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Clinical Research Article

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PSMA Expression in Differentiated Thyroid Cancer: Association With Radioiodine, ^{18}FDG Uptake, and Patient Outcome

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Abbreviations: ^{18}FDG, 18-fluorodeoxyglucose; ^{68}Ga, 68-gallium; ^{177}Lu, lutetium-177; CT, computed tomography; DTC, differentiated thyroid cancer; IHC, immunohistochemistry; IRS, immunoreactive score; LN, lymph node; PCa, prostate cancer; PDTC, poorly differentiated thyroid carcinoma; PET, positron emission tomography; PFS, progression-free survival; PRD, persistent or recurrent disease; PSMA, prostate-specific membrane antigen; RAI, radioiodine; RAIR, radioiodine-refractory; WBS, whole-body scan.

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Abstract

Context: Little is known about prostate-specific membrane antigen (PSMA) expression in patients with cervical involvement of differentiated thyroid cancer (DTC).

Objective: We investigated PSMA expression in neck persistent/recurrent disease (PRD) using immunohistochemistry and the association with radioiodine (RAI) or 18-fluorodeoxyglucose (^{18}FDG) uptake, and patient outcome.

Design, Setting, and Patients: Data from 44 consecutive DTC patients who underwent neck reoperation from 2006 to 2018 in a comprehensive cancer center.

Main Outcome Measure(s): Immunostaining was performed with vascular endothelial marker CD31 and PSMA. PSMA expression was quantified using the immunoreactive score (IRS). RAI and ^{18}FDG uptake were assessed before surgery using posttherapeutic RAI scintigraphy and ^{18}FDG positron emission tomography with computed tomography. Mean follow-up after reintervention was 6.5 ± 3.7 years.

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Results: Thirty patients (68%) showed at least 1 PSMA-positive lesion (IRS ≥ 2) with similar proportions in RAI-positive and RAI-negative patients (75% vs 66%). In RAI-negative patients, however, the proportion of PSMA-positive disease (79% vs 25%, $P < 0.01$) and the mean IRS (4.0 vs 1.0, $P = 0.01$) were higher in ^{18}FDG-positive than in ^{18}FDG-negative patients. Furthermore, mean IRS was higher in patients ≥ 55 years, large primary tumors (>40 mm) or aggressive subtypes, and was correlated with structural disease at last follow-up. Strong PSMA expression (IRS ≥ 9) was associated with shorter progression-free survival (PFS).

Conclusions: Our findings show that PSMA expression was present in two-thirds of patients with neck PRD, that it was related to poor prognostic factors and that very high expression was associated with poorer PFS. This preliminary study may offer new perspectives for the management of RAI-refractory DTC.

Key Words: prostate-specific membrane antigen, differentiated thyroid cancer, poorly differentiated thyroid cancer, immunohistochemistry, PSMA staining, radioiodine-refractory

Despite major therapeutic progress in the past decade (1), some patients with advanced radioiodine-refractory (RAIR) thyroid cancer still have a poor prognosis. The management of patients with RAIR cancer remains challenging and is based on the best combination of local treatments like surgery, external irradiation, interventional radiology, and/or targeted therapies such as tyrosine kinase inhibitors, depending at least in part on the patient's tumor burden and comorbidities. Imaging assessment of metastatic RAIR cancers relies on conventional radiology with Response Evaluation Criteria in Solid Tumors 1.1 criteria and on ^{18}fluorodeoxyglucose (^{18}FDG) positron emission tomography with computed tomography (PET/CT). High ^{18}FDG uptake is a well-known poor prognostic factor (2); however, it has been shown that the intensity of ^{18}FDG uptake is not correlated with tumor progression (3). If new markers that help in predicting tumor progression could be found, it would offer alternative perspectives in patients with RAIR cancer.

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein receptor expressed in prostate cancer (PCa) cells (4) and in the endothelium of the tumor-associated neovasculature of various malignancies such as breast, bladder, lung, gastric, colorectal, gynecologic, and head and neck cancers (5-9). Gallium-68 (^{68}Ga)-PSMA PET/CT is a relevant imaging modality in PCa for the initial diagnosis and the diagnosis of recurrence (10, 11) and helps in selecting patients eligible for radionuclide therapy. Radionuclide treatment with lutetium-177 (^{177}Lu)-PSMA-617 offers high response rates in patients with progressive metastatic castration-resistant PCa (12).

Some case reports of differentiated thyroid cancer (DTC) (13, 14) and medullary (15) thyroid cancers have been described in PCa patients with incidental focal thyroid findings during ^{68}Ga-PSMA PET/CT. PET/CT studies using ^{68}Ga-PSMA have also been performed in patients with DTC (16-21) or anaplastic thyroid cancer (22) as proofs of concept of PSMA uptake in thyroid malignancies. Recently, PSMA expression using immunohistochemistry (IHC) was shown to be increased in RAIR cancer samples, especially from patients with poorly differentiated thyroid carcinoma (PDTC) (23-25). However, the relationship between PSMA expression and scintigraphy, namely radioiodine (RAI) whole-body scan (WBS) or ^{18}FDG PET/CT, was not addressed.

In the present study, we investigated the expression of PSMA using IHC in neck persistent or recurrent disease (PRD) according to the RAI and ^{18}FDG uptake profile and correlated the findings with clinical outcome.

Materials and Methods

Patients' Data

The study was approved by the institutional review board. It was conducted in compliance with the French Research Standard MR-004 "Research not involving Human participants" (compliance commitment to MR-004 for the Centre François Baclesse number 2214228 v.0, dated from 07/03/2019) and is registered with the French Health Data Institute under the reference MR 2513060320. All patients received information and none of them expressed opposition to the use of their data. The records of 44 consecutive DTC patients with PRD who underwent a surgical reintervention in the neck from 2006 to 2018 at the Comprehensive Cancer Center in Caen, France, were reviewed. Patients were operated on levothyroxine treatment (n = 35) or after TSH stimulation in case of RAI-guided surgery (n = 9).

Pathology

Pathology was reported according to the World Health Organization criteria (26) and to the 2017 TNM classification (27). Aggressive histological subtypes and RAI refractoriness were defined according to the American Thyroid Association guidelines (28).

RAI Scintigraphy and ^{18}FDG PET/CT Scan

Within the routine management of DTC, all patients underwent a posttherapeutic RAI WBS with neck and thorax single-photon emission CT with CT (SPECT/CT) performed before surgery. Briefly, post-RAI scintigraphy was performed using a double-head gamma camera equipped with 1.5875 cm (5/8 in) NaI crystals, parallel-hole, high-energy collimators, and a multidetector (2 rows) spiral CT (Symbia T2, Siemens Medical Solutions, Malvern, PA, USA) (29). Patients were scanned either 2 days or 5 to 6 days after 1.1 or 3.7 GBq RAI administration, respectively, as previously described (30). ^{18}FDG PET/CT studies (n = 35) were acquired using a PET/CT scanner (Biograph TrueV, Siemens Medical Solutions) containing a 6-slice spiral CT component from mid-thigh to the skull base with a complementary dedicated 8-minute neck acquisition, as previously reported (31).

WBS with SPECT/CT and ^{18}FDG PET/CT studies were reviewed by 2 experienced nuclear medicine physicians. According to the results of WBS with SPECT/CT and ^{18}FDG PET/CT, a metabolic profile was established per patient as follows: neck PRD was scored RAI-positive when RAI uptake was observed in lymph nodes (LNs) or local disease (ie, disease in the thyroid bed), and RAI-negative otherwise. Neck PRD was scored ^{18}FDG-positive when ^{18}FDG uptake was observed in LNs or local disease, and ^{18}FDG-negative otherwise.

Patients also had neck ultrasound before reintervention and, when necessary, diagnostic contrast-enhanced CT scan. After surgery, patients were followed-up with serial measurements of serum thyroglobulin and thyroglobulin antibodies, and imaging if needed.

PSMA and CD31 Immunostaining

Immunohistochemistry was performed on paraffin-embedded tumor tissues using a Ventana Discovery XT autostainer on 4-µm-thick sections. Slides were deparaffinized with EZPrep buffer at 75°C for 8 minutes and epitopes were unmasked at 95°C for 8 minutes and 100°C for 4 minutes in EDTA buffer. Sections were incubated for 40 minutes at 37°C with PSMA antibody (ab133579, Abcam, 1/1000) or CD31 antibody (ab28364, Abcam, 1/50). Secondary antibody (Omnimap Rabbit) was incubated for 16 minutes at 37°C. After washing, staining was performed with 3,3′-diaminobenzidine and sections were counterstained with hematoxylin. Whole slide images were digitized at × 20 (0.5 µm/pixel) using the ScanScope CS scanner (Leica Biosystems, Nussloch, Germany). The identity of vascular structures was confirmed by CD31 expression, a marker for endothelial cells. All immunohistochemical analyses were performed by an experienced pathologist.

Immunoreactive Score

The 4-point immunoreactive score (IRS) was used to assess PSMA expression. It was first described by Kaemmerer et al. to assess somatostatin receptors expression in neuroendocrine tumors (32) and was further adapted by Woythal et al. for PSMA expression in PCa (33). The IRS combines intensity of staining and percentage of positive cells. Derlin et al. (34) reported PSMA uptake in a ^{68}Ga-PSMA PET/CT study with 5% of PSMA-positive cells. We adapted the system used by Woythal et al. to implement this threshold. IRS classification is described in Table 1. At patient level, if samples had different IRS values, the highest score was used for analysis.

Statistical Analysis

Quantitative variables were described with mean and standard deviations (±SD), and qualitative variables were described with numbers and percentages. Patient characteristics were compared using the Wilcoxon or Kruskal-Wallis tests and the χ^2 or Fisher exact tests, when appropriate. We used box plots to display IRS according to age, size of primary thyroid tumor, pathology, presence of aggressive pathological subtypes, and RAI or ^{18}FDG uptake. Finally, progression-free survival (PFS) and corresponding interquartile range (25%, 75%) were estimated with the Kaplan-Meier method. Time to progression after neck reintervention was calculated from the day of surgery to the date of progression or date of last follow-up visit. The nonparametric log-rank test was used for comparisons. For all tests, a 2-tailed P value < 0.05 was considered statistically significant. The analyses were conducted using STATA version 15.0 (Stata Corp, College Station, TX, USA).

Results

Patient Data

Among 44 patients, 35 (79%) had a PTC, 7 (16%) a PDTC, and 2 (5%) a Hürthle cell (ie, oncocytic) thyroid cancer. Twelve patients (27%) had aggressive pathological variants

(PDTC, n = 7; tall cell variant of PTC, n = 3; diffuse sclerosing variant of PTC, n = 2). Mean age at the time of neck reintervention was 52 ± 18 years. Time from initial surgery to neck reintervention was 3.9 ± 4.6 years.

Before surgery, 12 patients (27%) had RAI-positive PRD and 32 (73%) RAI-negative PRD. ^{18}FDG PET/CT was performed in all the 32 RAI-negative patients and in 3 RAI-positive patients because of high thyroglobulin level (n = 2) or poorly differentiated histology (n = 1). Of these 3 RAI-positive patients, 1 was ^{18}FDG-positive. Of the 32 RAI-negative patients, 24 (75%) were ^{18}FDG-positive.

At time of neck reoperation, the 32 RAI-negative patients were classified as RAIR disease and the 12 RAI-positive patients as non-RAIR.

Mean follow-up after reintervention for neck PRD was 6.5 ± 3.7 years.

Immunoreactive Score

One hundred and seventy-six tissue samples were reviewed: malignant LNs (n = 134), local disease (n = 4; 2 subcutaneous lesions, 1 tracheal lesion, and 1 muscular lesion) and benign LNs (n = 38). Representative slides of PSMA immunostaining in each of the 4 IRS classes are presented in Fig. 1.

Table 1. IRS classification (modified from Woythal et al. (33))

Percentage of positive cells	×	Intensity of staining	=	IRS
0: no positive cells		0: no color reaction		0-1: negative
1: < 5% of positive cells		1: mild reaction		2-3: positive, mild
2: 5%-30% positive cells		2: moderate reaction		4-8: positive, moderate
3: 31%-60% positive cells		3: intense reaction		9-12: positive, strong
4: ≥ 61% positive cells				

Abbreviation: IRS, immunoreactive score.

Patients' characteristics according to PSMA expression (negative, IRS 0-1 or positive, IRS 2-12) are reported in Table 2.

Analysis at lesion level

All 38 benign LNs had no PSMA expression (IRS = 0).

A positive PSMA expression (ie, IRS ≥ 2) was observed in the neovasculature of 85/138 (62%) malignant lesions: mild in 48, moderate in 33, and strong in 4.

Twenty-six patients had at least 2 malignant tissue samples and among them, 17 (65%) had samples with different IRS values (Fig. 2). No correlation was found between PSMA heterogeneity and ^{18}FDG uptake or pathological features.

Analysis at patient level

Of the 44 patients, 30 (68%) presented at least 1 lesion with IRS ≥ 2. Of these 30 patients, PSMA expression was mild in 15 (50%), moderate in 12 (40%), and strong in 3 (10%). The latter 3 patients had RAI-negative and ^{18}FDG-positive PRD. One patient with strong PSMA expression is presented in Fig. 3. PSMA expression according to RAI and ^{18}FDG uptake in the different groups of pathology subtypes is reported in Fig. 4.

The proportion of patients with PSMA expression (IRS ≥ 2) was similar in the RAI-positive and RAI-negative subgroups (9/12 [75%] vs 21/32 [66%], respectively; $P = 0.5$). Likewise, no mean IRS difference was found between these 2 subgroups of patients (3.2 ± 2.3 vs 3.2 ± 3.5). By contrast, significant differences between ^{18}FDG-positive and ^{18}FDG-negative patients were observed in RAI-negative individuals. Indeed, both the proportion of PSMA expression (IRS ≥ 2) (19/24 [79%] vs 2/8 [25%]; $P < 0.01$) and the IRS value (4.0 ± 3.7 vs 1.0 ± 2.0, $P = 0.01$) were higher in the ^{18}FDG-positive/RAI-negative than in the ^{18}FDG-negative/RAI-negative patients.

Figure 5 shows IRS values according to clinical or pathological data in the whole population (n = 44). IRS

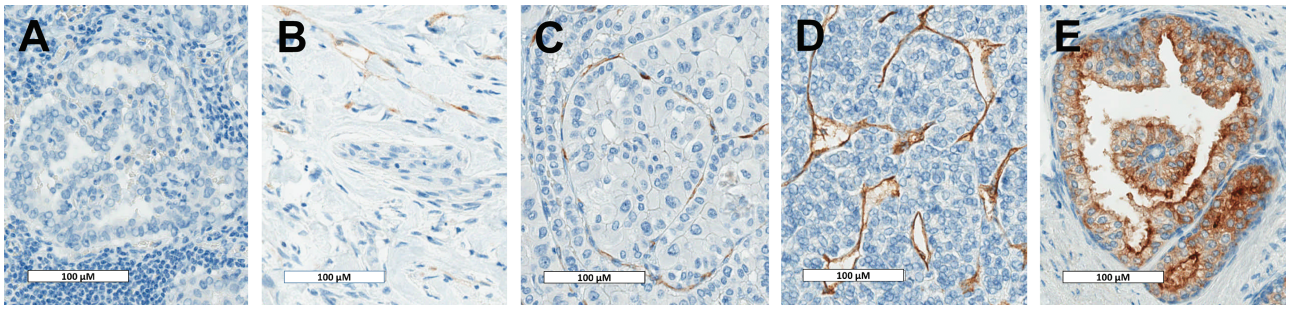

Figure 1. Representative slides of PSMA immunostaining displaying (A) negative, (B) mild, (C) moderate, and (D) strong PSMA expression in neovasculature of nodal tumoral disease. (E) Positive control: PSMA immunostaining in benign prostate glandular cells.

Table 2. Patient characteristics according to PSMA expression (negative, IRS: 0-1 or positive, IRS: 2-12) in persistent/recurrent disease

	PSMA-negative	PSMA-positive	*P* value
	n = 14	n = 30	
Age, y ± SD	42 ± 13	52 ± 18	0.09
Female	9 (64%)	13 (43%)	0.33
Initial surgery			
TNM 2017			
T status			0.37
T1a + T1b	5 (36%)	6 (20%)	
T2	6 (43%)	10 (33%)	
T3a + T3b	2 (14%)	12 (40%)	
T4a + T4b	1 (7%)	2 (7%)	
N status			0.06
Nx	3 (21%)	6 (20%)	
N0	4 (29%)	1 (3%)	
N1	7 (50%)	23 (77%)	
M status			0.95
M0	13 (93%)	28 (93%)	
M1	1 (7%)	2 (7%)	
Pathology			0.22
PTC/HCC	14 (100%)	23 (77%)	
PDTC	0	7 (23%)	
Aggressive subtype			0.16
No	12 (86%)	20 (67%)	
Yes	2 (14%)	10 (33%)	
Imaging before neck reintervention			
Posttherapeutic RAI WBS			0.72
Positive	3 (21%)	9 (30%)	
Negative	11 (79%)	21 (70%)	
^{18}FDG PET/CT			0.02
Not performed	2 (14%)	7 (23%)	
Negative	7 (50%)	3 (10%)	
Positive	5 (36%)	20 (67%)	
Pathology of PRD			
Tumor size, mm ± SD	12 ± 8	15 ± 10	0.04
Nodal extracapsular extension	1 (7%)	15 (50%)	<0.01
Last visit assessment			
Outcome according to ATA			0.1
ER	6 (43%)	10 (33%)	
IR/BIR	6 (43%)	6 (20%)	
SIR	2 (14%)	14 (47%)	
Death related to cancer	1 (7%)	5 (17%)	0.65

Abbreviations: ^{18}FDG, ^{18}fluorodeoxyglucose; ATA, American Thyroid Association guidelines; BIR, biochemical incomplete response; ER, excellent response; HCC, Hürthle cell cancer; IR, indeterminate response; PDTC, poorly differentiated thyroid cancer; PRD, persistent/recurrent disease; PTC, papillary thyroid cancer; RAI, radioiodine; SIR, structural incomplete response; WBS, whole-body scan.

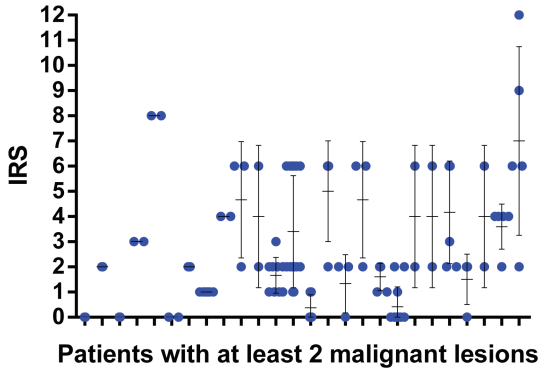

Figure 2. IRS values in 26 patients with at least 2 malignant lesions. Nine patients who presented lesions with identical IRS values are shown on left. Seventeen patients who presented lesions with different IRS values are shown on right.

was higher in patients aged ≥ 55 years at initial diagnosis, in patients with primary thyroid tumor > 40 mm, in PDTC, and in aggressive pathological variants. Mean IRS was higher in patients with (n = 16) than in those without nodal extracapsular extension (n = 28) (4.38 ± 3.42 vs 2.68 ± 3.02, $P = 0.04$).

Outcome

Median PFS was 1.3 year (0.9-2) in patients with IRS of 9 to 12, 4.4 years (2.2-7.2) in patients with IRS of 4-8, 5.8 years (2.7-10.4) in patients with IRS of 2 to 3, and 6 years (2.9-8) in patients with IRS of 0 to 1 ($P < 0.01$). PFS was poorer in patients with strong PSMA expression when considering either the whole population (log-rank test, $P < 0.01$) or patients with RAI-negative PRD (log-rank test, $P = 0.03$) (Fig. 6). Patients with indeterminate, biochemical, or structural response at last visit had higher IRS than those with an excellent response ($P = 0.03$). Among the 44 patients, 7 (16%) died, including 6 from progressive DTC (mean IRS = 5.2 ± 4.4; range, 0-12). Patients with ^{18}FDG-positive PRD had lower disease-specific survival than those ^{18}FDG-negative (59 vs 114 months, $P = 0.01$) but disease-specific survival was not different among the 4 IRS groups ($P = 0.45$).

Discussion

Our results confirm that PSMA expression is frequently observed in the tumor-associated neovasculature of persistent or recurrent DTC. As expected, PSMA expression was not present in benign LNs. We further showed that PSMA expression was also related to poor prognostic factors and that very high PSMA expression was associated with poorer PFS.

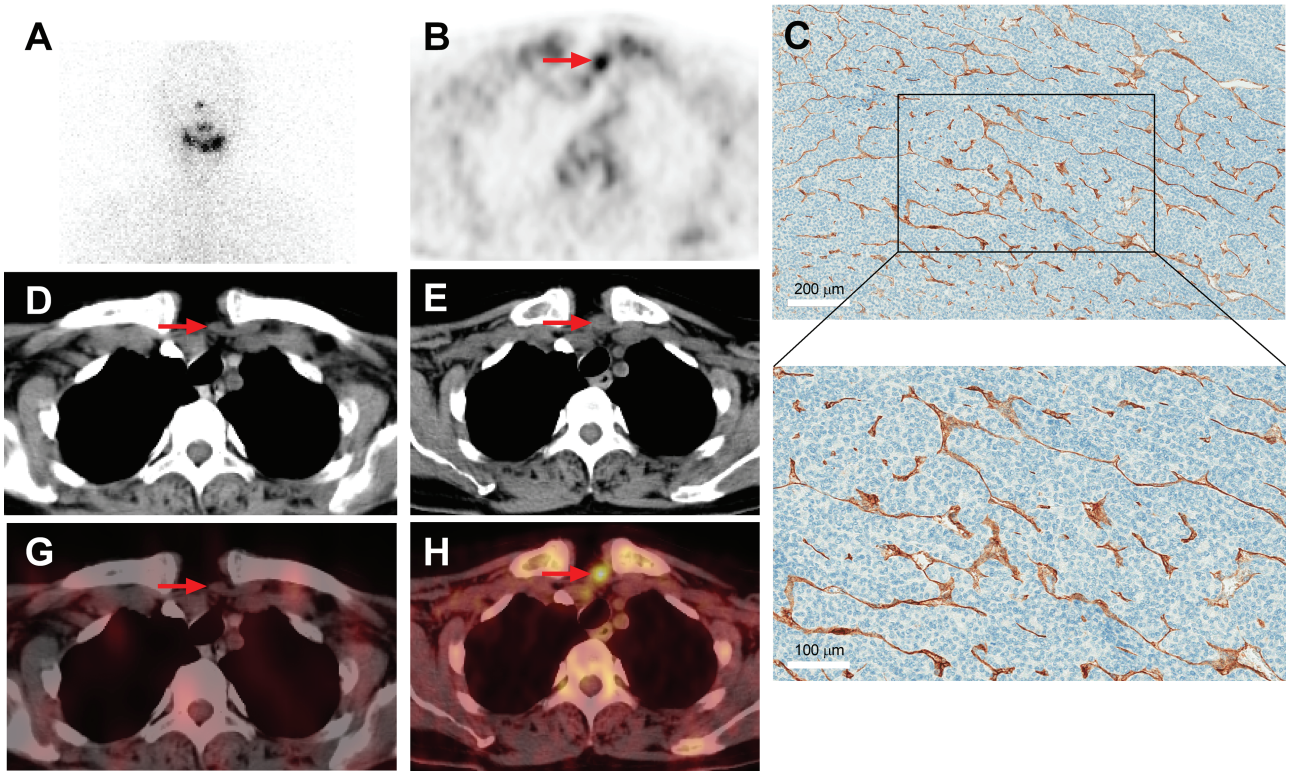

Figure 3. Clinical example of strong PSMA expression (IRS = 12) in neovasculature of nodal recurrent disease. A 63-year-old female patient with PDTC (pT3aNxMx) developed neck LN involvement 3 years after initial surgery. (A) Whole-body scan with (D, G) neck and thorax SPECT/CT performed 5 days after second RAI administration (3.7 GBq) did not show any RAI uptake in front of abnormal 8-mm LN of left central compartment (arrows). PET/CT showed high ^{18}FDG uptake (SUVmax = 7.3) in pathology-proven recurrent LNs (B, axial PET image; E, axial CT scan image; H, axial fused PET/CT image; arrows). (C) IHC showed strong PSMA staining with IRS of 12. Progression was observed 16 months after neck reintervention and patient had structural incomplete response at last follow-up assessment.

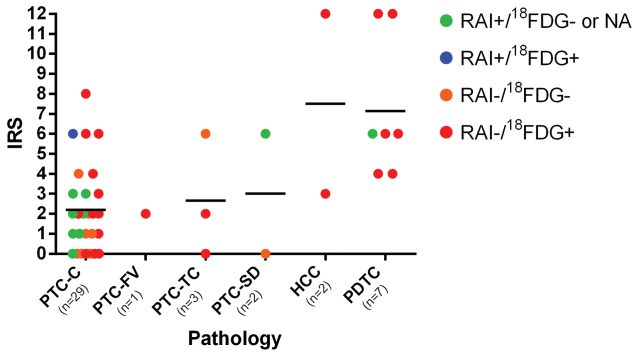

Figure 4. Immunoreactive score (IRS) according to RAI and ^{18}FDG uptake profile in different groups of histological subtypes (PTC-C, classic variant of papillary thyroid cancer; PTC-FV, follicular variant of PTC; PTC-TC, tall cell variant of PTC; PTC-SD, diffuse sclerosing variant of PTC; HCC, Hürthle cell thyroid cancer; PDTC, poorly differentiated thyroid cancer).

PSMA-positive expression was observed in 62% of the malignant tissue samples (ie, 68% of the patients in our cohort). A wide range of positive PSMA expression from 50% to 80% was previously reported in DTC (23-25, 35). Several factors accounted for this variability. First, assessment of PSMA expression differed from 1 study to another regarding staining, fraction of positive cells, use of composite scores, and different threshold values. We used a score published by Woythal (33), who reported PSMA expression in PCa using a 4-class IRS classification adapted from Kaemmerer (32). IRS combines intensity of PSMA staining and fraction of PSMA-positive cells. Then, IRS allows IHC data to be refined. We modified the lower threshold for the percentage of positive cells according to the report by Derlin (34). Likewise, 2 other studies also used Derlin's values to establish the threshold for PSMA

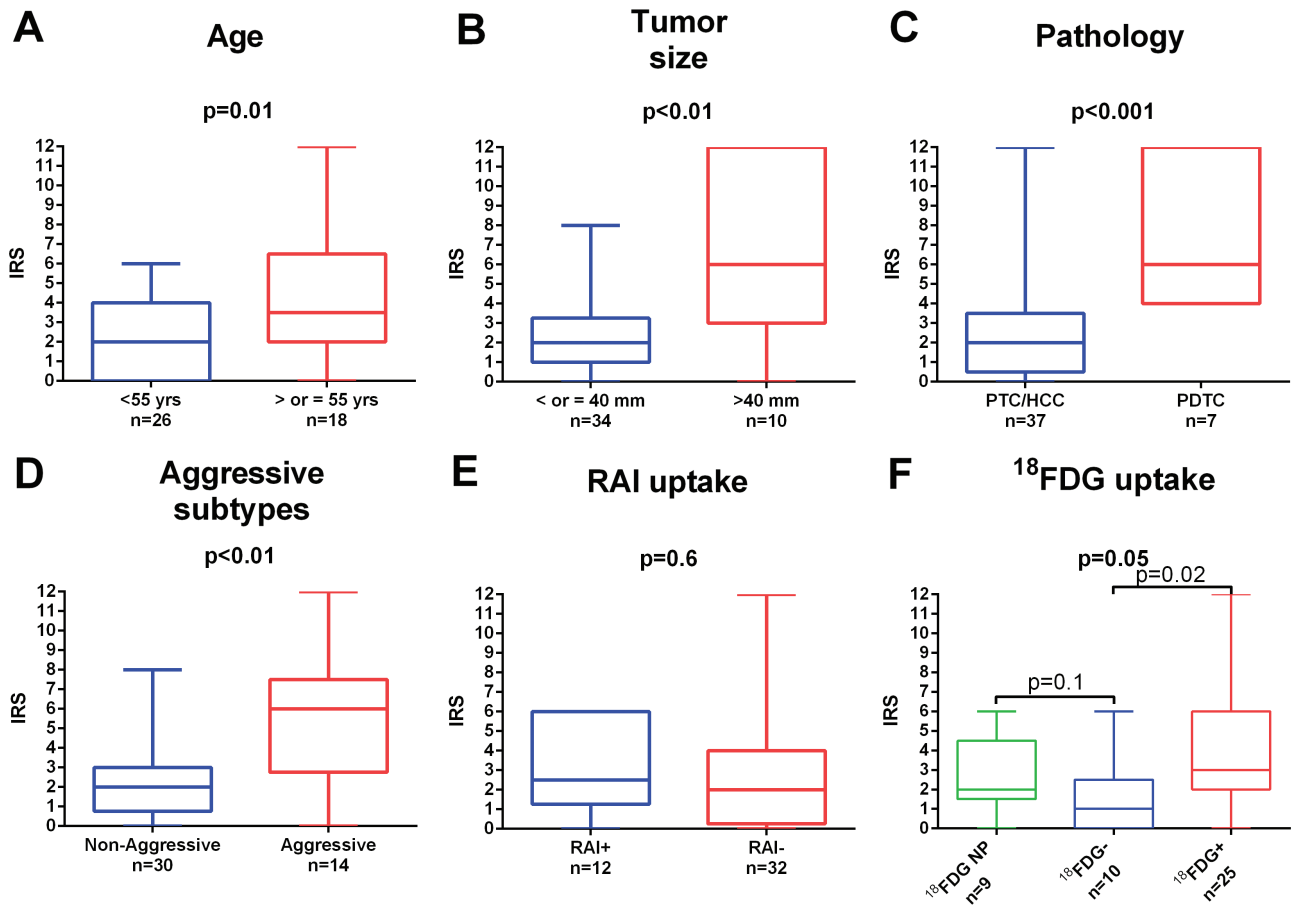

Figure 5. Immunoreactive score (IRS) according to age, size of primary thyroid tumor, pathology, aggressive histological subtypes, RAI, and ^{18}FDG uptake.

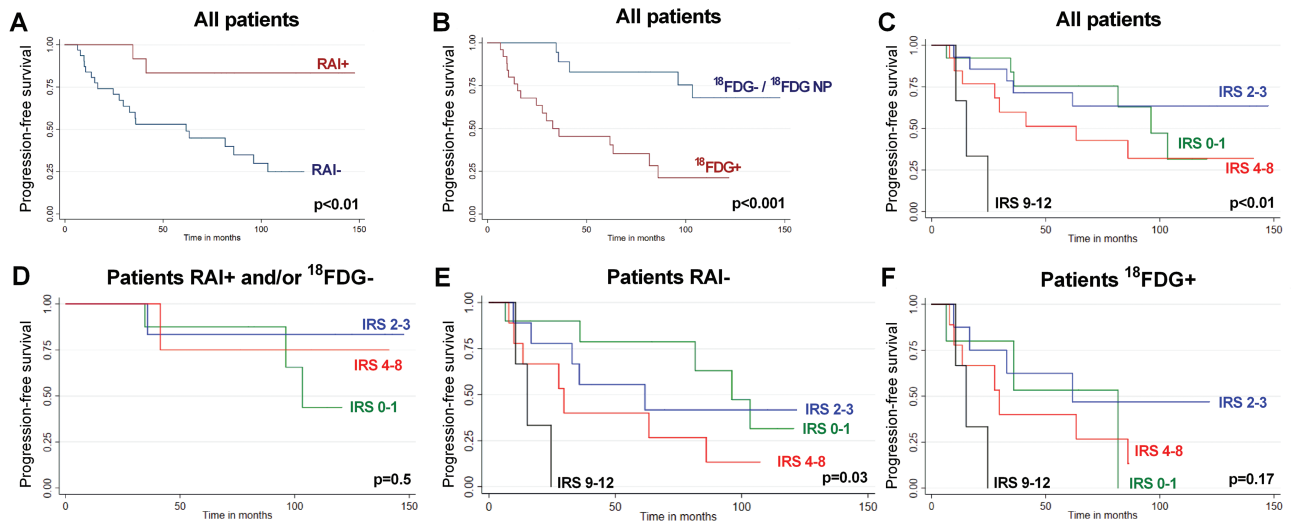

Figure 6. Progression-free survival (PFS) after neck reintervention according to (A) RAI uptake, (B) ^{18}FDG uptake, and (C) PSMA expression in 44 patients. PFS according to PSMA expression in subgroups of RAI and ^{18}FDG uptake profile are presented in panel D (patients RAI+ and/or ^{18}FDG-; n = 20), in panel E (patients RAI-; n = 32), and in panel F (patients ^{18}FDG+; n = 25).

cell positivity at 5% (23, 35). Second, PSMA expression might depend on patient selection because a high proportion of RAIR cancers would increase the proportion of PSMA-positive patients. When considering only RAIR patients, the proportion of patients with positive PSMA expression in our study (66%) is consistent with previous

reports (ie, 63% in the study by Bychkov (23) and 83% in that of Sollini (35)). Third, it was previously reported that PSMA expression might also differ according to tumor localization (ie, primary tumor, LNs, or distant metastases) (23, 25). In the present study, PSMA expression was assessed in LNs or local disease, but not in primary tumor or distant metastases. We also observed that among patients with at least 2 malignant tissue samples, 65% had different IRS values, meaning that intrapatient variability frequently occurs in cervical LN samples.

Interestingly, we were able to correlate PSMA expression with RAI and ^{18}FDG uptake, a relationship not addressed until now. The proportion of patients with a positive PSMA expression was similar in RAI-positive (75%) and RAI-negative (66%), and the mean IRS was similar in both groups. These results suggest that ^{68}Ga-PSMA PET/CT is not specific to RAIR lesions and that RAI-avid metastases are also able to take up PSMA. Verma et al. showed in 8 patients that there was a good match between RAI-positive and ^{68}Ga-PSMA-positive sites of uptake (21). Furthermore, we were able, in RAI-negative patients, to differentiate patients according to ^{18}FDG uptake. Patients with ^{18}FDG-positive PRD frequently presented positive PSMA expression (79%) in contrast to those with ^{18}FDG-negative PRD (25%). Similarly, the intensity of PSMA expression was markedly higher in patients with ^{18}FDG-positive lesions than in those with ^{18}FDG-negative lesions. These results suggest that, as with ^{18}FDG, PSMA expression might be a marker of aggressiveness in RAIR patients. PSMA-positive LNs were observed in 2 of the 8 patients with RAI-negative and ^{18}FDG-negative disease, suggesting that ^{68}Ga-PSMA PET/CT could be a useful diagnostic tool in some patients without RAI or ^{18}FDG uptake, although we acknowledge that this situation remains rare in practice. This is in line with a clinical case which reported a patient with a negative RAI scan and a negative ^{18}FDG PET but with a ^{68}Ga-PSMA PET displaying a malignant intratracheal site of uptake (18).

Furthermore, our results showed that the intensity of PSMA expression was associated with PFS and with other known poor prognostic factors, such as age, primary tumor size, and aggressive histological subtypes. In our study, patients with an outcome other than an excellent response at last follow-up visit had a higher IRS than those with an excellent response. Patients with very high PSMA expression were identified as a subgroup with shorter PFS. However, high PSMA expression did not predict survival. Such a strong PSMA expression was rarely noted in our series (ie, 10% of the patients with IRS ≥ 2) and was observed only in RAIR and ^{18}FDG-positive lesions. Similarly, very high PSMA expression was not frequent in primary thyroid tumors in the studies by Sollini and Moore (19% and < 15%, respectively) (25, 35). In a small sample of 12 malignant LNs, Moore did not observe very high PSMA expression (25). Sollini suggested that patients with very high PSMA expression could experience a higher risk of failure, but statistical significance was not reached in their study (35). Our results suggest that RAIR patients with ^{18}FDG-positive disease and very high PSMA expression represent a small subgroup of patients at higher risk of recurrence. Consequently, more intensive treatment modalities or more active follow-up might be warranted in such patients, particularly after neck reintervention. It might also be interesting to further assess PSMA expression as a surrogate marker of progression after reoperation along with other pathological or clinical variables (36).

Although retrospective, the present study focused on a group of consecutive patients assessed with post-RAI WBS with neck and thorax SPECT/CT (29) and with ^{18}FDG PET/CT (37) in most of patients, especially all RAI-negative patients. Furthermore, although only 44 patients were involved, a large malignant tissue sample series was assessed (n = 138). Moreover, patients had significant follow-up after surgery and we were able to correlate PSMA expression with outcome. One limitation is that we did not study the relationship with oncogenic mutations, such as BRAF. We also acknowledge that our cohort is a selected group of surgical patients with small tumor burden. The prognosis of such patients might be more favorable than that of those with RAIR or poorly differentiated lesions and rapidly progressive distant metastases (≥1-2 cm), in whom systemic treatments are preferred, such as tyrosine kinase inhibitors. Consequently, PSMA expression in RAIR patients might be underestimated in our series. However, our results show a frequent (79%) and high PSMA expression level in lesions with ^{18}FDG avidity (mean IRS = 4). These results are in line with the few case reports each exploring 1 to 3 RAIR patients, who underwent ^{68}Ga-PSMA PET/CT and ^{18}FDG PET/CT, and which showed good correlation between both radiopharmaceuticals (16, 21, 38).

Another limitation is that IHC data were not correlated with ^{68}Ga-PSMA PET imaging. At the time of the study, ^{68}Ga-PSMA was not available and not routinely recommended, in contrast to ^{18}FDG PET scan. It would be of interest to investigate whether a putative link exists in DTC between the level of PSMA expression and PET quantitative analysis (ie, maximum standardized uptake value). Because ^{68}Ga-PSMA PET/CT data are associated with PSMA expression in other malignancies such as prostate cancer (33) and adenoid cystic carcinoma (39), a correlation might be observed. However, unlike prostate and adenoid cystic carcinomas, PSMA expression in DTC is not present in the tumor cells themselves.

Tyrosine kinase inhibitors are usually considered in patients with progressive RAIR metastatic disease, although significant side effects may occur. In PCa, ^{68}Ga-PSMA PET/CT is used to select patients for radioligand therapy with ^{177}Lu-PSMA. A preliminary study by de Vries et al. in DTC investigated ^{177}Lu-PSMA-617 therapy in 2 RAIR patients (38). One showed disease progression on imaging and the other reported a partial response before disease progression 7 months after treatment. The authors hypothesized that the localization of PSMA uptake in the tumor neovasculature might explain these disappointing preliminary results. The intra- and interindividual heterogeneity of PSMA expression demonstrated in our study by IHC, and that can be confirmed by PSMA PET imaging, could be another explanation for these poor preliminary therapeutic results. Finally, the relatively low intensity of PSMA uptake in the neovasculature of DTC cells compared with PCa cells could account for these data. Further research is needed to assess whether ^{68}Ga-PSMA PET can provide prognostic data in RAIR patients by selecting those who would be likely to respond to ^{177}Lu-PSMA therapy.

Conclusions

This study shows that two-thirds of patients with neck PRD present malignant lesions with PSMA expression. Data suggest that PSMA expression is related to poor prognostic factors such as old age, large tumor size, aggressive histology, and ^{18}FDG uptake, and that very high PSMA expression is associated with poorer PFS. These preliminary findings could pave the way for new perspectives in the management of some RAIR thyroid cancers.

Additional Information

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