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Is it practical and cost effective to detect differentiated thyroid carcinoma metastases by ^{18}F-FDG PET/CT, by ^{18}F-FDG SPET/CT or by ^{131}I SPET/CT?

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Hell J Nucl Med 2015; 18(1): 2-4 *Epub ahead of print: 13 February 2015* *Published online: 31 March 2015*

Fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography/computerized tomography (^{18}F-FDG PET/CT) plays an important role in detecting differentiated thyroid carcinoma (DTC) metastases with elevated thyroglobulin (Tg) and negative radioiodine (^{131}I) uptake. On the other hand, ^{18}F-FDG single photon emission tomography/CT (^{18}F-FDG SPET/CT) is also effective and has a comparatively lower expense and possible reimbursement paid by the government as is the case in China. The efficiency of the above-mentioned scanning techniques is compared with the whole body ^{131}I SPET/CT scan in detecting DTC metastases. It seems that both ^{18}F-FDG SPET/CT and ^{131}I SPET/CT are practical and cost effective to detect DTC metastases instead of ^{18}F-FDG PET but ^{131}I SPET/CT is cheaper and has a lower radiation burden, compared to ^{18}F-FDG SPET/CT. Therefore, ^{131}I SPET/CT may be preferred and is at present recommended and reimbursed in China as the first choice modality for diagnosing DTC metastatic disease. The overall usual protocol now is ^{131}I imaging, SPET/CT and Tg measurements. Future studies may address the choice of ^{131}I SPET/CT with more patients studied and be related to the actual mechanism of uptake of the radionuclide to DTC metastases.

Bone metastases from DTC occur in 2%-13% of the patients, mainly in the spine [1]. Nearly half of patients with bone metastases from thyroid cancer develop vertebral metastases. Spinal metastases are associated with significantly reduced quality of life due to pain, neurological deficit, and increased mortality [2]. For the detection of bone metastases in patients with DTC, it has been reported that the sensitivity of ^{18}F-FDG PET/CT is significantly lower than that of ^{18}F-fluoride PET/CT [1]. A recent study showed that a significant part of DTC patients has asolitary spinal involvement at the time of presentation and may be considered for aggressive treatment with the intention to improve quality of life and survival [2, 3].

Diagnostic surveillance for DTC metastases includes a ^{131}I whole body scan (^{131}I WBS) and measurement of serum Tg levels after endogenous or exogenous TSH stimulation. These metastases are usually positive for ^{131}I uptake and negative for ^{18}F-FDG PET uptake, whereas poorly differentiated thyroid carcinomas are negative for ^{131}I uptake and positive for ^{18}F-FDG uptake [4, 5]. On the other hand, DTC metastases with elevated Tg and negative ^{131}I uptake may be detected by ^{18}F-FDG PET/CT or SPET/CT scan [4-6]. The discrepancies between the uptakes of ^{18}F-FDG and ^{131}I in detecting metastases of DTC, which were called flip-flop phenomena have been observed and reviewed by us previously [5-7]. The uptake of ^{18}F-FDG in DTC metastases indicates the dedifferentiation of the carcinoma. Fluorine-18-FDG SPET/CT is useful in DTC patients with elevated Tg and negative ^{131}I WBS metastases [8]. A recent study has shown that ^{18}F-FDG PET/CT detected additional lesions in 14%, 40 of 286 patients with DTC [9]. On the other hand, the cost of the ^{18}F-FDG PET/CT scan in China is 1132$ while for the ^{18}F-FDG SPET/CT scan is 461$. The ^{18}F-FDG SPET/CT scan is commonly used in China since 2001 not only because of its lower expense but also because of its possible reimbursement by the government for detecting malignant disease. It is also simpler to detect DTC metastases by ^{18}F-FDG SPET/CT. The cost of the equally effective ^{131}I SPET/CT scan comparatively is only 200$. The ^{131}I SPET/CT scan after ^{131}I treatment causes no additional radiation burden as compared to ^{18}F-FDG SPET/CT or ^{18}F-FDG PET/CT who emit radiation by ^{18}F and CT. The effective dose of ^{18}F-FDG PET/CT to an adult is

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~0.019mSv/MBq [10]. All these advantages make ^{131}I SPET/CT scan an important diagnostic tool for thyroid cancer staging and risk stratification [11] better than ^{18}F-FDG SPET/CT. Iodine-131 SPET/CT is often used post-therapy in DTC patients with suspicious cervical lymph nodes, 4-5 days after the ^{131}I WBS, while ^{18}F-FDG SPET/CT is commonly used for stage T3 or T4 DTC patients at regular follow-up.

We refer here to a recent case of ours of detecting DTC metastases in a 43 years old man, who had been treated 8 times with 5.5GBq by ^{131}I, for having lung metastases. His Tg was 1321.59ng/mL and TSH 129μIU/mL. Post-therapy ^{131}I WBS showed multiple functioning metastases in the left parotid gland and the left mandible, in both lungs and the thoracic vertebrae (Figure 1A). The pre-therapy ^{18}F-FDG SPET/CT was performed. The post-therapy transverse images of ^{131}I SPET/CT (Figure 1B) and of ^{18}F-FDG SPET/CT also showed the same metastases (Figure 2). Histopathology confirmed the above (Figure 3 A and B). Of the three mentioned modalities both ^{131}I SPET/CT and ^{18}F-FDG SPET/CT better showed these metastases and also lung metastases. It is worth mentioning that for the above case, DTC metastases were diagnosed both by ^{131}I and ^{18}F-FDG SPET/CT scans which have been reported for the first time.

In DTC patients lymph nodes metastases are an important prognostic factor for tumor recurrence, indicating poor prognosis [4]. Usually DTC metastases are of the papillary type and appear in the regional lymph nodes (30%-80%) and less often in the lungs [12-14]. Therefore, long-term monitoring of patients with DTC is essential throughout the patient's life after total or nearly total thyroidectomy followed by ^{131}I remnant ablation and suppression of TSH [5-7]. Sensitive surveillance for DTC recurrence and metastases includes diagnostic ^{131}I WBS and SPET/CT and measurement of serum Tg levels after endogenous or exogenous TSH stimulation. The ^{131}I SPET/CT scan determines more accurately the site and size of cervical lymph node metastases and of distant metastases than ^{131}I WBS alone, although this usually does not change the therapeutic procedure [15, 16]. The ^{131}I SPET/CT scan is also valuable in finding rare metastases from DTC including brain [17], eye, breast, liver, kidney, muscle and skin [18]. It seems that ^{131}I SPET/CT scan is an important diagnostic tool for thyroid cancer staging and risk stratification [9, 10], while ^{18}F-FDG SPET/CT as in the above example may fail to detect the lung metastases. Therefore, post-therapy ^{131}I WBS and SPET/CT are highly recommended for the appropriate management of DTC patients who have undergone total thyroidectomy [19].

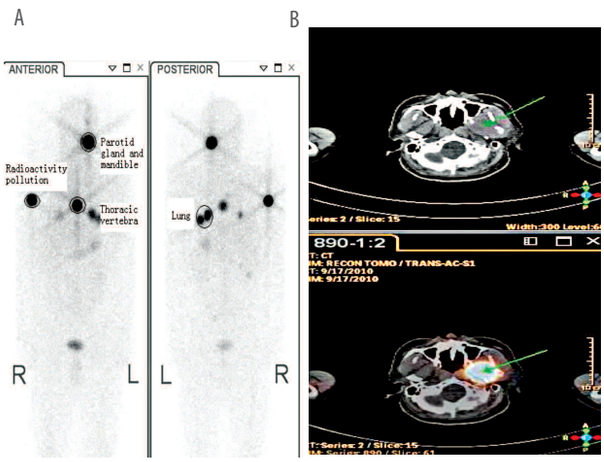

Figure 1. Post-therapy ^{131}I SPET/CT whole body scan (A) and transverse images (B).

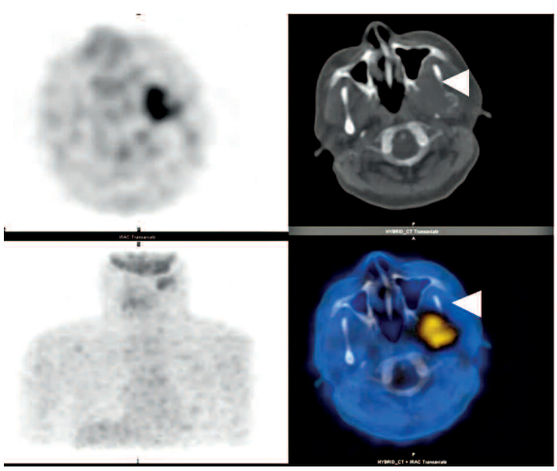

Figure 2. Pre-therapy ^{18}F-FDG SPET/CT scan showing the parotid and mandibular DTC metastases but no lung metastases.

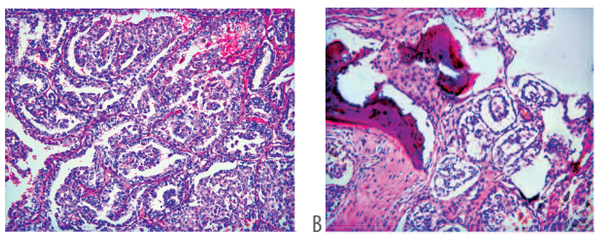

Figure 3. Histopathology showed DTC metastases in the parotid (A) and the mandible (B).

Salivary gland cells, which are similar to thyroid gland cells, also express NIS protein and are capable of accumulating iodide, albeit to a lesser degree [20]. The differentiated diagnosis should be made between the primary tumor with false positive ^{131}I and/or ^{18}F-FDG uptake [21-23] and DTC metastases [24-29].

In conclusion, ^{18}F-FDG PET/CT may fail to detect all DTC metastases, while ^{131}I WBS combined with^{131}I SPET/CT may be a better cheaper diagnostic tool as suggested by the case we presented here. Positive metastases in both ^{131}I and ^{18}F-FDG SPET/CT may indicate worse prognosis. Future research may add more evidence as to which is the best diagnostic imaging modality and relate it to the molecular mechanism of the uptake of the radionuclide used.

The authors declare that they have no conflicts of interest.

Bibliography

1. Ota N, Kato K, Iwano S et al. Comparison of ^{18}F-fluoride PET/CT, ^{18}F-FDG PET/CT and bone scintigraphy (planar and SPECT) in detection of bone metastases of differentiated thyroid cancer: a pilot study. *Br J Radiol* 2014; 87(1034): 20130444.
2. Kushchayeva YS, Kushchayev SV, Wexler JA et al. Current treatment modalities for spinal metastases secondary to thyroid carcinoma. *Thyroid* 2014; 24(10): 1443-55.
3. Kushchayeva YS, Kushchayev SV, Carroll NM et al. Spinal metastases due to thyroid carcinoma: an analysis of 202 patients. *Thyroid* 2014; 24(10): 1488-500.

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4. Ma C, Kuang AR, Xie J. Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases. *Cochrane Database Syst Rev* 2009; 21(1): CD006988.
5. Ma C. Management of differentiated thyroid cancer with rising thyroglobulin and negative diagnostic radioiodine whole body scan. *Clin Oncol* (R Coll Radiol) 2010; 22(6): 438-47.
6. Ma C,Xie J, Kuang A. The Possible Explanations for Patients with Dis cordant Findings of Serum Thyroglobulin and ^{131}I Whole-body Scan. *J Nucl Med* 2005; 46(9): 1473-80.
7. Lim CY, Sohn EJ, Lee J et al. The significant predicting factors influencing lateral neck node metastasis in papillary thyroid carcinoma. *J Korean Surg Soc* 2006; 71: 326-30.
8. Ma C, Wang X, Shao M et al.^{18}F-FDG SPECT/ CT in the diagnosis of dif ferentiated thyroid carcinoma with elevated thyroglobulin and negative iodine-131 scans. *Q J Nucl Med Mol Imaging* 2014 May 21. [Epub ahead of print]
9. Lee JW, Lee SM, Lee DH et al. Clinical utility of ^{18}F-FDG PET/CT con current with ^{131}I therapy in intermediate-to-high-risk patients with differentiated thyroid cancer: dual-center experience with 286 patients. *J Nucl Med* 2013; 54(8): 1230-6.
10. ICRP Publication 80. Radiation dose to patients from radiopharmaceuticals. *Annals of ICRP* 1998; 28: 3.
11. Avram AM. Radioiodine scintigraphy with SPECT/CT: an important diagnostic tool for thyroid cancer staging and risk stratification. *J Nucl Med Technol* 2014; 42(3): 170-80.
12. Jun HH, Kim SM, Kim BW et al. Overcoming the limitations of fine needle aspiration biopsy: detection of lateral neck node metastasis in papillary thyroid carcinoma. *Yonsei Med J* 2015; 56(1): 182-8.
13. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin En docrinol Metab* 2001; 86: 1447-63.
14. Kim E, Park JS, Son KR et al. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid* 2008; 18: 411-8.
15. Mizokami D, Kosuda S, Shiotani A et al. Impact of ^{131}I SPECT/CT on the management of differentiated thyroid carcinoma outpatients with radioablation. *Nihon Jibiinkoka Gakkai Kaiho* 2014; 117(5): 673-80.
16. Xu YH, Shen CT, Xue YL et al. Iodine-131 SPET/CT and ^{18}F-FDGPET/CT for the identification and localization of mediastinal lymph node metastases from differentiated thyroid carcinoma. *Hell J Nucl Med* 2013; 16(3): 199-203.
17. Xu YH, Song HJ, Qiu ZL, Luo QY. Brain metastases with exceptional features from papillary thyroid carcinoma: report of three cases. *Hell J Nucl Med* 2011; 14(1): 56-9.
18. Song HJ, Xue YL, Qiu ZL, Luo QY. Uncommon metastases from differentiated thyroid carcinoma. *Hell J Nucl Med* 2012; 15(3): 233-40.
19. Moon SH, Oh YL, Choi JY. Comparison of ^{18}F-Fluorodeoxyglucose uptake with the expressions of glucose transporter type 1 and Na+/I- symporter in patients with Untreated Papillary Thyroid Carcinoma. *Endocr Res* 2013; 38(2): 77-84.
20. La Perle KM, Kim DC, Hall NC et al. Modulation of sodium/iodide symporter expression in the salivary gland. *Thyroid* 2013; 23(8): 1029-36.
21. Broekhuizen-de Gast H, van Isselt H, Roef M et al. Oncocytoma of the parotid gland causing false-positive result on I-131 whole-body scintigraphy. *Clin Nucl Med* 2011; 36(8): 701-3.
22. Gekeler J, Luers JC, Krohn T et al. False positive findings in F-18 FDG PET and whole body scans with I-131 in Warthin tumor of the parotid gland. *Clin Nucl Med* 2010; 35(2): 105-6.
23. Caglar M, Tuncel M, Usubutun A. Increased uptake on I-131 whole-body scintigraphy in Warthin tumor despite false-negative Tc-99m pertechnetate salivary gland scintigraphy. *Clin Nucl Med* 2003; 28(11): 945-6.
24. Cao X. Two cases of parotid gland metastases from papillary thyroid cancer. *J Chinese Clin Stomatol* 1990; 4: 196.
25. Wang G, Chen H, Xu G.. Parotid gland metastases of papillary thyroid cancer. *West China J Stomatol* 1990; 4: 286.
26. Pasupula AP, Dorankula SP, Thokala MR et al. Metastatic follicular thyroid carcinoma to the mandible. *Indian J Dent Res* 2012; 23(6): 843.
27. Algahtani M, Alqudah M, Alshehri S et al. Pathologic fracture of the mandible caused by metastatic follicular thyroid carcinoma. *J Can Dent Assoc* 2009; 75(6): 457-60.
28. Vishveshwaraiah PM, Mukunda A, Laxminarayana KK et al. Metastatic follicular thyroid carcinoma to the body of the mandible mimicking an odontogenic tumor. *J Cancer Res Ther* 2013; 9(2): 320-3.
29. Anil S, Lal PM, Gill DS et al. Metastasis of thyroid carcinoma to the mandible. Case report. *Aust Dent J* 1999; 44(1): 56-7.