Can the American Thyroid Association Risk of Recurrence Predict Radioiodine Refractory Disease in Differentiated Thyroid Cancer?

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Key Words

Radioiodine refractory disease · Differentiated thyroid cancer · American Thyroid Association risk classification · TNM in iodine resistance · ¹⁸F-fludeoxyglucose PET/CT scan

Abstract

Objective: The aim of this study was to compare the TNM staging system and the American Thyroid Association (ATA) recurrence risk classification in predicting radioiodine refractory disease (RRD) in differentiated thyroid cancer (DTC) and to analyze the correlation of stimulated thyroglobulin (Tg) levels and rate of Tg elevation with the standardized uptake value on ¹⁸F-fludeoxyglucose (FDG) PET/CT scan. **Methods:** RRD was indicated through the retrospective analysis of consecutive ¹⁸F-FDG PET/CT scans in DTC with stimulated Tg >10 ng/ml and negative ¹³¹I Nal whole-body scans (WBS). Tg elevation velocity was compared to the likelihood of a positive scan. The ATA recurrence risk and TNM staging system were compared to see which of them better predicted the subsequent development of RRD. **Results:** Fifty-eight of 636 subjects developed RRD: 52 papillary and 6 follicular thyroid cancer. The median time between diagnosis and a negative WBS was 24 months (range 12–240). RRD developed in 11 low-risk, 32 intermediate-risk and 15 high-risk patients. A

better response to therapy was seen in the low-risk versus the intermediate- and high-risk groups. ¹⁸F-FDG PET/CT scans had a diagnostic accuracy of 94.8%, sensitivity of 97.7%, specificity of 85.7%, positive predictive value of 95.6% and negative predictive value of 92%. There was no correlation between the Tg level or rate of rise and a positive scan. Overall, PET-CT upstaged 18 (31%) cases, leading to a change in management in 20 (35%) cases. **Conclusion:** The TNM and ATA staging systems show no significant difference in predicting the development of RRD. RRD is less likely in stage I, II and low-risk patients. There is no correlation between the level or rate of Tg rise and a positive ¹⁸F-FDG PET/CT scan.

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Introduction

Differentiated thyroid cancer (DTC) is typically indolent if treated early and appropriately. A small subset of more aggressive disease progresses to radioiodine resistance. Based on the American Thyroid Association (ATA) risk of recurrence classification at baseline [1] and response to initial therapy 6–24 months after radioactive iodine (RAI) ablation [2], the more aggressive subset of

patients should theoretically be identified in whom the chance of developing radioiodine refractory disease (RRD) would potentially be higher. There has so far been no study defining the role of ATA risk stratification or TNM classification in predicting which patients will progress to develop iodine resistance/dedifferentiation with biochemical evidence of disease presence.

Although the ^{18}F -fludeoxyglucose (FDG) PET/CT scan has a well-established role in detecting disease in RRD [1], the relation of the rate of thyroglobulin (Tg) rise or stimulated Tg level with the likelihood of disease detection has not been established. The purpose of our study was to (1) stratify the RRD patients based on ATA risk and TNM staging systems to see which of the two, if either, can predict the subsequent development of iodine resistance; (2) evaluate the association of Tg rise velocity to ^{18}F -FDG PET/CT scan positivity and study the role of the ^{18}F -FDG PET/CT scan in the further management of these patients, and (3) study the subsequent behavior of RRD after directed treatment.

Methods

Setting and Data Collection

The study was performed at the department of Nuclear Medicine at Shukat Khanum Memorial Cancer Hospital and Research Centre, a cancer specialist center in Lahore, Pakistan. A retrospective analysis was conducted of all ^{18}F -FDG PET/CT scans performed over 5 years in DTC patients with stimulated Tg levels >10 ng/ml or positive anti-Tg antibody (TgAb) and a negative ^{131}I NaI whole-body scan (WBS). Patients were classified based on their TNM stage and ATA risk categorization.

Clinical Management

At baseline all patients underwent total thyroidectomy and RAI remnant ablation. Patients were followed up regularly every 6–12 months, as per the standard protocol. We classified our patients as low, intermediate and high risk according to the 2010 ATA guidelines for recurrence risk classification.

ELISA testing of Tg levels was done using a chemiluminescence immunoassay analyzer. A Tg value <0.2 ng/ml was considered normal in postthyroidectomy patients. In TgAb cases, a level of >20 IU/ml was considered elevated. In such cases, the Tg value was regarded as invalid and the disease status was evaluated by following the TgAb levels.

The ^{18}F -FDG PET/CT scans were performed on a dedicated Phillips Gemini TOF scanner. After a 4- to 6-hour fast, 300 MBq of ^{18}F -FDG was injected intravenously followed by a 60-min uptake period. Three-minute images were acquired from the base of the skull to mid-thigh for each of 8–9 bed positions. A contrast-enhanced CT scan was acquired with a voltage of 70–140 kVp and tube current of 80 mA for attenuation correction and lesion localization. Iodinated contrast was not administered. Each scan was reported by a board-certified nuclear medicine physician and a

radiologist. Regions of interest were drawn on attenuation-corrected images to calculate standardized uptake values (SUV) normalized to body weight. Maximum SUV (SUVmax) was calculated after rescaling the overall activity concentration (Bq ml^{-1}). The uptake of all abnormal sites was recorded. The hepatic SUVmax was used as the reference value.

Based on ^{18}F -FDG PET/CT scan findings, if the hypermetabolic lesion was accessible, surgical resection was the preferred option. If surgery was not possible, external beam radiation therapy was performed in symptomatic patients. Where neither was a viable option an empirical RAI therapy was administered. In instances where there was an overlap of two or three of these modalities, we evaluated the response to optimal treatment and classified it as biochemically complete, biochemically incomplete, structural and biochemical progression, or death.

Data Analysis

Patient demographics and clinical characteristics were assessed using standard descriptive statistics applicable on quantitative and qualitative data. Nonparametric correlation of Tg levels, ATA risk stratification and TNM versus ^{18}F -FDG PET/CT outcome were assessed by applying Spearman's correlation.

The Tg velocity was calculated taking into account the stimulated Tg levels, approximately 12 months apart, using the formula: $\text{pre-}^{18}\text{F}\text{-FDG PET/CT Tg} - \text{Tg on last follow-up/pre-}^{18}\text{F}\text{-FDG PET/CT Tg} \times 100$. Spearman's correlation between the Tg velocity and time duration was assessed. p values <0.05 were considered statistically significant. The study was approved by the institutional review board.

Results

Out of a total of 954 patients with DTC registered at our institute over a 19-year period, 636 patients (538 papillary cancer, 98 follicular cancer) were analyzed. In total, 58 (9%) developed RRD during follow-up. This included 33 (57%) females and 25 (43%) males; 52 (90%) had papillary cancer and 6 (10%) had follicular cancer.

The median time between DTC diagnosis and a negative ^{131}I WBS was 24 months (range 12–240). Pre- ^{18}F -FDG PET/CT stimulated Tg levels ranged from 10 to 17,355 ng/ml. Five patients underwent ^{18}F -FDG PET/CT scan due to rising TgAb levels.

Out of 58 ^{18}F -FDG PET/CT scans, 43 (74%) were positive and 37 showed FDG avid disease, while 6 had sub-centimeter non-FDG avid pulmonary nodules which were below the scan resolution. Two with nodal uptake were found to be reactive nodes on histology, representing a false positive finding. Twelve (20.6%) showed no uptake or morphologic abnormality. The false negative rate was 1.7%. One patient had no evidence of FDG avid disease; however, neck dissection confirmed nodal metastases.

Table 1. Stratification of data based on ATA low-, intermediate- and high-risk categories

	Low risk (n = 11)	Intermediate risk (n = 32)	High risk (n = 15)
Female/male, %	50/50	54.5/45.5	60/40
Mean stimulated Tg, ng/ml	228 (10–1,144)	764 (21–17,355)	570 (58–1,623)
Mean time to negative WBS, months	42 (12–84)	30.5 (12–240)	36 (12–72)
Mean SUVmax	5.7 (2.4–14.5)	5.3 (2.6–16)	8.7 (4.4–22.6)

The diagnostic accuracy of ^{18}F -FDG PET/CT scan was 94.8%, sensitivity 97.7%, specificity 85.7%, positive predictive value 95.6%, and negative predictive value 92%. The ^{18}F -FDG PET/CT scans led to a change in management in 34% of patients.

The SUV of positive sites ranged from 2.6 to 22.6. There was no correlation between the Tg level and scan negativity ($r = 0.093$, $p = 0.51$), and no association between SUV and Tg levels ($r = 0.13$, $p = 0.33$) in the positive scans. An overview of the ^{18}F -FDG PET/CT results in relation to Tg levels is provided in figure 1. Tg level was not found to be useful in determining PET/CT positivity. The ROC curve showed an AUC of 0.568 ($p = 0.508$, 95% CI 0.365–0.771).

Tg velocities were calculated to evaluate the rate of change. The data were analyzed based on the ATA risk categories. There was no statistically significant correlation between Tg velocity and the likelihood of a positive ^{18}F -FDG PET/CT scan in the low- ($r = 0.087$, $p = 0.81$), intermediate- ($r = 0.395$, $p = 0.069$) or high-risk groups ($r = 0.318$, $p = 0.290$).

ATA Risk Stratification

On the basis of the ATA risk classification, 4.5% of 243 low-risk patients, 11.6% of 238 intermediate-risk patients, and 12.8% of 117 high-risk patients developed RRD (table 1).

Low-Risk Group

The low-risk group consisted of 11 patients (18.9%). The ^{18}F -FDG PET/CT scan was positive in 73% of the cases. Hypermetabolic disease was identified in 7 patients (63.6%), of whom 1 had false positive uptake in a neck node found to be reactive on histology. Nonavid structural disease was identified in 1 (9%) patient, while the ^{18}F -FDG PET/CT was unremarkable in 3 (27%) cases. Two out of 11 had elevated anti-Tg (TgAb) levels.

The PET-CT scan upstaged disease in 3 (27%) patients. Most patients with a positive ^{18}F -FDG PET/CT scan were

Fig. 1. ^{18}F -FDG PET/CT outcome in relation to Tg levels.

given empirical RAI therapy, and surgical resection of avid disease was performed in 3 (27%) patients. The details of the subsequent follow-up of these low-risk patients are presented in figure 2. In all 3 patients with a negative ^{18}F -FDG PET/CT scan, stimulated Tg levels normalized after an empirical dose of RAI.

Intermediate-Risk Group

Thirty-two (55.2%) patients had an intermediate risk of recurrence at baseline. Out of these, the ^{18}F -FDG PET/CT scan was positive in 78%: hypermetabolic disease was identified in 23 (72%), nonavid pulmonary nodules were identified in 2 (6.2%), and 7 (22%) were negative. Of these, 2 had elevated TgAb levels.

The PET/CT scan upstaged the disease in 10 (31%) patients. Of 25 patients with a positive ^{18}F -FDG PET/CT scan, 10 (40%) underwent surgical resection or radiotherapy where applicable, and 23 were given empirical RAI therapy, alone or in combination with surgery or radiation. Details of the subsequent follow-up of these patients

Fig. 2. ATA risk-based groups with post-¹⁸F-FDG PET/CT clinical outcome.

Table 2. ATA risk groups and ¹⁸F-FDG PET/CT outcome

ATA risk	¹⁸ F-FDG PET-CT outcome			Total
	hypermetabolic disease	unremarkable	nonavid structural disease	
Low	7 (63.6)	3 (27.3)	1 (9)	11
Intermediate	23 (72)	7 (21.8)	2 (6.2)	32
High	9 (60)	2 (13.3)	4 (26.7)	15

Data are presented as n (%).

with an intermediate risk of recurrence are displayed in figure 2.

High-Risk Group

Fifteen (25.9%) patients were classified as high risk at baseline. Out of these, the ¹⁸F-FDG PET/CT scan was positive in 13 (87%) cases, with 9 showing hypermetabolic structural disease and 4 displaying nonavid pulmonary nodules. The ¹⁸F-FDG PET/CT scan was negative in 2 (13%) cases. Both showed progression on follow-up and 1 had elevated TgAb levels.

The PET-CT scan upstaged disease in 5 (33.3%) patients. Surgery and radiation therapy was given in 7 (47%) cases and 9 (60%) received empirical RAI therapy. Details

of the subsequent follow-up of these patients with a high risk of recurrence are presented in figure 2. Out of 46 patients who were given an empirical dose, radioiodine avid disease was demonstrated in 14% on posttherapy scans.

Elevated TgAb Level

In 5 subjects, the ¹⁸F-FDG PET/CT scan was acquired for elevated TgAb with a negative RAI diagnostic WBS (low risk, n = 2, intermediate risk, n = 1, and high risk, n = 2; TgAb range 341–3,000). All had hypermetabolic disease on their ¹⁸F-FDG PET/CT scan. Follow-up after appropriate therapy resulted in a biochemical incomplete response in 4 with further elevation in TgAb levels, while in 1 case the levels declined. There was no statistically significant correlation between the ATA risk categories and the chance of developing RRD (p = 0.117; table 2; fig. 3).

TNM Stage

On the basis of TNM staging, 7.3% of 436 stage I patients, 8.6% of 58 stage II patients, 15% of 46 stage III patients and 14% of 96 stage IV patients developed RRD. There was no statistically significant correlation between the TNM stage and development of RRD (p = 0.221; fig. 4).

ATA Risk Stratification versus TNM Stage

On bivariate analysis the ATA classification (hazard ratio 1.31, 95% CI 0.83–2.06, p = 0.24) was a better pre-

Fig. 3. ^{18}F -FDG PET-CT and RRD in the ATA risk groups.

Fig. 4. ^{18}F -FDG PET-CT and RRD according to TNM stage.

dictive staging system than the TNM classification (hazard ratio 0.903, 95% CI 0.70–1.16, $p = 0.41$). However, this difference in predictive value was not statistically significant. Both TNM staging and ATA risk assessment did not predict the chance of a positive PET/CT scan once RRD had developed (fig. 3, 4).

Discussion

DTC develops radioiodine resistance in approximately 2–11% of cases, and physicians are urged to enter such patients into clinical trials where possible [3]. Following thyroidectomy, patients are treated with RAI and monitored with WBS using RAI, serum tumor markers, Tg and TgAb, and cervical ultrasonography at intervals of 6–12 months with individualized care plans. Radioiodine resistance in DTC represents an aggressive subset of patients, and once iodine resistance develops the disease becomes more challenging.

Details of the overall survival of our DTC population have already been published [4, 5]. In the present study, although ^{18}F -FDG PET/CT played an instrumental role in detecting sites of disease in RRD, there was no clear-cut prediction of the development of RRD using the TNM staging or ATA risk assessment systems. An increase in FDG uptake is typically seen in more aggressive, high-grade thyroid cancer [6]. In our study there was no association between the chance of a positive FDG scan and the TNM stage or ATA risk category.

At our institution, the iodine-resistant population was treated aggressively with surgical resection and, if indi-

cated, radiation therapy based on ^{18}F -FDG PET/CT findings. RAI therapy was given to several patients in the earlier years when conflicting data were available as to the efficacy of empirical RAI therapy. Several studies have shown that when a diagnostic WBS is negative, empirical RAI therapy is not useful diagnostically or therapeutically in patients with negative ^{18}F -FDG PET/CT findings [7]. However, according to Ma et al. [8] Tg levels decreased after RAI therapy in 63% of patients, while in 62% there was uptake on the posttherapy scan. Pineda et al. [9] showed a decrease in follow-up Tg levels in 81% of patients undergoing first-line therapy, 90% undergoing second-line therapy, and in 100% of patient undergoing third-line therapy.

In our study, 12 patients had no metabolic or morphologic evidence of disease on their ^{18}F -FDG PET/CT scan although their Tg levels were elevated. According to Vural et al. [10] a negative ^{18}F -FDG PET/CT is a good prognostic indicator of prolonged symptom-free survival and, therefore, empirical therapy may not be justified. In some patients Tg follows a fluctuant course, and biochemically incomplete response to therapy may with time convert to no evidence of disease with a normalization of Tg levels.

The sensitivity of ^{18}F -FDG PET/CT in our population was very high, which is in line with other studies. Ong et al. [11] and Nahas et al. [12] reported a sensitivity of 88%, while the latter group also reported a specificity of 100% and positive predictive value of 100%. Petrich et al. [13] reported the sensitivity of ^{18}F -FDG PET/CT to be 53% during thyroid-stimulating hormone (TSH) suppression and 87% following recombinant human (rh) TSH stimulation.

We did not find any relation between the actual level of Tg and the likelihood of a positive ^{18}F -FDG PET/CT scan. Similarly, there was no correlation with the rate of rise of Tg and the probability of a positive scan. This is contrary to the findings of Schluter et al. [14], who reported a positive scan in 11% of patients with Tg levels of 10 ng/ml or less, increasing to 50% when Tg levels were between 10 and 20 ng/ml, and rising to 93% at Tg levels above 100 ng/ml. In a study of 40 patients with negative ^{131}I scans and elevated TgAb levels, Asa et al. [15] reported a positive ^{18}F -FDG PET/CT in 50% and concluded that ^{18}F -FDG PET/CT can be used effectively in the detection of recurrence/metastasis during follow-up.

The limitations of our study include the fact that the data were retrospectively gathered. However, it is difficult to gather prospective data for the evaluation of thyroid cancer since the disease expectancy is long and decades of follow-up are not conveniently recorded prospectively.

Our study spanned 2 decades of data, and since the understanding of disease behavior has evolved over this time frame there was variation in treatment choices. In the last decade microcarcinoma has been defined as <1 cm in size, while prior to that no difference in treatment was made based on size.

Furthermore, empirical RAI therapy was initially given to all patients with elevated Tg levels, even when no iodine avid disease was seen on the pretherapy scan. Our center did not have a PET/CT scanner before 2009 and,

therefore, at that time patients with RRD did not have an ^{18}F -FDG PET/CT scan and instead underwent RAI therapy followed by a posttherapy scan.

Others report that, due to the frequent normalization of Tg levels in untreated patients, RAI therapy should be administered on a case by case basis [16]. Even if there is no evidence of radioiodine avid disease an empirical RAI therapy can be performed to identify the location of recurrent or metastatic disease [17–19]. An ^{18}F -FDG PET/CT scan may also serve a prognostic role considering that patients with high SUV and large-volume hypermetabolic disease have a higher 3-year mortality than those with nonavid disease on an ^{18}F -FDG PET/CT scan [20, 21].

Conclusion

The TNM or ATA staging systems show no significant difference in predicting the development of RRD. RRD is less likely in stage I, II and low-risk patients. There is no correlation between the level or rate of Tg rise and a positive ^{18}F -FDG PET/CT scan.

Disclosure Statement

The authors have no conflicts of interest to report.

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