follow-up) and are reported as such.

Statistical analysis. All statistical computations were performed using IBM SPSS statistics (version 19.0 © Copyright SPSS Inc. 1989, 2010; link or supplier and address) and CIA (Confidence Interval Analysis, Version 2.0.2; Trevor Bryant, University of Southampton). Nominal data are presented using absolute frequencies and percentages. Metric data like age and calcitonin levels are expressed either using mean±SD when approximately normal distributed or using median and range when skewed. Furthermore, 95% confidence intervals (CI) for sensitivity, specificity and percentages were calculated. CIs are presented in square brackets.

Image interpretation. According to the original reports, the images of PET and US, CT and MRI were analyzed retrospectively by one nuclear medicine physician, one radiologist with lengthy experience in their respective medical specialties. An analysis of imaging results was conducted per diagnostic modality, anatomical region and per lesion with the following gold standards: histological proof and/or 2 corresponding imaging in the follow-up.

Results

Sensitivities and specificity according to basal calcitonin levels. Table I summarizes the results of 18F-DOPA PET and, when performed, the other imaging methods analyzed (64 18F-DOPA PET scans, 28 neck US, 28 CTs and 8 MRIs) in relation to the basal calcitonin levels in ascending order. The diagnostic procedures were performed at detectable basal calcitonin levels (3.2-20,891 pg/ml). Thirty 18F-DOPA PET scans, 12 US, 8 CTs and 4 MRIs were carried-out below the cut-off of 150 pg/ml (range=3.2-141 pg/ml), while 34 PET scans, 16 neck US, 20 CTs and 4 MRIs were performed when the basal calcitonin value exceeded 150 pg/ml (range=171-20,981 pg/ml). Taking the calcitonin cut-off of 150 pg/ml, we found the following sensitivities and specificities: respectively, 79.4% (63.2; 89.7) and 80% (62.7; 90.5) for 18F-DOPA PET (64 cases), 75% (50.5; 89.8) and 91,7% (64.6; 98.5) for neck US (28 cases), 80% (58.4; 91.9) and 25% (7.1; 59.1) for CT (which includes the neck, thorax and abdomen regions, 28 cases) and 50% (15.0; 85.0) and 75% (30.1; 95.4) for MRI (8 cases).

Without consideration of any basal calcitonin cut-off, we found sensitivities as follows at detectable calcitonin levels (biochemical relapse, >2 pg/ml): 51.6% (39.6; 63.4) for 18F-DOPA PET (64 cases), 46.4% (29.5; 64.2) for neck US (28 cases), 78.6% (60.5; 89.8) for CT (28 cases) and 37.5% (13.7; 69.4) for MRI (8 cases). As we do not possess any scans performed at an undetectable calcitonin level, it was not possible to calculate the specificity for the above mentioned imaging procedures.

Table I. *Calcitonin levels (in ascending order) and imaging results.*

Patient number	Basal calcitonin pg/ml	PET	neck US	CT	MRI
1.4	3.2	neg.	n.p.	n.p.	pos.
1.3	3.4	neg.	n.p.	n.p.	neg.
38	4.4	pos.	n.p.	neg.	n.p.
25.1	13.4	neg.	neg.	n.p.	n.p.
24	15.2	pos.	n.p.	pos.	n.p.
17.2	15.5	pos.	n.p.	n.p.	n.p.
19	19.9	neg.	n.p.	n.p.	n.p.
1.1	20	neg.	pos.	n.p.	neg.
1.2	23.2	neg.	n.p.	n.p.	neg.
29.1	28.7	neg.	neg.	n.p.	n.p.
13.1	28.8	neg.	n.p.	n.p.	n.p.
8.1	31	neg.	n.p.	n.p.	n.p.
25.2	32.2	neg.	neg.	n.p.	n.p.
13.2	43	pos.	n.p.	n.p.	n.p.
20	43	neg.	neg.	n.p.	n.p.
29.2	46.9	neg.	neg.	pos.	n.p.
30.1	48.8	neg.	neg.	pos.	n.p.
8.3	49	neg.	n.p.	n.p.	n.p.
30.2	50	pos.	n.p.	pos.	n.p.
8.2	51	neg.	n.p.	n.p.	n.p.
17.1	56.1	neg.	neg.	n.p.	n.p.
11	63.4	neg.	neg.	n.p.	n.p.
13.3	64.1	neg.	neg.	n.p.	n.p.
27.1	96.3	neg.	neg.	n.p.	n.p.
27.4	99.7	neg.	n.p.	pos.	n.p.
36	105	pos.	n.p.	pos.	n.p.
28.2	107	neg.	n.p.	n.p.	n.p.
27.3	126	neg.	n.p.	n.p.	n.p.
27.2	128	neg.	neg.	n.p.	n.p.
28.3	141	neg.	n.p.	neg.	n.p.
10.2	172	neg.	n.p.	n.p.	n.p.
12	176.1	pos.	neg.	pos.	n.p.
10.1	201.7	neg.	n.p.	n.p.	n.p.
15	202	pos.	n.p.	pos.	n.p.
14	266	neg.	neg.	n.p.	n.p.
26.1	268	pos.	pos.	n.p.	n.p.
9	341	pos.	pos.	pos.	n.p.
25.3	509	neg.	n.p.	neg.	n.p.
28.1	523	pos.	pos.	n.p.	n.p.
37	807	pos.	n.p.	pos.	n.p.
26.2	831	pos.	n.p.	pos.	n.p.
26.3	840	pos.	n.p.	n.p.	n.p.
21	875	pos.	neg.	neg.	n.p.
39	885	pos.	pos.	pos.	n.p.
23.2	1121	pos.	n.p.	n.p.	n.p.
23.1	1129	pos.	pos.	n.p.	n.p.
34	1215	pos.	pos.	pos.	n.p.
35	1231	pos.	n.p.	pos.	n.p.
4	1353	neg.	n.p.	neg.	n.p.
23.3	1439	neg.	n.p.	neg.	n.p.
22	1484	neg.	pos.	n.p.	n.p.
32.1	1503	pos.	n.p.	pos.	n.p.
33	1796	pos.	pos.	pos.	neg.
32.2	1975	pos.	n.p.	pos.	n.p.
31.1	1982	pos.	n.p.	n.p.	n.p.
31.2	1982	pos.	n.p.	pos.	n.p.
7	2586	pos.	pos.	pos.	neg.
5	2926	pos.	n.p.	n.p.	n.p.
18	4162	pos.	pos.	n.p.	n.p.
16	4362	pos.	n.p.	pos.	n.p.
6	5115	pos.	pos.	n.p.	n.p.
2.1	5826	pos.	neg.	pos.	n.p.
2.2	6157	pos.	n.p.	n.p.	pos.
3	20891	pos.	pos.	pos.	pos.

Table ordered by ascending basal calcitonin levels. In the cases where a patient underwent more than one 18-Fluorine-Fluorodihydroxyphenylalanine (18F-DOPA) scan a decimal number was added to the actual number of the patient. pos., positive; neg., negative; n.p., not performed. PET, positron emission tomography; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.

Analysis of imaging results per diagnostic modality and anatomical region. Our gold standards were histological proof and/or 2 corresponding imaging in the later follow-up.

A. Below 150 pg/ml (Table II). PET results (30 cases): In the neck region we found 25 true negatives, 1 false positive, no true positives or false negatives and the remaining 4 negative cases were not verified in the follow up. In the thoracic region, we found 3 true negatives, 2 true positives, 4 false negatives, 1 false positive and the remaining 20 negative cases were not verified in the follow-up. In the abdominal region we found 7 true negatives, no true positives, false negatives or false positives and the remaining 1 positive and 22 negative cases were not verified in the follow-up.

US results (12 cases): In the neck region we found 11 true negatives, 1 false positive and no true positive, false negative or false positive cases.

CT results (8 cases): In the neck region we found 7 true negatives, 1 false positive, no true positive or false negative cases. In the thoracic region, we found 4 true negatives, 2 true positives, no true positives or false negatives and the remaining 2 positive cases were not verified in the follow-up. In the abdominal region we found 6 true negatives, 1 false positive, no true positives or false negatives and the remaining 1 negative case was not verified in the follow-up.

MRI results (4 cases): In the neck region we found 3 true negative cases, no true positives and no false negatives or positives. In the spine we found 1 true positive case, no true negatives and no false negatives or positives.

B. Above 150 pg/ml (Table III). PET results (34 cases): In the neck region we found 9 true negative scans, 20 true positives, 4 false negatives, no false positives and the

Table II. *Imaging results at a basal calcitonin level <150 pg/ml.*

	True neg.	True pos.	False neg.	False pos.	Lost to follow up
PET - Neck	25	0	0	1	4 negative scans
PET - Thorax	3	2	4	1	20 negative scans
PET - Abdomen	7	0	0	0	1 positive & 22 negative scans
US - Neck	11	0	0	1	0
CT - Neck	7	0	0	1	0
CT - Thorax	4	2	0	0	2 positive scans
CT - Abdomen	6	0	0	1	1 negative scan
MRI - Neck	3	0	0	0	0
MRI - Spine	0	1	0	0	0

PET, Positron emission tomography; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.

Table III. *Imaging results at a basal calcitonin level > 150 pg/ml.*

	True neg.	True pos.	False neg.	False pos.	Lost to follow up
PET- Neck (3 double)	9	20	4	0	3 negative & 1 positive scan
PET - Thorax (6 double)	5	11	3	1	16 negative & 4 positive scans
PET - Abdomen	17	6	1	0	10 negative scans
US - Neck	3	12	1	2	0
CT - Neck	7	11	1	0	1 negative scan
CT - Thorax (3 double)	4	8	1	1	3 negative & 6 positive scans
CT - Abdomen	14	4	1	0	1 negative scan
MRI - Neck	0	1	1	0	0
MRI - Spine	0	1	0	0	0
MRI - Abdomen	1	0	0	0	0

PET, Positron emission tomography; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.

remaining 3 negative and 1 positive cases were not verified in the follow up. (In 3 cases, the PET was true positive as well as false negative for some lesions, hence the discrepancy in the sum of scans). In the thoracic region, we found 5 true negatives, 11 true positives, 3 false negatives, 1 false positive and the remaining 16 negative and 4 positive cases were not verified in the follow-up. (In 6 cases, the PET was true positive for some lesions, as well as false negative or not confirmed for others). In the abdominal region we found 17 true negatives, 6 true positives, 1 false negative, no false positives and the remaining 10 negative cases were not verified in the follow-up.

US results (16 cases): In the neck region we found 3 true negatives, 12 false positives, 1 false negative and 2 false positive cases. (In 2 cases the US was true positive for some lesions, as well as false positive for others).

CT results (20 cases): In the neck region we found 7 true negatives, 11 false positives, 1 false negative, no true positives and the remaining 1 negative case could not be verified in the follow-up. In the thoracic region, we found 4 true negatives, 8 true positives, 1 false negative, 1 true positive and the remaining 3 negative and 6 positive cases were not verified in the follow-up. (In 3 cases, the CT was true positive for some lesions, as well as not confirmed in the further follow-up for others). In the abdominal region we found 14 true negatives, 4 true positives, 1 false negative, no false positives and the remaining 1 negative case was not verified in the follow-up.

MRI results (4 cases): In the neck region we found 1 true positive, 1 false negative, no true negative, no false positive cases. In the spine we found 1 true positive case, no true negative and no false negatives or positives. In the abdominal region we found 1 true negative, no true positives and no false negative or positive cases.

C. Percentage of positive scans (Table IV). As seen in Table IV, the percentage of positive results increases for PET and US with increasing calcitonin values, reaching a 100%-positivity in the case of PET when performed at a calcitonin level >1,500 pg/ml, disregarding our previous analysis of

true negative and true positive results. Interestingly, CT results do not show the same trend. In fact it is only positive in about half the cases at a calcitonin interval between 500 and 1,500 pg/ml, even if it shows again a 100% positivity when calcitonin exceeds the level of 1,500 pg/ml. We cannot make any statement about MRI as we do not possess enough cases.

D. Overlap of 18F-DOPA PET and conventional imaging (Table V). We subsequently analyzed the overlap of 18F-DOPA PET and the conventional imaging analyzed (US, CT, MRI) per lesion and per region, in the case of CT and MRI.

In the case of neck US, we found that it overlapped completely with 18F-DOPA PET in 78.6% (60.6; 89.8) which represents 22 of 28 cases, in 10.7% (3 cases, (3.7; 27.2)) they overlapped for some but not for all lesions and in 10.7% (3 cases, (3.7; 27.2)) they showed completely different results. 18F-DOPA PET was false negative in 4 cases, while US was false negative in one case only.

By comparing CT and 18F-DOPA PET, we saw that they matched fully only in 46% (13 cases) of the 28 cases; in 43% (12 cases) they matched only for some lesions and in 11% (3 cases) they did not coincide at all. However, when comparing 18F-DOPA PET with CT it is also important to see how many times the one or the other imaging modality spotted out a region that was not detected at all by the other: indeed, in 7 cases CT found metastatic lesions in the thorax, which were not detected at all by PET; 2 of these cases turned out to be false positive and the other 5 cases could not be finally classified as true or false positive. In one case, neither CT nor 18F-DOPA PET found a metastatic lesion in the liver, which was then definitely diagnosed in the MRI. In another case, both CT and 18F-DOPA PET were both false positive in the thoracic region.

Comparing 18F-DOPA PET with MRI, we can see that they coincided in 50% (4 cases) of 8 cases. 18F-DOPA PET was always false negative for vertebral metastases, except in one case where this scanning method diagnosed one true positive vertebral metastasis but failed to detect further spine lesions.

Table IV. *Positive results expressed in percentages at the various calcitonin intervals.*

Calcitonin interval in pg/ml	PET	US	CT	MRI
3-100	20%	9%	83%	25%
100-500	42%	40%	80%	n.p.
500-1500	71%	83%	55%	n.p.
>1500	100%	83%	100%	50%

PET, Positron emission tomography; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.

Table V. *Overlap of 18F-DOPA PET with US, CT and MRI.*

	US	CT	MRI
100% overlap	78%	46%	50%
Incomplete overlap	11%	43%	12.5%
No overlap	11%	11%	37.5%

US, Ultrasonography; CT,computed tomography; MRI, magnetic resonance imaging.

Discussion

It could be assumed that local MTC recurrences and/or its metastases are present as soon as the basal calcitonin is detectable (>2 pg/ml). The prevalence of locoregional recurrence varies widely from 4.8% at 5 years to 50% at 7.3 years (12, 13, 14). However, it must be emphasized that the management of patients with metastatic disease outside the neck remains very controversial (15) and that only local recurrences can be more easily cured with a chance of complete remission. Due to the recent promising results with systemic therapy, (2, 3, 4) it is of out most importance to implement an accurate imaging modality to correctly identify the anatomical correlate for the biochemical relapse (local recurrence/metastases).

The PET scintigraphy with the tracer 18F-DOPA is currently used for the detection of neuroendocrine tumors, such as MTC. To our knowledge, our study group included the most numerous 18F-DOPA cases (n= 68) of MTC patients (39 patients in total) in the follow-up after thyroidectomy with biochemical evidence of disease. We found, on the one hand, an overall low sensitivity (52%) taking the detectable calcitonin level of >2 pg/ml in MTC patients in the follow-up after thyroidectomy. On the other hand, 18F-DOPA showed a high sensitivity and specificity (79%, 82%) given the calcitonin cut-off proposed by ATA of 150 pg/ml. Luster *et al*. (8) found the same sensitivity in their study with 26 patients in the follow-up of MTC, considering the detectable basal calcitonin levels. Koopmans *et al*. (9) found a sensitivity of 71% in their study with 31 patients. Hoegerle *et al*. (16) in their study with 11 patients (primaries and relapses) found a sensitivity of 63%. The higher sensitivity of Hoegerle *et al*. and Koopmans *et al*. in comparison to Luster *et al*. and our study might be explained by the fact that these two latter studies included patients with very high calcitonin levels. Koopmans *et al*. (9) in fact state that MTC lesions are best detectable when serum calcitonin was >500 pg/ml. Also in our study the increase in calcitonin levels paralleled with the increase in positivity of PET and US, whereas CT shows an equal distribution.

Kauhanen *et al*. (11) confirmed the results of Hoegerle *et al*. (16). Moreover, they found that the best discriminative value for detecting metastasis with any of the imaging methods they analyzed (including 18F-DOPA PET/CT) was a cut-off of 54 pmol/l (=192 pg/ml).

The above-mentioned studies, with regard to sensitivity and specificity of 18F-DOPA PET and other imaging modalities, were not calculated with the same gold-standards, as some studies used biochemical measurements, others a radiologist-consensus and only rarely the decision was taken on a basis of histological results. The most accurate work was performed by Kauhanen (11) as his group either used histology or scan findings by at least 2 imaging methods, as performed in our study. In general, the main problem in studies of MTC is the lack of histological confirmation and the relative small number of patients, given the rarity of MTC.

Finally, Luster *et al*., as well as Hoegerle *et al*., Marzola *et al*. (17), Koopmans *et al*., Kauhanen *et al*. (11) and Behesti *et al*. (18) are all unanimous in declaring that 18F-DOPA PET/CT might be the best non-invasive diagnostic method, as it combines morphological and functional imaging.

As we have stated before, ATA strongly recommends additional imaging procedures from a basal calcitonin level of 150 pg/ml. In our patient population this recommendation is only partially followed as 18F-DOPA PET and other procedures were commissioned at levels which were widely below this value; however, true positive findings (confirmed by histology or by various other imaging procedures) were found also at levels <150 pg/ml.

At a basal calcitonin level below 150 pg/ml, 18F-DOPA PET correctly identified 25 true negative scans in the neck region, 3 in the thorax and 7 in the abdomen; PET, moreover, spotted 2 true positive scans of the thorax. Nonetheless, we could also uncover 4 false negative scans of the thoracic region. At a basal calcitonin level above 150 pg/ml, 18F-DOPA PET correctly identified 9 true negative scans in the neck region, 5 in the thorax and 17 in the abdominal region, as well as 20 true positive scans in the neck, 11 in the thorax and 6 in the abdomen. Even so, also at these levels, we could definitely spot-out false negatives (4 in the neck, 3 in the thorax and 1 in the abdomen), which is not surprising, given the high basal calcitonin levels. In this context it has to be underlined once more that our gold-standard were histological findings and/or imaging follow-ups.

In addition we also examined a relative high number of patients and an even more important number of 18F-DOPA PET scans (64 in total). Such a high number might even compensate our insecurity –the lack of additional imaging procedures- in some cases. We also operate a case-based analysis as well as a lesion-based analysis.

The biggest discrepancies were found between 18F-DOPA PET and CT: in most of the cases CT discovered more lesions than PET (in total 62 lesions of CT versus 41 of PET) however only in 7 out of 28 scans did CT detect more positive regions than PET, of these cases, 2 CT positive regions turned out to be false positive. In the 5 other cases, none are surely false negatives of 18F-DOPA, as we did not possess any further diagnostic tool to be able to surely assess the negativity or positivity of the region. In one case neither 18F-DOPA PET nor CT successfully detected a liver metastasis. In this context we want to mention the sensitivity of stand-alone CT found by Luster *et al*. on a per-patient basis, namely 68%; the specificity was 78% (8). The sensitivity of morphologic imaging (CT/MRI) on a region-based analysis found by Koopmans *et al*. was 64%.

The neck US did perform quite similarly to 18F-DOPA PET; however, 18F-DOPA PET was false negative in 4 cases (6.25%), US in one case only (3.6%). In addition, we cannot omit to underline the better practicability and absence of radiation in the case of US.

The bone MRI was more sensitive than 18F-DOPA PET in detecting bone metastases: it detected more lesions per region and also bone metastases, not identified at all by 18F-DOPA PET. Also Kauhanen *et al*. (11) state that MRI is indeed very sensitive, even though in his study it had the highest rate of false positive results, especially in the neck region.

It is important to underline that up to now, the best –and often only- curative options are reserved for patients with local recurrences and/or local metastases, as these only need reoperation. In this respect, it is crucial to detect metastatic disease at the early locoregional stage, where reoperation with curative purpose can be planned (17). With these patients, as with virtually any other patients too, imaging modalities cannot yet offer a gold standard; we still have to rely more on the biochemical relapse.

Yet, Modigliani *et al*. (5) found out that survival rate of MTC patients appears better than expected even in non-cured patients. Also van Heerden *et al*. (19) only advocate actively non-invasive pursuing of MTC localizations to identify resectable disease; they also state that truly occult disease does exist, even if it is very rare. In fact, not in every patient, hypercalcitoninemia is resolved by re-operation. However, even with persistent elevated calcitonin levels, these patients have a rather good 10-year survival rate (15). Finally, van Heerden and his group also confirmed the good overall course of patients who are treated conservatively. Thus, the question remains whether 18F-DOPA PET or any other full body scan is indeed relevant in the management of patients. The definite proof of metastases might frighten more than assure a patient if there is still no curative option. In fact, up to now, patients with distant metastases may be offered systemic therapy with possible surgery mostly for palliative intent (17); in most of these cases, operations are still experimental. Chemotherapy does not play an important role so far. Indeed, in our patient population only one underwent chemotherapy.

In our patient population (39 patients, 64 scans) we found a sensitivity of 79% and a specificity of 80% for 18F-DOPA PET according to the calcitonin cut-off of 150 pg/ml proposed by the ATA. Of all the PET scans that were performed at a basal calcitonin level below 150 pg/ml, 7% were true positive. Astonishingly, 24% of all PET scans performed at a calcitonin level above 150 pg/ml were false negative. Focusing on the neck region, 18F-DOPA PET has an important number of false negatives (4 cases), which is relatively high given the fact that local recurrences can be easily reoperated; US did perform quite good, with only one false negative result. CT found more positive lesions per patient and in 7 cases per region: 2 out of these were false positives and the remaining 5 could not be confirmed. MRI showed to have a higher sensitivity in detecting bone metastases in comparison to 18F-DOPA PET.

Our study contains several limitations due to its retrospective character. Regarding the laboratory work up, we lack CEA levels, calcitonin doubling times and pentagastrin stimulation tests. Moreover, we do not possess the complete history of the patients. For this rare tumor entity a large patient population should be analyzed for statistical analysis; nonetheless, it is relatively large in comparison with the other studies. Assuming that local MTC recurrences and/or their metastases are present as soon as the basal calcitonin is detectable (>2 pg/ml), the definition itself of "true negative" is controversial, but necessary for a subsequent morphological evaluation. Our gold-standard were histological findings and/or imaging follow-ups. Naturally, histological proof is the most precise tool, however it is not always practicable.

In conclusion, we cannot confirm the calcitonin cut-off proposed by the ATA (150 pg/ml) for detecting MTC recurrences, as true positive imaging results are found beneath this value, but contemporaneously we cannot state that 18F-DOPA PET has a very good sensitivity in the detection of MTC recurrences. For the neck region 18F-DOPA PET and US have similar results. 18F-DOPA PET in combination with CT (18F-DOPA PET/CT) is the best imaging modality for whole-body tumor detection. Bone metastases are best detected by MRI.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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