Research article

Head-to-head comparison of F-18 FDG PET/CT in radioiodine refractory thyroid cancer patients with elevated versus suppressed TSH levels a pilot study

Ludmila Santiago Almeida a, Maidane Luisi Araújo a, Allan Oliveira Santos a, Lígia Vera Montali da Assumpção b, Mariana Lopes Lima a, Celso Darío Ramos a, Denise Engelbrecht Zantut-Wittmann b, Elba Cristina Etchebehere a,**

a Division of Nuclear Medicine of the Department of Radiology, Campinas State University (UNICAMP), São Paulo, Brazil
b Division of Endocrinology of the Department of Internal Medicine, Campinas State University (UNICAMP), São Paulo, Brazil

ARTICLE INFO

Keywords:
Health sciences
Clinical genetics
Physiology
Oncology
Internal medicine
Medical imaging
Nuclear medicine
Endocrinology
Thyroid cancer
TSH
F-18 FDG
PET/CT

ABSTRACT

Introduction: To perform a head-to-head comparison of the uptake pattern of F-18 fluorodeoxyglucose in positron emission computed tomography (FDG PET/CT) in radioiodine refractory thyroid carcinomas (RAIR) in the same patient under elevated TSH levels (eTSH) and suppressed TSH levels (sTSH).

Methods: FDG PET/CT studies were performed under two conditions: levothyroxine intake (sTSH) and 30 days after hormonal withdrawal (eTSH). SUVmax values and the number of lesions detected (local recurrence and metastases in cervical and distant lymph nodes, lungs and bone) where blindly evaluated. Blood serum TSH and Tg levels were obtained prior to both studies. FDG PET/CT imaging, neck ultrasound, biopsy and follow-up were considered the reference standard.

Results: Fifteen patients performed both eTSH and sTSH FDG PET/CT studies. Both were positive for metastases in 80% of the patients. eTSH FDG PET/CT studies did not reveal increased uptake (p = 0.0640) and did not demonstrate a higher number of lesions (p = 0.320) when compared to sTSH FDG PET/CT studies. There was no change in the clinical management of these patients.

Conclusions: eTSH FDG PET/CT in patients with RAIR did not show more metastases in comparison to sTSH FDG PET/CT and there was no impact in clinical management of patients. Elevating TSH levels (whether by hormonal withdrawal or recombinant TSH) in patients being submitted to FDG PET/CT may not be necessary.

1. Introduction

Differentiated thyroid carcinoma (DTC) require lifelong monitoring as approximately 20% of patients recur [1, 2]. Whole body iodine scintigraphy (WBS) is an effective method of localizing the source of rising thyroglobulin levels (Tg). However, in the scenario of a negative WBS, localizing non-iodine-avid lesions is essential to adequate therapy [1, 3, 4].

Most of the patients with DTC have a benign evolution and treatment response. However, as thyroid cancers become more aggressive, they develop a reduction of the sodium iodide symporter and overexpression of the GLUT1 transporter, thus becoming radioiodine refractory (RAIR). The RAIR presentation accounts for approximately 2% of all DTC patients and thus studies in this population tend to have small samples, even in multicentric studies [5, 6]. In consequence, these cancers develop an overexpression of the GLUT1 transporter and tend to concentrate F-18 FDG. F-18 FDG PET/CT (FDG PET/CT) has been able to improve the diagnostic work-up of patients with a negative WBS and elevated Tg levels [7, 8].

Although elevated TSH levels (eTSH) increase the sensitivity for recurrent or metastatic DTC in WBS this increased sensitivity is not necessarily required in FDG PET/CT images in patients with RAIR [9]. Some studies have shown that FDG PET/CT may be more accurate to detect RAIR recurrence under eTSH [10, 11]. However, others have not been able to demonstrate the clear benefit or additive role of eTSH [12, 13, 14, 15, 16]. Therefore there is no convincing evidence that eTSH increases the sensitivity of FDG PET/CT imaging in RAIR, mainly due to

* Corresponding author.
E-mail address: elba@hc.unicamp.br (E.C. Etchebehere).

https://doi.org/10.1016/j.heliyon.2020.e03450
Received 19 March 2019; Received in revised form 5 August 2019; Accepted 17 February 2020
2405-8440/© 2020 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
lack of studies within the same patient and/or represented by a limited number of patients \[16, 17, 18\]. The purpose of this study was to prospectively compare in RAIR DTC patients the uptake pattern of FDG PET/CT within the same patient in two different conditions: with elevated TSH levels (eTSH) versus suppressed TSH levels (sTSH).

2. Materials and methods

2.1. Study design

All patients that participated in the study with histology-proven differentiated thyroid cancer (DTC) gave written consent prior to enrollment (between July 2013 and January 2017). The institution’s ethics committee and review board approved the study (CAAE: 18759313.0.0000.5404).

2.2. Inclusion and exclusion criteria

DTC patients under 18 years old, pregnant and/or breast-feeding or with clinical morbidity that contraindicated levothyroxine (T4) withdrawal, were excluded. DTC patients that had undergone total thyroidectomy plus central neck dissection and at least one cycle of I-131 therapy were included if presenting sings of RAIR cancer: increasing serum Tg levels (with suppression of Tg levels above 1 ng/ml and/or stimulated Tg levels above 10 ng/ml) or increasing Tg antibodies (ATg) levels.

2.3. Suppressed TSH levels (sTSH) and elevated TSH levels (eTSH)

Suppressed TSH levels (sTSH) were considered suppressed when below 1 μU/L. After a 30-day hormonal withdrawal period the TSH levels were considered elevated (eTSH) when above 40 μU/L.

All DTC patients underwent FDG PET/CT imaging in these two different conditions of TSH levels. Blood samples were obtained in the morning prior to all of the F-18 FDG doses administered. Ninety days after the end of all imaging studies, new blood samples of suppressed Tg and ATg levels were obtained. These were required in order to compare the suppressed Tg levels obtained prior to the first suppressed Tg levels, before commencing the protocol. This was done in order to exclude disease progression between sTSH and eTSH FDG PET/CT studies.

2.4. F-18 FDG PET/CT acquisition

FDG PET/CT images were performed following intravenous administration of 3.7 MBq/kg (0.1 mCi/kg) of F-18 FDG after fasting for at least 6 h and with serum glucose levels below 150 mg/dl.

After the 60-minute F-18 FDG uptake time, images were acquired on a PET/CT (SIEMENS Biograph mCT-True Point–TOF-full HD, Erlangen, Germany) from the base of the skull to the mid-thigh.

The 3D PET scan was acquired at 90 seconds/bed using a 512 × 512 pixels matrix (pixel size = 1 mm). The CT scan was performed with 80 mA, 120 Kv. Images were reconstructed by a true X + TOF (ultra HD; two iterations and twenty-one subsets) and displayed in 3.5mm slices on dedicated workstations.

2.5. F-18 FDG PET/CT image analyses

Two different groups composed of one radiologist and one nuclear medicine physician blindly evaluated the PET, CT and fused images available in axial, coronal and sagittal planes as well in three-dimensional cine mode.

The groups recorded the number and site of lesions and the SUVmax of each lesion. Lesions were classified as follows: local recurrence, cervical lymph node (LN) metastases, distant LN metastases, lung metastases, bone metastases or other sites. When there were more than ten lesions in each site they were classified as above ten (>10).

PET/CT studies were visually and quantitatively evaluated (SUVmax). We reported all suspicious sites of focal F-18 FDG uptake, considering the lesion contrast with background.

2.6. Reference standard

All imaging methods available (neck ultrasound (US), CT and MRI); any biopsy when possible and clinical follow-up with consensus among investigators in the end of the study were used as the reference standards. The reference standard was compared to the findings of the FDG PET/CT images obtained under eTSH and under sTSH levels.

2.7. Statistical analysis

Each set of patient images (eTSH FDG PET/CT versus sTSH FDG PET/CT) were compared considering number of lesions regarding local recurrence, cervical and distant lymph node metastases, and metastases in the lungs, bones and other sites.

Patient and clinical characteristics were summarized using descriptive statistics. Frequencies and percentages were provided for categorical variables; meanwhile, standard deviation (SD), mean, median and range were provided for continuous variables.

The Wilcoxon test was used to compare the SUVmax values and number of metastases between both studies because our sample is small and due to this fact, the distribution was not normal. When the quantity of variables analyzed were equal or under two the Wilcoxon test could not be calculated (NC). Therefore this test could not be applied for a completeness of the data.

The kappa coefficient was used to compare the agreement between F-18 FDG PET/CT studies performed in different moments (with eTSH versus sTSH). The significance level was 5%.

3. Results

Seventeen patients with DTC (mean time of diagnosis = 9.7 ± 4.3 years) were included. Among these, two patients were excluded. One patient was excluded because radioiodine (131I) therapy was performed between the sTSH and eTSH FDG PET/CT studies; and the other patient requested to be removed from the study. Fifteen patients with DTC were eligible for analysis (12 women; 55.7 ± 16.2 years old) (Table 1).

All patients had undergone total thyroidectomy and central neck dissection. DTC of non-aggressive subtype was identified in 40% of the patients (classic, follicular, and mixed-papillary and follicular variants) while the aggressive ones were found in 60% of the patients (tall cell, columnar cell, diffuse sclerosing, solid/trabecular, or insular variants).

Approximately 50% of the patients were initially diagnosed as stage I (7/15) and the other half in stage III (7/15). Only one patient was diagnosed as having a stage II cancer and none had stage IV disease at initial staging.

The mean cumulative 131I dose was 19.1 ± 14.6 GBq (518 ± 397 mCi) (Table 1) and the mean clinical follow-up period was 3.5 years.

The time interval between sTSH and eTSH FDG PET/CT images was 57 ± 105 days (range 27–202 days; median = 56 days). The elevation of serum TSH levels after T4 withdrawal at the time of the FDG PET/CT acquisitions was appropriate: eTSH levels were significantly higher (p = 0.0001) than sTSH levels (Table 2). Likewise, stimulated Tg levels (obtained with eTSH) were significantly higher (p = 0.001) than suppressed Tg levels (obtained with sTSH) (Table 2). In addition, for all patients,
there were no laboratory signs of progression between FDG PET/CT exams because no differences between the serum TSH and Tg of all patients prior to and 90 days after the last FDG PET/CT were found (Table 3). eTSH and eTg were not collected prior beginning the study and 90 days after the last FDG PET/CT because the endocrinologists’ team were not comfortable to submit the patients to three thyroxin withdrawal (prior beginning the study, for the eTSH FDG PET/CT study and another time submitting patients to a new eTSH 90–120 days after the last PET/CT). That is the reason why there are no data for eTSH and eTg in Table 3.

Previous imaging studies (WBS, US or CT) were negative in 9/15 (60%) despite of increasing thyroglobulin levels. FDG PET/CT detected sites of metastases in 12/15 (80%) patients with eTSH and sTSH images. In the three remaining patients (20%) neither eTSH nor sTSH FDG PET/CT studies detected metastases; in two of these three patients, the reference pattern showed stable disease (Table 4).

eTSH FDG PET/CT presented higher sensitivity (S), compared to sTSH for cervical lymph nodes (S: 75% vs 50%) and for distant lymph nodes (S: 80% vs 60%); probably due to the trend in SUVmax rising (p = 0.750). Both eTSH and sTSH FDG PET/CT studies had high specificity and accuracy, especially for detection of lung, bone and other metastases (Table 5).

3.1. Local recurrence

Both the eTSH FDG PET/CT and sTSH FDG PET/CT images identified local recurrence in 13% of the patients; a strong correlation (kappa = 1) was noted between both studies (Table 6).

Because of the small number of cases, on a per-lesion basis and in the SUVmax analysis, the eTSH FDG PET/CT presented a not calculable difference compared to sTSH FDG PET/CT (N ≤ 2) (Table 7).

3.2. Cervical and distant lymph node metastases

The detection rate of eTSH FDG PET/CT scans were higher and identified cervical lymph node metastases in 67% of the patients while in the sTSH FDG PET/CT scans, cervical lymph node metastases were

### Table 1. Patient characteristics prior to enrollment.

| Patient (N = 15) | Age | Sex | Time of cancer Diagnoses | Subtype | Stage | Surgery | I-131 cumulative Dose (mCi) | sTg prior to F-18 FDG PET/CT |
|------------------|-----|-----|--------------------------|---------|-------|---------|---------------------------|---------------------------|
| 1                | 73  | F    | 8                        | NA      | III   | TT      | 440                       | 217                       |
| 2                | 73  | M    | 9                        | NA      | III   | UND     | 828                       | 69                        |
| 3                | 75  | F    | 17                       | NA      | III   | BND     | 1218                      | 4500                      |
| 4                | 70  | M    | 8                        | A       | II    | UND     | 420                       | 2856                      |
| 5                | 59  | F    | 8                        | A       | III   | BND     | 550                       | 4500                      |
| 6                | 76  | F    | 18                       | A       | III   | TT      | 1066                      | 4.40                      |
| 7                | 47  | F    | 7                        | NA      | I     | TT      | 1224                      | 1214                      |
| 8                | 60  | F    | 11                       | A       | III   | TT      | 700                       | 16.70                     |
| 9                | 37  | F    | 15                       | NA      | I     | BND     | 350                       | 4.60*                     |
| 10               | 36  | F    | 9                        | A       | I     | UND     | 150                       | 1.27*                     |
| 11               | 45  | M    | 6                        | A       | I     | TT      | 162                       | 0.20*                     |
| 12               | 41  | F    | 7                        | A       | I     | TT      | 172                       | 0.40*                     |
| 13               | 46  | F    | 9                        | NA      | I     | UND     | 150                       | 0.74*                     |
| 14               | 67  | F    | 12                       | A       | III   | TT      | 200                       | 9.25                      |
| 15               | 31  | F    | 2                        | A       | I     | TT      | 153                       | 0.20*                     |
| Mean             | 55.7| -    | 9.7                      | -       | -     | -       | 518                       | 892.9                     |
| S.D.             | 16.2| -    | 4.3                      | -       | -     | -       | 397                       | 1596.3                    |

F = Female; M = Male; NA = Non-aggressive; A = Aggressive; TT = Total Thyroidectomy + Central node dissection; UND = Total Thyroidectomy + Central dissection + Unilateral neck dissection; BND = Total Thyroidectomy + Central dissection + Bilateral dissection. * = patients with increased Tg antibody levels.

### Table 2. Blood serum levels of TSH, Tg and At in patients undergoing F-18 FDG PET/CT with suppressed and elevated TSH levels.

|                      | sTSH F-18 FDG PET/CT | eTSH F-18 FDG PET/CT | p-values |
|----------------------|----------------------|----------------------|----------|
| Mean                 | 0.15                 | 0.26                 | 0.3101   |
| SD                   | 0.21                 | 0.30                 | 0.6772   |

|                      | p-values             |
|----------------------|----------------------|
| TSH (μIU/L)          | 0.0001<sup>1</sup>   |
| Tg (ng/mL)           | 0.001<sup>1</sup>    |
| ATg (IU/mL)          | 0.750                |

sTSH = suppressed TSH; eTSH = elevated TSH; *p < 0.05. Bold highlights the values that are significant.

### Table 3. Serum sTSH and Tg values obtained for all patients prior to and 90 days after the last F-18 FDG PET/CT study.

| Serum levels prior to F-18 FDG PET/CT studies | Serum levels 3 months after F-18 FDG PET/CT studies | p-values |
|----------------------------------------------|-----------------------------------------------------|----------|
| Mean                                         | Mean                                               |          |
| Mean                                         | Mean                                               |          |
| sTSH (μIU/L)                                 | 0.15                                                 | 0.26     |
| sTg (ng/mL)                                  | 892.9                                               | 893.45   |

Obs: Each patient performed the exam in a different day according to last F-18 FDG PET/CT study scheduled.
sTSH = suppressed TSH; *p < 0.05.
identified in only 47% of the patients. However, a high agreement (kappa = 0.6087) was noted among the studies (Table 6) (Figure 1).

The uptake was slightly higher in the eTSH FDG PET/CT scans (p = 0.4258) (Table 8). Probably due to these increase in uptake we demonstrated disease in additional three patients (kappa = 0.6087) (Table 6).

Although, an increase in the mean quantity of cervical lymph node metastases was not noted under sTSH (p = 1.0) the number of cervical levels was higher when performed with eTSH (p = 0.1250) (Table 7).

Distant lymph node metastases were identified in 20% of the patients in sTSH FDG PET/CT and in 27% of the eTSH FDG PET/CT scans (kappa = 0.8148) but the difference in the mean number of lymph node metastases between exams was not significant (p = 1.000) (Table 7). The mean SUVmax was slightly higher (although not significant) in the eTSH scan (p = 0.750) (Table 8).

### 3.3. Lung and bone metastases

Lung metastases were found in 47% of the patients on both the eTSH and sTSH FDG PET/CT scans (kappa = 1.000). The intensity of uptake

| Sites of metastases | sTSH F-18 FDG PET/CT | eTSH F-18 FDG PET/CT |
|---------------------|----------------------|-----------------------|
|                     | Sensitivity | Specificity | Accuracy | Sensitivity | Specificity | Accuracy |
| Local recurrence    | 40%         | 100%        | 80%       | 40%         | 100%        | 80%      |
| Cervical lymph nodes| 50%         | 100%        | 60%       | 75%         | 100%        | 80%      |
| Distant lymph nodes | 60%         | 100%        | 87%       | 80%         | 100%        | 93%      |
| Lung                | 100%        | 100%        | 100%      | 100%        | 100%        | 100%     |
| Bone                | 100%        | 100%        | 100%      | 100%        | 100%        | 100%     |
| Others              | -           | 93%         | 93%       | -           | 87%         | 87%      |
| Mean                | 58%         | 99%         | 87%       | 66%         | 98%         | 90%      |

sTSH = suppressed TSH; eTSH = elevated TSH; *p < 0.05.
Table 6. Per-patient analysis of sTSH and eTSH F-18 FDG PET/CT images for detecting metastases.

| Sites of metastases | sTSH F-18 FDG PET/CT N (%) | eTSH F-18 FDG PET/CT N (%) | Kappa |
|---------------------|-----------------------------|-----------------------------|-------|
| Local recurrence    | 2 (13)                      | 2 (13)                      | 1     |
| Cervical LNs        | 7 (47)                      | 10 (67)                     | 0.6087|
| Distant LNs         | 3 (20)                      | 4 (27)                      | 0.8148|
| Lung                | 7 (47)                      | 7 (47)                      | 1     |
| Bone                | 2 (13)                      | 2 (13)                      | 1     |
| Other               | 1 (7)                       | 2 (13)                      | 0.8865|

LNs = lymph nodes; sTSH = suppressed TSH; eTSH = elevated TSH; *p < 0.05.

Table 7. Per-lesion analysis of sTSH and eTSH F-18 FDG PET/CT images for detecting metastases.

| Sites of metastases | sTSH F-18 FDG PET/CT Mean ± SD | eTSH F-18 FDG PET/CT Mean ± SD | p-values |
|---------------------|---------------------------------|---------------------------------|----------|
| Local recurrence    | 0.13 ± 0.35                     | 0.13 ± 0.35                     | NC       |
| Cervical LNs        | 2.3 ± 2.9                       | 1.73 ± 1.71                     | 1        |
| Cervical LN levels  | 0.9 ± 1.2                       | 3.7 ± 3.9                       | 0.1250   |
| Distant LNs         | 0.6 ± 1.8                       | 0.3 ± 0.6                       | 1        |
| Lung                | 1.3 ± 1.4                       | 1.3 ± 1.4                       | 1        |
| Bone                | 0.1 ± 0.3                       | 0.1 ± 0.3                       | NC       |
| Other               | 0.1 ± 0.3                       | 0.1 ± 0.3                       | NC       |
| Total lesions       | 4.5 ± 3.5                       | 3.6 ± 3.9                       | 0.3203   |

LNs = lymph nodes; sTSH = suppressed TSH; eTSH = elevated TSH; *p < 0.05; NC = not calculable (N ≤ 2).

Figure 1. eTSH PET/CT images demonstrated uptake of F-18 FDG in cervical lymph node metastasis not evidenced in sTSH exam. A 73-year-old male was diagnosed 9 years ago with a non-aggressive DTC subtype. He had multiple radiiodine doses (cumulative dose = 30.6 GBq = 827 mCi) and rising sTg levels = 69 ng/ml. The sTSH F-18 FDG PET/CT trans axial A) PET B) CT and C) fused images show normal F-18 FDG biodistribution. The eTSH F-18 FDG PET/CT trans axial D) PET E) CT and F) fused images demonstrated intense uptake in the same right cervical lymph node level IIa (SUV = 3.9). Histopathology confirmed a metastasis.

Table 8. SUVmax values of the metastases in sTSH and eTSH F-18 FDG PET/CT studies.

| Sites of metastases | sTSH F-18 FDG PET/CT Mean ± S.D. | eTSH F-18 FDG PET/CT Mean ± S.D. | p-values |
|---------------------|---------------------------------|---------------------------------|----------|
| Local recurrence    | 9.3 ± 4.3                       | 12.5 ± 9.3                      | NC       |
| Cervical LNs        | 15.1 ± 22.2                     | 11.8 ± 16.4                     | 0.4258   |
| Distant LNs         | 7.6 ± 2.6                       | 7.2 ± 3.2                       | 0.7500   |
| Lung                | 8.2 ± 7.4                       | 9.2 ± 8.1                       | 1        |
| Bone                | 8.7 ± 3.6                       | 7.3 ± 1.7                       | NC       |
| Other               | 6.1 ± 0.0                       | 5.2 ± 2.6                       | 1        |

sTSH = suppressed TSH; eTSH = elevated TSH. LNs = lymph nodes; *p < 0.05, NC = not calculable (N ≤ 2).
and the number of lesions were similar between scans \( (p = 1.000) \) (Tables 8 and 7, respectively).

Bone metastases were identified in 13% of patients on both the tTSH and sTSH F-18 FDG PET/CT scan \( (\text{kappa} = 1.000) \). The differences among sTSH and tTSH F-18 FDG PET/CT for SUVmax values and the quantity of bone metastases identified was not calculable \( (N \leq 2) \).

Metastases in other sites were identified in 13.3% patients in the tTSH F-18 FDG PET/CT scan and in 7% in the sTSH F-18 FDG PET/CT scan. Differences among sTSH and tTSH F-18 FDG PET/CT scans were also not calculable \( (N \leq 2) \) for SUVmax values and for the quantity of metastases.

We found a trend in detecting higher total number of lesions \( (p = 0.3203) \) and higher total SUVmax \( (p = 0.0640) \) when the patients performed the exam under tTSH (Figure 2).

3.4. Patient management change

Prior to our investigation 60% of the RAIR patients had negative imaging studies. F-18 FDG PET/CT studies changed clinical management in 44% of patients. There was no difference in clinical management change when comparing tTSH with sTSH F-18 FDG PET/CT scans.

4. Discussion

We demonstrated that the head-to-head comparison of the uptake pattern of F-18 FDG in radioiodine refractory dedifferentiated thyroid cancer under elevated and suppressed TSH levels does not show significant differences. We were able to demonstrate that in RAIR patients, F-18 FDG PET/CT imaging is a sensitive method to detect F-18 FDG-avid metastases regardless of TSH levels. Performing F-18 FDG PET/CT with either suppressed or elevated TSH levels in patients with radioiodine-refractory thyroid cancer has been a matter of debate. Studies evaluating the influence of TSH serum levels in the uptake pattern of F-18 FDG has shown discrepant findings \( [10, 12, 13, 14, 15, 17, 19] \). TSH has been shown to increase F-18 FDG uptake in benign thyroid culture cells, supporting the rationale that F-18 FDG could have a higher detection rate in differentiated thyroid cancer metastases if F-18 FDG PET/CT images were performed under elevated TSH levels \( [20, 21] \). However, the contrary was found in thyroid carcinoma cell lines; elevated TSH did not influence the uptake of F-18 FDG \( [22] \).

Other studies have also demonstrated similar findings, with mean SUVmax and number of lesions bearing minimal or no difference between tTSH and sTSH levels \( [12, 13, 14, 15] \). The advantage of our study was the ability to investigate all the patients under both conditions, and thus the uptake pattern of F-18 FDG and the number of lesions could be directly compared and influenced solely by TSH levels. Cervical and distant lymph node metastases were better identified in the tTSH FDG PET/CT scans, probably due to increase in uptake although this higher uptake was not significant. The detection rate of tTSH FDG PET/CT scans were higher and identified cervical lymph node metastases in 67% versus 47% in the sTSH FDG PET/CT scans. This difference in detection rate could be noted, probably, due to the fact that three patients among the small total of fifteen patients were significant maybe; in a greater number of patients, these differences would not appear.

Furthermore, there was a trend towards detecting a higher total number of lesions and higher SUVmax values with tTSH and on a per-patient based analysis; 20% of our population had additional sites of metastases detected by tTSH FDG PET/CT, although again these differences were not significant.

We found F-18 FDG avid lesions in 80% of our patients with high specificity \( (\text{sTSH} = 99%; \text{tTSH} = 98\%) \) and accuracy \( (\text{sTSH} = 87\%; \text{tTSH} = 90\%) \). F-18 FDG PET/CT performed with tTSH presented higher sensitivity for cervical lymph nodes when compared to sTSH \( (75\% \text{ vs } 50\%) \) and distant LN \( (80\% \text{ vs } 60\%) \). This might be due to the increase in mean Tg levels \( (1226.1 \text{ ng/mL vs } 892.9 \text{ ng/mL}; p = 0.001) \). However, not all of our patients presented high levels of suppressed Tg; some presented progressively increasing levels of anti-Tg antibodies and therefore were also included in our study. In the remaining 20% of patients where F-18 FDG avid metastases were not detected, the mean sTSH levels of these patients was 6.3 ng/mL. This findings support studies showing that F-18 FDG PET/CT sensitivity increases according to increase in Tg levels, especially when above 10 ng/mL, with sensitivities ranging from 28.6% \( \text{(with Tg levels } 2–5 \text{ ng/mL) up to } 85.7\% \text{ (with Tg levels } \geq 20 \text{ ng/mL)} [15, 23, 24, 25, 26] \). Two patients out of three \( (66\%) \) of our study with a negative F-18 FDG PET/CT presented stable disease confirming the prognostic role of F-18 FDG PET/CT that has also been described in other studies \( [27] \).

Age is related with a higher risk disease and worst prognosis; a positive F-18 FDG PET indicates a higher risk of progression in patients above 45 years \( [28] \). In our study, the elderly (above 60 years of age) patient group \( (53\%) \), presented a more aggressive behavior, with higher Tg levels \( (1559 \text{ ng/mL vs } 934 \text{ ng/mL}, \text{respectively}) \). The elderly group of patients also presented higher SUVmax values for all sites compared to the younger group \( \text{(local recurrence } 12.3 \text{ vs } 6.2\%; \text{cervical lymph node metastases } 12.8 \text{ vs } 3.8\%; \text{distant lymph node metastases } 8.7 \text{ vs } 5.3\%; \text{lung metastases } 6.3 \text{ vs } 4.8\%; \text{bone metastases } 11.2 \text{ vs } 6.1\%, \text{respectively}) \).

The detection of new lesions with F-18 FDG PET/CT can change clinical management in 21%–51% of patients \( [14, 19, 29] \). Prior to our investigation 60% of our patients had negative imaging studies despite signs of RAIR. F-18 FDG PET/CT studies changed clinical management in 44% of them. No significant difference in management change was observed between F-18 FDG PET/CT studies with tTSH or sTSH levels.

One limitation of our study was the small number of patients. RAIR patients are rare, account for approximately 2% of a population of patients with DTC \( [5, 6] \). One multicentric study was able to analyze only 33 patients while another study, with 5163 DTC, only 2.2% had the RAIR.

Figure 2. tTSH F-18 FDG PET/CT demonstrated an additional lymph node not evidenced by sTSH exam. A 60-year-old female was diagnosed 18 years ago with an aggressive DTC subtype. She had multiple radioiodine doses \( (\text{cumulative dose } = 25.9\text{GBq } = 700\text{mCi}) \) and signs of radioiodine refractory thyroid cancer \( (\text{rising sTg levels } = 16.7 \text{ ng/mL}) \). The sTSH F-18 FDG PET/CT trans axial A) PET B) CT and C) Fused images show marked uptake in a right cervical lymph node level IIb (SUV = 5.3). The tTSH F-18 FDG PET/CT trans axial D) PET E) CT and F) Fused images demonstrated higher uptake (SUV = 6.5) in the same lymph node and an additional adjacent lymph node (SUV = 4.8) not evidenced on the sTSH F-18 FDG PET/CT. Histopathology confirmed both metastases.
F-18 FDG PET/CT images of the same patient were compared in two
data.

Funding statement

data.

interpreted the data; Contributed reagents, materials, analysis tools or

the data.

Author contribution statement

declarations

This research did not receive any specific grant from funding agencies
in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] S.J. Sherman, Thyroid carcinoma, Lancet 361 (2003) 501–511.
[2] M.J. Schlumberger, Papillary and follicular thyroid carcinoma, N. Engl. J. Med. 338 (1998) 297–306.
[3] H.R. Mason, H.S. Smith, Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer, Endocrinol Metab. Clin. N. Am. 19 (1990) 685–718.
[4] J.C. Sisson, T.J. Giordano, D.A. Jamadar, E.A. Kazerouni, B. Shapiro, M.D. Gross, et al., 131I treatment of microinvasive pulmonary metastases from papillary thyroid carcinoma, Cancer 78 (1996) 2184–2192.
[5] G.J. Hanna, N.L. Busaidy, N.G. Chau, L.J. Wirth, J.A. Barletta, A. Calles, et al., Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a phase II study, Clin. Canc. Res. 24 (2018) 1546–1553.
[6] G. Li, J. Lei, L. Song, K. Jiang, T. Wei, Z. Li, et al., Radioiodine refractoriness score: a multivariable prediction model for postoperative radioiodine-refractory differentiated thyroid carcinomas, Cancer Med. 7 (2018) 5484–5456.
[7] F. Grabellus, J. Nagarajah, A. Bockisch, K.W. Schmid, S.V. Shue, Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma, Clin. Nucl. Med. 37 (2012) 121–127.
[8] F. Grönewald, C. Menzel, H. Bender, H. Palmedo, F. Willkomm, J. Ruhlmann, et al., Comparison of 18F-Fluorodeoxyglucose with 131Iodine and 99mTc-sestamibi scintigraphy in differentiated thyroid cancer, Thyroid 7 (1997) 327–335.
[9] V. Fatourechi, I.D. Hay, Treating the patient with differentiated thyroid carcinoma with therapeutic optimization of TSH on uptake of 18F-Fluorodeoxyglucose Positron Emission Tomography in patients with suspected recurrence or metastatic differentiated thyroid carcinoma with elevated serum thyroglobulin and negative I-131 whole body scan, Nucl. Med. Rev. Cent. East. Eur. 17 (2014) 87–93.
[10] J.K. Choi, K.P. Jung, S.S. Lee, Y.S. Park, S.M. Lee, S.K. Lee, Clinical usefulness of F-18 FDG PET/CT in papillary thyroid cancer with negative radioisotope scan and elevated thyroglobulin level or positive anti-thyroglobulin antibody, Nucl. Med. Mol. Imaging 50 (2010) 130–136.
[11] A. Jagur, J.E. Kalinsky, L.R. McGougall, F-18 FDG PET/CT in the management of thyroid cancer, Clin. Nucl. Med. 32 (2007) 690–695.
[12] W. Wang, H. Macapinlac, S.M. Larson, S.D. Yeh, T. Akhurst, R.D. Finn, et al., 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131)I whole body scans and elevated serum thyroglobulin levels, J. Clin. Endocrinol. Metab. 84 (1999) 2291–2302.
[13] F. Bertagna, G. Bosio, G. Biasiotti, C. Rodella, F. Puia, S. Gabanelli, et al., F-18 FDG PET/CT evaluation of patients with differentiated thyroid cancer with negative I-131 total body scan and high thyroglobulin level, Clin. Nucl. Med. 34 (2009) 756–761.
[14] J.C. Sisson, R.J. Ackermann, M.A. Meyer, R.L. Wahl, Uptake of 18F-2-fluoro-2-deoxy-D-glucose by thyroid cancer: implications for diagnosis and therapy, J. Clin. Endocrinol. Metab. 77 (1993) 1090–1094.
[15] F. Moog, R. Linke, N. Manthey, R. Tiling, P. KneseWitch, K. Tatsch, et al., Influence of thyroid-stimulating hormone levels on uptake of FDG in recurrent and metastatic differentiated thyroid carcinoma, J. Nucl. Med. 41 (2000) 189–195.
[16] T. Petrich, A.R. Borner, E. Weckesser, B. Soudah, O. Otto, A. Widjaja, et al., Follow-up of differentiated thyroid cancer patients using rTSH-predictive results, Nuklearmedizin 40 (2001) 7–14.
[17] K.M. van Tol, P.I. Jager, D.A. Pier, J. Eum, E.G.E. de Vries, R.F.F. Dullaart, et al., Better yield of 18F-fluorodeoxyglucose-potassium positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyroidreceptor stimulation, Thyroid 12 (2002) 381–387.
[18] J.T. Deichen, C. Schmidt, O. Prante, M. Schasch, T. Papadopoulos, T. Kuwert, Influence of TSH on uptake of 18Ffluorodeoxyglucose in human thyroid cells in vitro, Eur. J. Nucl. Med. Mol. Imag. 31 (2004) 507–512.
[19] D. Blaser, S. Maschauer, T. Kuwert, O. Prante, In vitro studies on the signal transduction of thyroid uptake of 18F-FDG and 131I-Iodide, J. Nucl. Med. 47 (2006) 1382–1388.
[20] O. Prante, S. Maschauer, V. Fremont, J. Reinfelder, R. Stoehr, M. Szukdlinski, et al., Regulation of uptake of 18F-FDG by a follicular human thyroid cancer cell line with mutation-activated K-ras, J. Nucl. Med. 41 (2000) 1384–1395.
[21] G. Altenvoerde, H. Lerch, T. Kuwert, P. Mathesha, M. Schaefer, O. Schobert, Positron emission tomography with F-18-fluorodeoxyglucose in patients with differentiated thyroid carcinoma, elevated thyroglobulin levels, and negative iodine scans, Langenbecks Arch. Surg. 383 (1998) 160–163.
[22] S.J. Na, I.R. Yoo, O. Ji, C. Lin, Q. Lin, S.H. Kim, et al., Diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in differentiated thyroid cancer patients with elevated thyroglobulin and negative (131)I whole body scan: evaluation by thyroglobulin level, Ann. Nucl. Med. 26 (2012) 26–34.
[23] S.Y. Kwon, J. Kim, S.H. Jung, A. Chong, H.C. Song, H.S. Bom, et al., Preablative stimulated thyroglobulin levels can predict malignant potential and therapeutic responsiveness of subcentimeter-sized, 18F-fluorodeoxyglucose-Avid cervical lymph nodes in patients with papillary thyroid cancer, Clin. Nucl. Med. 41 (2016) e32–e38.
[24] F. Bertagna, D. Albano, G. Bosio, A. Piccardo, B. Dib, R. Giubbini, 18F-Fluorodeoxyglucose PET/CT in patients affected by differentiated thyroid carcinoma with positive thyroglobulin level and negative 131I whole body scan. It’s value confirmed by a biometric experience, Curr. Radiat. 7 (2016) 228–234.
[25] A. Kukulska, J. Krajewska, Z. Kolezna, E. Palicka-Cieslik, Z. Puch, E. Gubala, et al., The role of FDG-PET in localization of recurrent lesions of differentiated thyroid cancer (DTC) in patients with asymptomatic hyperthyrogblobulinemia in a real clinical practice, Eur. J. Endocrinol. 175 (2016) 379–385.
[26] P. Chen, H. Feng, W. Ouyang, J. Wu, J. Wang, Y. Sun, et al., Risk factors for nonremission and progression-free survival after I-131 therapy in patients with lung metastasis from differentiated thyroid cancer: a single-institute, retrospective analysis in southern China, Endocr. Pract. 22 (2016) 1048–1056.
[27] S.J. Rosenbaum-Krumme, R. Gorgen, A. Bockisch, I. Bins, In-18FDG-PET/CT changes therapy management in high-risk DTC after first radioiodine therapy, Eur. J. Nucl. Med. Mol. Imag. 39 (2012) 1573–1380.