

# Secretive and proliferative tumor profile helps to select the best imaging technique to identify postoperative persistent or relapsing medullary thyroid cancer

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## Abstract

In patients with postoperative persistent medullary thyroid cancer (MTC), the tumor detection rate is generally low for most of the imaging techniques now available. The aim of this study was to investigate if the clinico-biological profile of the tumor may indicate which imaging technique to perform in order to identify postoperative persistent or relapsing MTC foci. Thirty-five consecutive MTC patients with detectable and progressively increasing postoperative serum concentrations of calcitonin were enrolled in the study. The detection rates of 18F-deoxy-D-glucose (FDG)-positron emission tomography (PET), somatostatin receptor scintigraphy (SRS), and 131I-metaiodobenzylguanidine scintigraphy (MIBG) were compared in relation with calcitonin and carcinoembryonic antigen serum concentrations, Ki-67 score and results of conventional imaging techniques (CIT). FDG-PET positivity was significantly associated with calcitonin serum concentrations >400 pg/ml and Ki-67 score >2.0% ( $P < 0.05$ ), while SRS positivity was associated with calcitonin serum concentrations >800 pg/ml ( $P < 0.05$ ). SRS positivity significantly correlated with tumor appearance at CIT ( $P < 0.01$ ), while FDG-PET was positive in nine CIT-negative patients. The secretive and proliferative tumor profile may guide the choice of the imaging technique to use in the follow-up of patients with MTC. A Ki-67 score >2.0% suggests to perform a FDG-PET in addition to conventional imaging. Calcitonin secretion predicts both FDG-PET and SRS uptake but SRS positivity is generally found only in patients with well defined MTC lesions that are also detectable at the conventional imaging examination. MIBG outcome is not predicted by any clinico-biological factors here investigated.

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## Introduction

Medullary thyroid cancer (MTC) is a calcitonin-secreting neuroendocrine tumor arising from C cells. It represents 5–10% of all thyroid cancers. Surgery is the only curative treatment for patients with localized disease, but the cure rates account only 20–30% of the cases whenever lymph-node metastases are present (Saad *et al.* 1984, Leboulleux *et al.* 2004). In patients

with post-surgical persistent calcitonin levels, the detection of tumor foci is often not achieved with conventional imaging techniques (CIT). These include: neck ultrasonography, neck mediastinum, and liver computed tomography (CT), magnetic resonance (MR), and bone scintigraphy (Shulkin & Shapiro 1990, Kebebew *et al.* 2000, Leboulleux *et al.* 2004). Different radioisotopic techniques have been also tested in order to increase the detection rate. Some of these seem more

sensitive and specific in the detection of MTC metastases while their diagnostic performance appears much lower in the detection of tumor remnant or recurrences after surgery. <sup>131</sup>I-metaiodobenzylguanidine scintigraphy (MIBG) has been reported and able to detect tumor lesions in approximately one in every three patients with residual or recurrent disease after surgery, while <sup>99m</sup>Tc-dimercaptosuccinic acid and somatostatin receptor scintigraphy (SRS) tumor detection rate ranged between 35–70% and 20–64% respectively (Udelsman *et al.* 1989, Hoefnagel *et al.* 1991, Celentano *et al.* 1995, Anthony *et al.* 1996, Baudin *et al.* 1996, Adams *et al.* 1998a, Berna *et al.* 1998, Arslan *et al.* 2001). Postoperative unsuppressed calcitonin and carcinoembryonic antigen (CEA) concentrations may persist elevated during 2–3 months after surgery due to their long half-life in the blood, while progressively increasing calcitonin and CEA concentrations after this time represent a sensitive marker of MTC persistence (Leboulleux *et al.* 2004). Postoperative calcitonin concentrations  $\leq 500$  pg/ml, generally indicate a small residual disease in the neck or mediastinal lymph nodes, not easily detectable by both conventional imaging and SRS. <sup>18</sup>F-deoxy-D-glucose (FDG)-positron emission tomography (PET) seems more sensitive than CIT and radioisotopic procedures in detecting MTC metastases (Musholt *et al.* 1997, Szakall *et al.* 2002, de Groot *et al.* 2004). This gain in diagnostic performance appears more evident in patients with large metastatic spread and biologically aggressive disease (Mucha *et al.* 2006), although the role of FDG-PET in the clinical management of MTC remain controversial.

The aim of this study is to investigate how the clinico-biological profile of the tumor may influence the sensitivity of FDG-PET, SRS, and MIBG in patients with postoperative persistent or relapsing MTC.

## Patients and methods

### Patients

Thirty-five consecutive MTC patients (17 males and 18 females, 32–82 years) were enrolled in this retrospective multicenter study after their informed consent had been obtained. A total thyroidectomy with central compartment lymphadenectomy was performed in all cases but two undergone prophylactic thyroidectomy only for MEN type 2A, according to the International Guidelines (Brandi *et al.* 2001). An additional unilateral or bilateral neck dissection was required to be performed in 16 cases. A diagnosis of MTC was histologically proved on surgical samples in all cases. At immunohistochemistry, all cases were positive for anti-calcitonin and negative

for anti-thyroglobulin antibodies. Calcitonin and CEA serum concentrations were measured every 3 months during the postoperative follow-up. In all patients, calcitonin serum concentrations were not undetectable after surgery and progressively increased during the follow-up. To search for the site of tumor recurrence, CIT, MIBG, SRS, and FDG-PET were performed 6–24 months after surgery. Twenty-four of the 35 MTC patients were positive at one or more imaging techniques: MTC foci were histologically demonstrated on neck lymph node lesions in 15 and on thyroid tissue residue in one of them while in the remaining 8 out of the 24 patients, the positively imaged lesions in lymph node, liver, lung, and bone were confirmed to be MTC foci by the clinical and radiological follow-up. In 11 out of the 35 MTC patients, tumor foci remained unidentified in spite of the biological activity of the disease. These 11 patients are now under investigation with recently developed nuclear medicine procedures, including <sup>68</sup>Ga-DOTATOC-PET and <sup>18</sup>F-DOPA-PET.

### Methods

FDG-PET was performed by injecting 222–370 MBq of FDG in fasting patients. After an uptake period of 60–90 min, each patient underwent a total body scan with an acquisition time of 4 min per bed position (from the chin to the pelvis). SRS was performed by intravenously injecting 120–200 MBq of <sup>111</sup>Indium-DTPA-Phe1-octreotide. As recommended, anterior and posterior spot views of whole body were acquired at 4, 24, and 48 h when needed (Kwekkeboom & Krenning 1996). MIBG was performed by intravenously injecting 130–185 MBq of <sup>123</sup>I-MIBG, after pre-treatment with Lugol solution. Anterior and posterior views were acquired at 10 min, 22, and 48 h post-injection (Kaltsas *et al.* 2001). CIT included neck ultrasonography, neck mediastinum, abdomen spiral CT/MR imaging (MRI) scan, and bone scintigraphy.

Calcitonin and CEA measurements were measured in each center by using the same diagnostic kit: An ELISA-hCT assay (Cis Bio International Yvette, France; normal values,  $< 12$  pg/ml) was used to measure calcitonin serum concentrations; commercially available kits were used to assayed CEA serum concentrations.

In 18 cases, the Ki-67 score was immunohistochemically evaluated on MTC samples by using the Mib1 primary antibody, expressed as the percentage of positive cells over 10 high power fields.

### Statistical analysis

The statistical analysis was performed by SPSS for Windows version 10 (SPSS Inc., Chicago, IL, USA).

The comparison between the categorical data was performed by using the  $\chi^2$ -test with the Yates correction followed by Fisher's exact test if appropriate. Receiver operator characteristics (ROC) curves were used to find a significant calcitonin and CEA serum concentration and Ki-67 score cut-offs to predict a positive result of FDG-PET, SRS, and MIBG. P values were given for these analyses. The significance was set at 5%.

## Results

FDG-PET, SRS, and MIBG detected tumor recurrence in 13/26 (50%), 9/29 (31%), and 9/22 (41%) MTC patients respectively (Table 1). As a whole, tumor foci could be identified with at least one of the imaging techniques in 24 out of 35 (69%) patients. Postoperatively identified MTC foci were located in neck and/or mediastinal lymph node in 23 cases, in liver in three and in bone and lung in one case each one, while a thyroid tumor residue was found in one other case (Table 1).

On the ROC analysis, a significant cut-off was found both for calcitonin serum concentrations ( $P < 0.05$ ) and Ki-67 score ( $P < 0.05$ ) according to FDG-PET result and for calcitonin serum concentration ( $P < 0.05$ ) according to SRS result. Neither CIT nor MIBG were related to both calcitonin serum concentration and Ki-67 score. FDG-PET positivity was significantly associated to calcitonin serum concentrations  $> 400$  pg/ml (sensitivity 69%, specificity 77%) and Ki-67 score  $> 2.0\%$  (sensitivity 65%, specificity 90%; Fig. 1), while SRS positivity was associated to calcitonin serum concentrations  $> 800$  pg/ml (sensitivity 67%, specificity 85%).

By comparing FDG-PET, SRS, MIBG with CIT results, there was a significant association between SRS positivity but not FDG-PET and MIBG positivity with tumor appearance at CIT ( $P < 0.01$ ). In particular, FDG-PET was able to detect tumor foci in nine CIT-negative patients (Table 1, Fig. 2) while failed to recognize a CIT-positive tumor in one case, SRS was able to detect tumor foci in three CIT-negative patients but remains negative in two CIT-positive patients, MIBG was able to detect tumor foci in five CIT-negative patients but remains negative in three CIT-positive patients (Table 1).

## Discussion

The analysis of the results of this study highlights how the evaluation of the clinico-biological tumor profile may be used in order to select the imaging technique to

be performed in patients with postoperative persistent or relapsing MTC. In particular, a positive correlation between FDG-PET and SRS uptake and calcitonin levels was highlighted. FDG-PET uptake was also directly correlated to proliferation index resulting negative in patients with lower Ki-67 score. On the contrary, secretory pattern and proliferation index were not correlated with MIBG uptake, suggesting in this case the involvement of peculiar biological mechanisms.

In spite of the high rate of persistent/relapsing disease after primary surgery (Saad *et al.* 1984, Leboulleux *et al.* 2004), the detection of postoperatively persistent MTC is often difficult to be achieved when only CIT are performed. Taken together CIT, including neck ultrasonography, CT, and MR of neck mediastinum, liver, and bone scintigraphy, is associated with a low detection rate in this setting since at least 50% of MTC metastatic lesions remain unidentified (Shulkin & Shapiro 1990, Shi *et al.* 1998, Kebebew *et al.* 2000, Leboulleux *et al.* 2004).

In the last years, new functional imaging techniques based on the clinical application of different radiopharmaceuticals, have been tested in MTC patients raising each time enthusiastic initial results (Ohta *et al.* 1984, Hoefnagel *et al.* 1988, Guerra *et al.* 1989, Troncone *et al.* 1989). However, for the most, initial results have not been confirmed by subsequent studies. The most difficult challenge was to find a technique with high sensitivity and specificity in detecting tumor remnant or relapse after surgery (Sasaki *et al.* 1992). For MIBG,  $^{99m}\text{Tc}$ -dimercaptosuccinic acid and SRS, a proportion of patients ranging between 30–80% had unidentified lesions despite the biological evidence of postoperative disease persistence (Clarke 1988, Udelsman *et al.* 1989, Hoefnagel *et al.* 1991, Celentano *et al.* 1995, Anthony *et al.* 1996, Baudin *et al.* 1996, Adams *et al.* 1998a, Berna *et al.* 1998, Arslan *et al.* 2001). FDG-PET seems to be more informative than CIT and other functional techniques, especially in detecting postoperative persistent or relapsing MTC lesions (Musholt *et al.* 1997, Adams *et al.* 1998b, Diehl *et al.* 2001, Szakall *et al.* 2002, de Groot *et al.* 2004). However, the detection rate of postoperatively persistent or recurrent MTC remains low for all the imaging modalities investigated.

As emerged even in this study, not negligible proportion of MTC patients with occult postoperative disease remain unidentified even when FDG-PET, SRS, and MIBG are used. The best detection rate of MTC foci obtained in this study was 50% by using FDG-PET. However, it is interesting to note that the detection rate was increased to 70% when a combined

**Table 1** Comparison between 18F-deoxy-D-glucose-positron emission tomography (FDG-PET), somatostatin receptor scintigraphy (SRS), <sup>131</sup>I-metaiodobenzylguanidine scintigraphy (MIBG) results and conventional imaging techniques (CIT) results, in the detection of occult disease in patients with postoperative persistence of medullary thyroid cancer

Patients	FDG-PET	SRS	MIBG	CIT	Confirmation after imaging	Therapeutic strategy after imaging
1.	Negative	M lymph node	M lymph node	Negative	Follow-up	Systemic therapy
2.	Negative	Negative	Negative	Negative	–	–
3.	Negative	Negative	Negative	Negative	–	–
4.	Negative	Negative	NE	Negative	–	–
5.	N–M lymph node, liver	N–M lymph node, liver	N–M lymph node	N–M lymph node, liver	FNC	Systemic therapy +TAE
6.	Negative	M lymph node	Negative	N–M lymph node	Follow-up	Systemic therapy
7.	Negative	Negative	NE	Negative	–	–
8.	M lymph node, liver	Negative	NE	N–M lymph node, liver	FNC	Systemic therapy
9.	M lymph node	Negative	Negative	Negative	Follow-up	Follow-up
10.	N lymph node, bone	Negative	Negative	Negative	Histology	Surgery + radiotherapy
11.	N lymph node	N lymph node	Negative	Negative	Follow-up	Systemic therapy
12.	N lymph node	Negative	Negative	Negative	Histology	Surgery
13.	Negative	Negative	Negative	Negative	–	–
14.	Negative	Negative	Thyroid tumor residue	Negative	FNC	Surgery
15.	N lymph node	NE	NE	N lymph node	Histology	Surgery
16.	NE	NE	N lymph node	N lymph node	FNC	Radiotherapy
17.	NE	NE	N lymph node	N lymph node	Histology	Surgery
18.	N lymph node	NE	N lymph node	Negative	Histology	Surgery
19.	N lymph node	Negative	Negative	Negative	FNC	Radiotherapy
20.	N lymph node	N lymph node	N lymph node	Negative	Histology	Surgery
21.	NE	NE	Negative	N lymph node	Histology	Surgery
22.	NE	N–M lymph node, lung	NE	N–M lymph node, lung	Follow-up	Systemic therapy
23.	Negative	Negative	Negative	Negative	–	–
24.	Negative	Negative	Negative	Negative	–	–
25.	Negative	Negative	NE	Negative	–	–
26.	Negative	Negative	Negative	Negative	–	–
27.	NE	N–M lymph node	NE	M lymph node	FNC	Systemic therapy
28.	M lymph node	Negative	NE	Negative	Follow-up	Systemic therapy
29.	NE	NE	NE	N lymph node	Follow-up	Follow-up
30.	NE	N–M lymph node	N lymph node	N–M lymph node	FNC	Systemic therapy
31.	Negative	Negative	NE	Negative	–	–
32.	N lymph node	Negative	N lymph node	Negative	Follow-up	Radiotherapy
33.	NE	Negative	NE	N lymph node	Histology	Surgery
34.	NE	Negative	NE	Negative	–	–
35.	N lymph node, liver	N lymph node, liver	NE	N–M lymph node	FNC	Radiotherapy

N, neck; M, mediastinum; NE, not evaluated; FNC, fine-needle cytology; TAE, transarterial embolization of liver metastases.

use of different imaging techniques was performed. However, the use of a large panel of imaging techniques in MTC is limited by the cost analysis (Kwekkeboom *et al.* 1996). In this view, the biology of the tumor may help to guide the choice of the technique that is expected to have the best diagnostic performance. Of consequence, in patients with persistent calcitonin secretion after surgery, a radiopharmaceutical imaging procedure may be unhelpful if calcitonin

levels are under 400 pg/ml. A low-moderate calcitonin hypersecretion is related to a very small tumor mass that is difficult to be detected by any imaging technique (Baudin *et al.* 1996). An appropriate follow-up might be limited in this case to periodically perform measurements of calcitonin and CEA serum levels as well as conventional imaging procedures. The increase of calcitonin secreting activity is correlated to an increase of sensitivity both for FDG-PET and SRS





from MTC with Ki-67 score equal or below 2% are slowly growing tumors that can remain confined for long time to micro-lesions unidentifiable to all imaging procedures. This finding strongly suggests to systematically immunostain Ki-67 in MTC samples in order to select patients who are expected to be positive at the FDG-PET. As far as MIBG is concerned, its uptake was found to be unrelated to tumor mass and calcitonin secreting activity as well as it was independent by tumor proliferation activity as expressed by Ki-67 score, confirming that MIBG uptake in MTC is unreliable and unpredictable (Poston *et al.* 1986). The degree of incorporation of amine precursors seems to be the only mechanism explaining the positive MIBG uptake in a subgroup of MTC (Oishi *et al.* 1986).

In conclusion, the secretive and proliferative tumor profile may guide the choice of the imaging technique to use in the follow-up of patients with MTC. In case of progressively increasing calcitonin levels after surgery, FDG-PET should be added to the conventional imaging work-up when the Ki-67 tumor score is higher than 2.0%. Calcitonin secretion predicts both FDG-PET and SRS uptake but SRS positivity is generally found only in patients with well defined MTC lesions that are also detectable at the conventional imaging examination. MIBG outcome is not predicted by any clinico-biological factors investigated here.

### Declaration of interest

No competing financial interests exist.

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### Author contribution statement

The study was conceived by A Faggiano and designed by A Faggiano and P Ferolla. Acquisition of data was performed by A Faggiano, F Grimaldi, L Pezzullo, M Chiofalo, C Caracò, P Ferolla. Statistical analysis and data interpretation were performed by A Faggiano, F Grimaldi, P Ferolla, G Angeletti, A Colao. Text manuscript was prepared by A Faggiano, F Grimaldi, P Ferolla and critically revised and supervised by N Mozzillo, G Angeletti, F Santeusano, G Lombardi, A Colao, N Avenia for important intellectual contributions.

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