



PET/CT in thyroid carcinoma

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SUMMARY

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The diagnostic imaging procedures that have a role in detection of malignant thyroid tissue are radioiodine (¹³¹I) diagnostic whole-body scintigraphy (WBS), neck ultrasound, and CT and MRI for evaluation of the mediastinal area. Despite excellent morphologic characterization of metastatic nodal recurrences, MRI cannot reliably make a differentiation between benign and malignant lymph nodes. Although it detects enlarged metastatic lymph nodes, there are also many small nodal metastases that are usually missed. In one-third of patients with well differentiated thyroid carcinoma, there are carcinomas with dedifferentiated tumor cells: metastatic tissue may not concentrate radioiodine well; thus ¹³¹I-WBS is negative despite elevated thyroglobulin (Tg) levels. Although MRI helps in detection of these non-iodine avid metastases, FDG PET/CT can perform more effectively. Due to its high glycolytic rate, changes in glucose transport systems and hexokinase activity, [¹⁸F] fluorodeoxyglucose (FDG) accumulates in malignant tissue and is useful for identification of distant metastases in these patients. Iodine positive metastases are often negative with FDG-PET imaging while iodine negative metastases exhibit increased FDG-uptake. If a metastatic lesion is identified by FDG positron emission tomography/ computed tomography (PET/CT), the usual approach is to first send the patient to surgery for removal of neoplastic tissue, if possible. This is followed by re-treatment with ¹³¹I therapy after tumor redifferentiation with retinoic acid. In a limited number of patients, iodine negative thyroid cancer may express somatostatin receptors and radiopeptide therapy may be utilized. FDG PET/CT is a hybrid imaging diagnostic tool which helps in detection of non-iodine avid metastases. It has a role in exact localization of recurrences which will assist in the decision to remove the malignant tissue surgically.

Key words: Positron-Emission Tomography and Computed Tomography; Fluorodeoxyglucose F18; Thyroid Neoplasms; Diagnostic Imaging; Neoplasm Metastasis

Thyroid carcinoma is the most common endocrine neoplasm. It is a rare disease but the incidence is increasing during the last decades. According to a report from 2010, approximately 37,000 new cases of thyroid cancer are diagnosed in the US every year (1). Better diagnostic imaging procedures, as well as better clinical assessment, contribute to the increasing incidence of thyroid carcinoma. According to the Surveillance, Epidemiology and End Results Program (SEER) database for the period of 1988-2005, there was an increased incidence in thyroid cancers across gender, age, and tumor size, without a significant change in its mortality. This significant increase in incidence was mainly the result of better detection of papillary thyroid carcinoma, which is the most frequent histological type of thyroid cancer in the US and Europe (2).

DIAGNOSTIC PROCEDURES DURING THE FOLLOW-UP OF DIFFERENTIATED THYROID CARCINOMA (DTC)

After initial treatment of thyroid carcinoma including surgery followed by radioiodine ablation, life-long follow-up is indicated for all patients. Thyroglobulin (Tg) is a sensitive tumor marker. It plays an important role in the follow-up of DTC patients to monitor recurrent disease (3-6). Thyroglobulin under the TSH stimulation (endogenous or exogenous elevation of TSH) is considered to be the most valid indicator for persistent and/or recurrent tumor (7). Special caution is necessary when there are positive serum thyroglobulin autoantibodies since they may falsely decrease the serum Tg (8).

Ultrasound (US) and whole body scintigraphy with radioactive iodine-131 (¹³¹I-WBS) are the most frequent and useful diagnostic imaging procedures currently used to detect recurrent cancer. Ultrasound is most frequently used because it is a sensitive non-invasive diagnostic imaging tool for detection of local recurrence and cervical lymph node metastases. It should be per-

formed with fine needle aspiration biopsy (FNAB) in patients with pathologic cervical neck lymph nodes (9). Whole body scintigraphy using ¹²³I or ¹³¹I may detect recurrences in DTC patients and may help in deciding whether to use radioiodine as therapy (5,10,11). Computed tomography (CT) and magnetic resonance imaging (MRI) are used as sophisticated morphologic imaging tools to image the mediastinum. In 20%-30% of DTC, however, the tumor loses ability to accumulate radioactive iodine but can still secrete Tg (12). These tumors are less- or de-differentiated DTC tumors and consequently ¹³¹I-WBS is negative despite the increased Tg levels (11, 13, 14).

¹⁸F FDG-PET IN DTC

A modern imaging method for detection of the iodine non-avid metastases is FDG-PET. Several small series have shown that ¹⁸F-FDG-PET is efficient in detection of recurrent or metastatic disease in DTC patients with negative iodine-131 whole body scans (15-21). FDG-PET scanning is called metabolic imaging for several reasons: a) FDG accumulates in tumor cells in proportion to the glycolytic metabolic rate; b) Cancer cells generate energy by anaerobic/glycolytic metabolism, while benign cells use aerobic metabolism; c) Glycolysis is inefficient; cancer cells increase their metabolic rate to obtain enough energy for rapid replication. In a tumor, biologic changes precede morphologic changes thus allowing earlier detection of malignancy. It also makes possible evaluation of treatment response in patients with neoplasms. Recently, PET and CT image fusion became available. PET/CT combines morphologic and metabolic imaging and increases diagnostic accuracy while decreasing false positive results due to artifacts and it may guide therapeutic management (22-24). FDG PET/CT allows better anatomical localization of metastatic disease and thus may improve surgical planning and provide a target for radiation therapy. This method

has changed patient management in 44% of cases (24). Some authors suggested even higher percentages – 67% (25) to 74% (23).

In the past, several different radionuclides such as ^{201}Tl , $^{99\text{m}}\text{Tc}$ -tetrofosmin, $^{99\text{m}}\text{Tc}$ -sestamibi and ^{111}In -octreotide were used to detect recurrences in DTC patients with tumors that do not accumulate iodine (26-29). Based on low spatial resolution of single photon emitters, between 15% and 25% of recurrences were missed by these imaging tools. ^{18}F -FDG-PET, however, plays a significant role in the evaluation of non-iodine-avid recurrences in DTC patients. It is the most accurate method compared to those previously mentioned (30). High sensitivity and specificity values (between 79%-95%, and 70%-85%, respectively) have been reported (23,31-35). Lind et al. reported an increasing sensitivity of FDG-PET for the detection of recurrences, from 77% in patients with elevated Tg, to 88% in those with elevated Tg but negative ^{131}I -WBS (36). Conti et al. studied a group of 30 patients. Positive FDG PET scans were confirmed by either surgery or elevated tumor markers such as Tg in papillary carcinoma as well as elevated calcitonin in medullary carcinoma of the thyroid (37).

Feine et al. investigated 41 patients with DTC during follow-up who underwent both ^{18}F -FDG-PET and ^{131}I -WBS. Combined imaging resulted in a sensitivity of approximately 95% detection of recurrences and metastases. ^{131}I -WBS negative and PET positive; or ^{131}I -WBS positive and PET negative

was found in 90% of patients. They reported that the uptake of ^{18}F -FDG tends to be an indicator of poor tumor differentiation (33). In a multicentric study by Grunwald et al., the sensitivity and specificity of ^{18}F -FDG-PET, ^{131}I -WBS and $^{99\text{m}}\text{Tc}$ -sestamibi / ^{201}Tl -WBS were compared. They detected the sensitivity of 75%, 50%, and 53%, respectively, and specificity of 90%, 99%, and 92%, respectively. The sensitivity of FDG-PET increased to 85% in a subgroup of patients with negative ^{131}I -WBS (30). Iwata et al. compared ^{18}F -FDG-PET with $^{99\text{m}}\text{Tc}$ -sestamibi and ^{131}I post-therapy WBS. In 19 patients, a total of 32 lesions were diagnosed as metastatic disease. ^{18}F -FDG-PET, $^{99\text{m}}\text{Tc}$ -sestamibi WBS, and post-therapy ^{131}I -WBS respectively, revealed a total of 26 (81%), 20 (62.5%), and 22 (68.8%) lesions (28). Altevorder et al. analyzed 32 DTC patients with elevated Tg and negative ^{131}I -WBS and performed ^{18}F -FDG-PET in 12 patients. In 6/12 patients, PET was positive, while Tg levels were much higher in patients with PET positive findings than in those with PET negative findings (23–277 ng/ml, and 1.5–17 ng/ml, respectively) (20). At the German Consensus Conference in 2000, the sensitivity and specificity of ^{18}F -FDG-PET for detection of ^{131}I negative metastases in cases of elevated Tg were 85%–94% and 90%–95%, respectively (38). In our institution, the FDG avid metastases were detected in two patients with WBS negative-Tg positive (Figure 1 and 2).

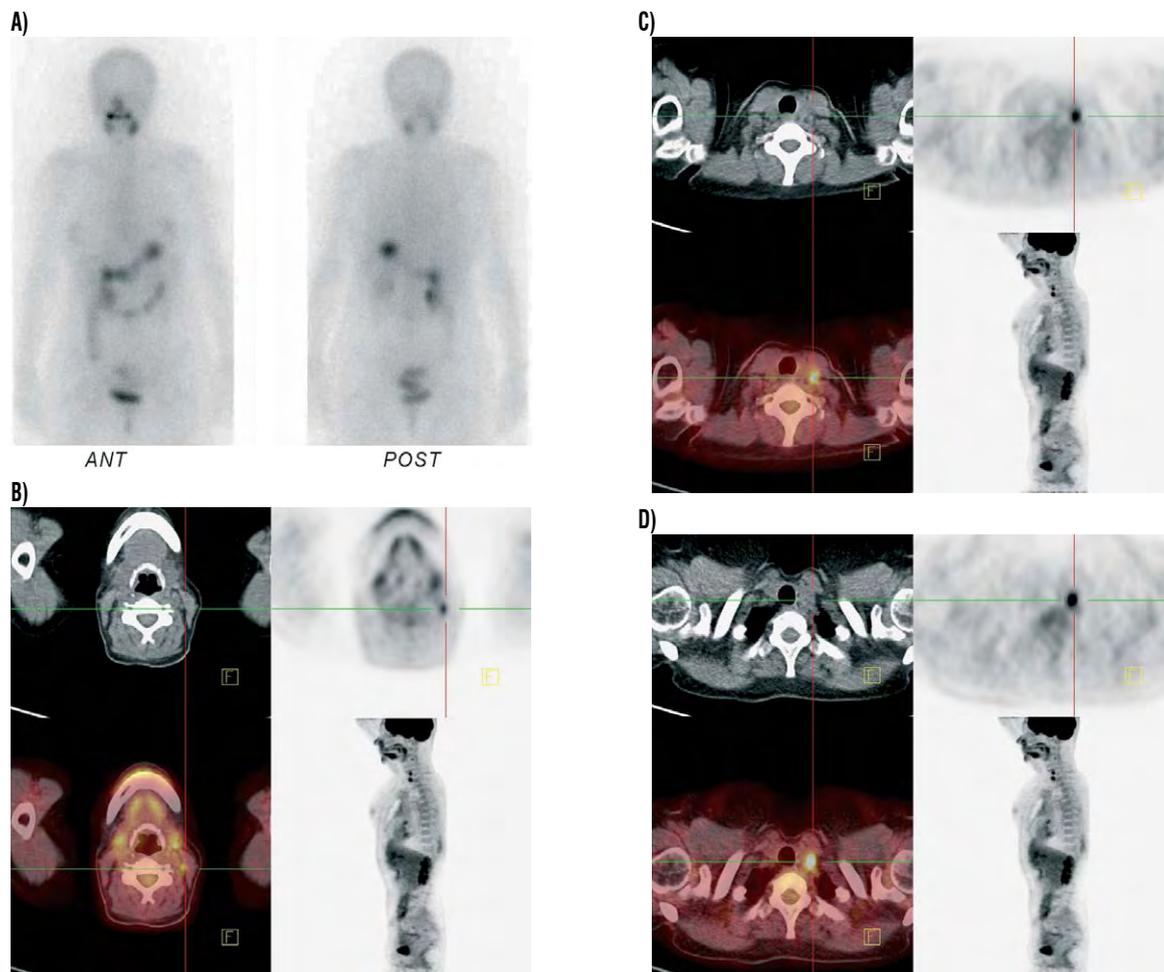


Figure 1. A 51 year-old female referred for PET/CT 4 years after near total thyroidectomy (NTT) and 3 cycles of radioiodine therapy (RAI) (the total activity of I-131 that was given is 22.2 GBq); staged as T1N1bM0/IV; Lab analysis showed increased levels of stimulated Tg (TSH >100 mIU/mL, Tg=520.7 ng/mL, TgAb=negative); A) Post therapy ^{131}I -WBS showed no pathological uptake in the neck; FDG PET/CT scan showed: B) one hypermetabolic left posterior triangular group V lymph node on the left, SUV=3.86; another two FDG avid thyroid group VI lymph nodes on the left, SUV=5.63 and SUV=6.69 (C and D).

* Patients were staged in accordance with the TNM staging system of the UICC/AJCC 6th edition

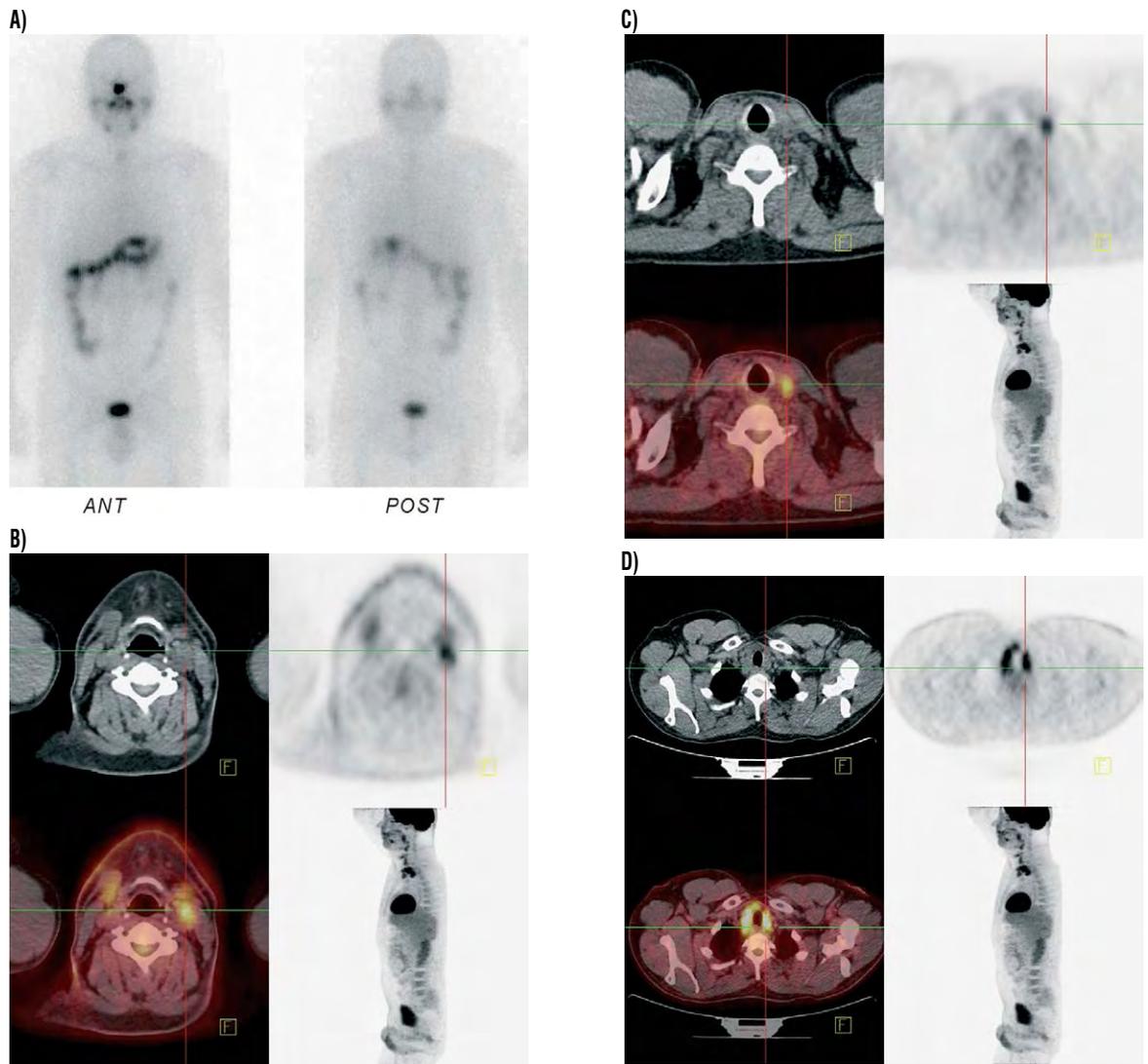


Figure 2. A 39 year-old male referred for PET/CT after NTT and 2 cycles of RAI (the total activity of I-131 that was given is 11.1 GBq); staged as T3N0M0/III; Lab analysis showed increased levels of stimulated Tg (TSH>100 mIU/mL, Tg>1000 ng/mL, TgAb=negative); A) Post therapy ^{131}I -WBS showed no pathological uptake in the neck; FDG PET/CT scan showed: B) hypermetabolic left jugular group III lymph node, SUV=4.86; C) FDG avid focus in the thyroid bed on the left, SUV=5.55; D) Multiple hypermetabolic lymph nodes in pretracheal and bilateral paratracheal area, at upper thorax aperture, SUV=7.23.

* Patients were staged in accordance with the TNM staging system of the UICC/AJCC 6th edition

Schluter et al. performed ^{18}F -FDG-PET in 64 patients with elevated Tg and negative ^{131}I -WBS. They reported that the PPV was 83% and NPV only 25%. Treatment strategy was changed in 55.9% of patients with true-positive PET scans (21).

There are a number of studies dealing with FDG sensitivity after the TSH stimulation. Wang et al. concluded that the TSH stimulation did not influence FDG-PET results (39). In a multicentric study, Grunwald et al. suggested lower FDG-PET sensitivity after thyroid hormone therapy was discontinued, compared to the continued L-thyroxine treatment (67% vs. 91%, respectively) (40).

There are experimental data suggesting that in cultured thyroid cells, the expression of GLUTs and glucose uptake is increased after the TSH stimulation. Consequently, elevated TSH raises the FDG uptake in both, time and concentration dependent manner (41-43). Some authors report higher GLUT-1 concentrations in thyroid cell membranes (44), most likely

due to GLUT translocation from the cytoplasm to the plasma membrane throughout P13-kinase activation (45, 46).

There are also some clinical studies reporting that the sensitivity of ^{18}F -FDG-PET is higher under endogenous or exogenous TSH stimulation (47,48). Thus, Moog et al. reported that FDG-PET is more sensitive under the TSH stimulation. They investigated a small group of DTC patients under T4 therapy (10 patients) and after the withdrawal of T4 therapy (TSH >22 mU/l). Target to background (T/Bg) ratio increased after the TSH stimulation from 3.85 to 5.84 with a significant difference ($p < 0.001$) (47). Petrich et al. studied a group of 30 patients with elevated Tg and negative ^{131}I -WBS. They reported greater tumor to background ratios and SUV after the TSH stimulation of 5.51 vs. 2.54 and 2.77 vs. 2.05, respectively (48).

^{124}I PET/CT imaging is a promising diagnostic tool to improve treatment strategy, and can be combined with tumor dosimetry in DTC patients with metastatic disease (49).

CONCLUSION

FDG-PET and FDG-PET/CT are modern imaging tools that depict metabolic activity. FDG PET is combined with anatomic imaging when fused with CT (PET/CT) and plays a role in the follow-up of DTC patients. It provides an alternate approach to the management of ^{131}I negative, Tg positive DTC patients. Since ^{18}F FDG uptake correlates with tumor aggressiveness, dedifferentiated lesions that show the greatest uptake are prediction of a poor prognosis. The sensitivity of ^{18}F FDG-PET for the detection of DTC recurrence is higher under the TSH stimulation.

Conflict of interest

We declare no conflicts of interest.

REFERENCES:

- Altekruse S, Kosary C, Krapcho M, et al. SEER cancer statistics review, 1975-2007. Bethesda, MD, National Cancer Institute (based on November 2009 SEER data submission, posted to the SEER web site, 2010). Available from: <http://seer.cancer.gov.csr/1975-2007/>. Accessed November 9, 2010.
- Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer*. 2009;115:3801-7.
- Van Herle AJ, Uller RP. Elevated thyroglobulin: a marker of metastases in differentiated thyroid carcinoma. *J Clin Invest*. 1975;56:272-6.
- Pacini F, Lari R, Mazzeo S, et al. Diagnostic value of single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. *Clin Endocrinol (Oxf)*. 1985;23:405-8.
- Ronga G, Fiorentino A, Paserio E, et al. Can iodine-131 whole body scan be replaced by thyroglobulin measurement in the postsurgical follow up of differentiated thyroid carcinoma? *J Nucl Med*. 1990;31:1766-71.
- Ozata M, Suzuki S, Miyamoto T, et al. Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. *J Clin Endocrinol Metab*. 1994;79:98-105.
- Pacini F. Follow up of differentiated thyroid cancer. *Eur J Nucl Med*. 2002;(Suppl 2):S492-S496.
- Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 1998;83:1121-7.
- Haber RS. Role of ultrasonography in the diagnosis and management of thyroid cancer. *Endocr Pract*. 2000;6:396-400.
- Filesi M, Signore A, Ventroni G, et al. Role of initial iodine-131 whole body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. *J Nucl Med*. 1998;39:1542-6.
- Aschraft MW, Van Herle AJ. The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow up study of patients with treated differentiated thyroid cancer. *Am J Med*. 2001;42:1464-9.
- Meng-Jie D, Zhen-Feng L, Zhao K, et al. Value of 18F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: a meta-analysis. *Nucl Med Commun*. 2009;30:639-50.
- Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic ^{131}I whole body scan: comparison of patients treated with high ^{131}I activities versus untreated patients. *J Clin Endocrinol Metab*. 2001;86:4092-7.
- Schlumberger M, Arcangioli O, Piekarski JD, et al. Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest x-rays. *J Nucl Med*. 1988;29:1790-4.
- Mirallie E, Guilan T, Bridji B, et al. Therapeutic impact of 18FDG-PET/CT in the management of iodine-negative recurrence of differentiated thyroid carcinoma. *Surgery*. 2007;142:952-8.
- Freudenberg LS, Antoch G, Frilling A, et al. Dual-modality FDG-PET/CT in follow-up of patients with recurrent iodine-negative differentiated thyroid cancer. *Eur Radiol*. 2007;17:3139-47.
- Uematsy H, Sadato N, Ohtsubo T, et al. Fluorine-18-fluorodeoxyglucose PET versus thallium-201 scintigraphy evaluation of thyroid tumors. *J Nucl Med*. 1998;39:453-9.
- Matsuno N, Minoshima S, Imazeki K. Diagnostic value of F18-FDG PET in primary and metastatic thyroid cancer. *J Nucl Med*. 1995;36:196P.
- Finkelstein SE, Grigsby PW, Siegel BA, et al. Combined (18F) fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) for detection of recurrent, 131 I-negative thyroid cancer. *Ann Surg Oncol*. 2008;15:286-92.
- Aletvoerde G, Lerch H, Kuwert T, et al. Positron emission tomography with F-18-deoxyglucose in patients with differentiated thyroid carcinoma, elevated thyroglobulin levels and negative iodine scans. *Langenbecks Arch Surg*. 1998;383:160-3.
- Schlutter B, Bohuslavizki KH, Beyer W, et al. Impact of FDG PET on patients with well differentiated thyroid cancer who present with elevated thyroglobulin and negative I-131 scan. *J Nucl Med*. 2001;42:71-6.
- Lind P, Kohlfurst S. Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. *Sem Nucl Med*. 2011;36:194-205.
- Palmedo H, Bucerius J, Joe A, et al. Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management. *J Nucl Med*. 2006;47:616-24.
- Shammas A, Degirmenci B, Mountz JM, et al. 18 F-FDG PET/CT in patients with suspected recurrent or metastatic well-differentiated thyroid cancer. *J Nucl Med*. 2007;48:221-6.
- Nahas Z, Goldenberg D, Fakhry C, et al. The role of positron emission tomography/computed tomography in the management of recurrent papillary thyroid carcinoma. *Laryngoscope*. 2005;115:237-43.
- Baudin E, Schlumberger M, Lumbroso J, et al. Octreotide scintigraphy in patients with differentiated thyroid carcinoma: contribution for patients with negative radioiodine scan. *J Clin Endocrinol Metab*. 1996;81:2541-4.
- Carril JM, Quirce R, Serrano J, et al. Total-body scintigraphy with thallium-201 and iodine-131 in the follow-up of differentiated thyroid cancer. *J Nucl Med*. 1997;38:686-92.
- Iwata M, Kasagi K, Misaki T, et al. Comparison of whole-body ^{18}F -FDG PET, $^{99\text{m}}\text{Tc}$ -MIBI SPET, and post-therapeutic ^{131}I -Na scintigraphy in the detection of metastatic thyroid cancer. *Eur J Nucl Med Mol Imaging*. 2004;31:491-8.
- Unal S, Menda Y, Adalel I, et al. Thallium-201, technetium-99m-tetrofosmin and iodine-131 in detecting differentiated thyroid carcinoma metastases. *J Nucl Med*. 1998;39:1897-552.
- Grunwald F, Menzel C, Bender H, et al. Comparison of ^{18}F FDG-PET with 131-iodine and 99m Tc-sestamibi scintigraphy in differentiated thyroid cancer. *Thyroid*. 1997;7:327-35.

- 31 Grunwald F, Schomburg A, Bender H, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med.* 1996;23:312-9.
- 32 Scott GC, Meier DA, Dickinson CZ. Cervical lymph node metastasis of thyroid papillary carcinoma imaged with fluorine-18-FDG. Technetium-99m-pertechnetate and iodine-131-sodium iodide. *J Nucl Med.* 1995;36:1843-5.
- 33 Feine U, Lizenmayer R, Hanke JP, et al. Fluorine-18 FDG and iodine-131 uptake in thyroid cancer. *J Nucl Med.* 1996;37:1468-72.
- 34 Wang W, Macapinlac H, Larson SM, et al. (18F)-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic ¹³¹I whole body scans and elevated serum thyroglobulin levels. *J Clin Endocrinol Metab.* 1999;84:2291-302.
- 35 Chung JK, So Y, Lee JS, et al. Value of FDG PET in papillary thyroid carcinoma with negative I-131 whole-body scan. *J Nucl Med.* 1999;40:986-92.
- 36 Lind P, Kresnik E, Kumnig G, et al. F-18-FDG PET in following up thyroid cancer. *Acta Med Austriaca.* 2003;30:17-21.
- 37 Conti PS, Durski JM, Bacqai F, et al. Imaging of locally recurrent and metastatic thyroid cancer with positron emission tomography. *Thyroid.* 1999;9:797-804.
- 38 Reske SN, Kotzerke J. FDG PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, "Onko PET III", 21. July and 19. September 2000. *Eur J Nucl Med.* 2001;28:1707-23.
- 39 Wang W, Macapinlac H, Larson SM, et al. (18F)-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (¹³¹I) whole body scans and elevated serum thyroglobulin levels. *J Clin Endocrinol Metab.* 1999;84:2291-302.
- 40 Grunwald F, Kalicke T, Feine U, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicentre study. *Eur J Nucl Med.* 1999;26:1547-52.
- 41 Filletti S, Damante G, Foti D. Thyrotropin stimulates glucose transport in cultured rat thyroid cells. *Endocrinology.* 1988;120:2576-81.
- 42 Haraguchi K, Rani CS, Field JB. Effects of thyrotropin, carbachol, and protein kinase C stimulators on glucose transport and glucose oxidation by primary cultures of dog thyroid cells. *Endocrinology.* 1988;123:1288-95.
- 43 Deichen JT, Schmidt C, Prante O, et al. Influence of TSH on uptake of (18F) fluorodeoxyglucose in human thyroid cells in vitro. *Eur J Nucl Med Mol Imaging.* 2004;31:507-12.
- 44 Prante O, Maschauer S, Fremont V, et al. Regulation of uptake of 18F-FDG by a follicular human thyroid cancer cell line with mutation-activated K-ras. *J Nucl Med.* 2009;50:1364-70.
- 45 Blaser D, Maschauer S, Kuwert T, et al. In vitro studies on the signal transduction of thyroidal uptake of 18F-FDG and 131 I-iodide. *J Nucl Med.* 2006;47:1382-8.
- 46 Samih N, Hovsepian S, Aouani A, et al. Glut-1 translocation in FRTL-5 thyroid cells: role of phosphatidylinositol 3-kinase and N-glycosylation. *Endocrinology.* 2000;141:4146-55.
- 47 Moog F, Linke R, Manthey N, et al. Influence of thyroid-stimulating hormone levels on uptake of FDG in recurrent and metastatic differentiated thyroid carcinoma. *J Nucl Med.* 2000;41:1989-95.
- 48 Petrich T, Borner AR, Weckesser E. Follow up of thyroid cancer patients using rhTSH –preliminary results. *Nucl Med.* 2001;40:7-14.
- 49 Abraham T, Schroder H. Thyroid cancer-indications and opportunities for positron emission tomography/computed tomography imaging. *Semin Nucl Med.* 2011;41:121-38.