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Management of thyroid cancer associated with elevated serum thyroglobulin and negative radioiodine scanning

Aim: Differentiated thyroid carcinoma has a favorable prognosis, even in the presence of distant metastases, if the tumor cells are able to concentrate radioiodine. Nonetheless, up to 30% of thyroid cancer patients with elevated serum thyroglobulin (Tg) and negative radioiodine whole-body scan findings represent a diagnostic dilemma. In this study we assessed the diagnostic contribution of anatomical and functional imaging procedures, including US of the thyroid bed and neck, CT scanning of the chest and mediastinum, and FDG PET whole-body scanning, in iodine-negative/Tg-positive thyroid cancer patients.

Materials and methods: The study included 28 patients (20 female, 8 male; age range: 21-85 years; mean age: 56 years) with a proven diagnosis of thyroid carcinoma. The pathological diagnosis was papillary carcinoma in 26 patients, and Hurtle-cell carcinoma and poorly differentiated thyroid carcinoma, respectively, in the 2 remaining patients. All patients had undergone thyroid surgery and subsequent high-dose radioablation 3-8 years before participating in the study. In all, 27 patients presented with elevated serum Tg levels (3.1-3080 ng/mL, median 93) and 1 presented with multiple metastatic lesions in the lungs, despite the fact that Tg was within normal limits. All patients had a US examination of the thyroid bed and neck to determine if locoregional persistent disease was present. The patients were scheduled for high-dose radioiodine treatment because Tg was elevated after cessation of L-thyroxin for approximately 6 weeks. Those with a negative or equivocal post-treatment scan proceeded to whole-body 18-fluorodeoxyglucose PET. We assessed the diagnostic contribution of imaging procedures, including US of the thyroid bed and neck, CT of the chest and mediastinum, and PET, in patients that presented with elevated Tg levels and negative radioiodine scanning.

Results: In total, 62 tumor sites were identified in the thyroid bed and neck (7 patients), lung and mediastinum (6 patients), both in the neck and lungs (5 patients), lung and bone (2 patients), neck and bone (1 patient), and neck, lung, and bone (1 patient). In 6 patients no thyroid tumor was detected with any imaging modality. US was useful in detecting cervical lymph nodes in 14 patients and CT revealed metastatic foci in the lung and mediastinum, and bone in 15 patients. In 25 patients post-treatment scanning was negative and in 3 there was faint uptake in the neck. FDG-PET revealed thyroid tumor sites in 18 patients; however, it was false-positive in 3 cases and missed 2 cervical adenopathies and 1 metastatic bone lesion.

Conclusion: US and CT provided diagnostic information for detecting cervical adenopathy and metastatic lesions in the lungs and mediastinum, respectively. PET complemented the existing anatomical findings and enabled whole-body scanning in a single imaging session. It was particularly useful in detecting iodine-negative differentiated thyroid cancer associated with elevated serum Tg levels, thereby facilitating appropriate treatment.

Key words: Thyroid cancer, thyroglobulin, FDG-PET, radioiodine scanning

Yüksek serum tiroglobulini ve negatif radyoaktif iyot taramasıyla beraber olan tiroit kanserlerinin yönetimi

Amaç: Diferansiye tiroit karsinomaları uzak metastaz varlığında bile eğer tümör hücreleri radyoaktif iyot tutabiliyorsa iyi bir prognoza sahiptir. Ancak, yüksek serum tiroglobulin düzeyi ve negatif radyoaktif tüm vücut tarama bulguları olan tiroit kanser hastalarının % 30 kadarında tanı koymak sıkıntılıdır. Bu çalışmada, iyot negatif/tiroglobulin pozitif tiroit kanser hastalarında tiroit yatağı ve boyun ultrasonu, göğüs ve mediastinum BT ve tüm vücut FDG-PET taramasını içeren anatomik ve fonksiyonel görüntüleme tekniklerinin tanısal değeri araştırılmıştır.

Yöntem ve gereçler: Kanıtlanmış tiroit karsinomalı 28 hasta (20 kadın, 8 erkek; yaş aralığı, 21-85 yaş; ortalama, 56) çalışmaya dahil edildi. 26 hastada patolojik tanı papiller kanser, kalan iki hastada Hurtle-hücreli karsinoma ve az diferansiye tiroit kanseridir. Çalışmadan 3-8 yıl öncesi tüm hastalara tiroit cerrahisi yapılmış ve bunu izleyen dönemde yüksek doz radyoablasyon uygulanmıştır. Hastaların 27'sinde serum tiroglobulin düzeylerinde yükseklik (3,1-3080 ng/mL, median 93) ve birinde tiroglobulin normal sınırlarda olmasına rağmen akciğerde birden fazla metastatik lezyon saptandı. Tüm hastalarda tiroit yatağı ve boyun ultrasonu ile boyunda kalıntı hastalık veya nüks araştırıldı. Yaklaşık 6 haftalık levotiroksin kullanımının kesilmesinden sonra serum tiroglobulin yüksekliği nedeniyle yüksek doz radyoaktif iyot tedavisi için planlama yapıldı. Tedavi sonrası taraması negatif veya şüpheli olan hastalara tüm vücut 18-florodeoksiglukoz pozitron emisyon tomografisi çekildi. Bu çalışmada artmış tiroglobulin düzeyleri ve negatif radyoaktif iyot taraması olan hastalarda boyun ultrasonu, göğüs ve mediastinum bilgisayarlı tomografisi ve pozitron emisyon tomografisini içeren görüntüleme tekniklerinin tanıya katkısı araştırılmıştır.

Bulgular: Tiroit yatağı ve boyunda (7 hasta), akciğer ve mediastinumda (6 hasta), boyun ve her iki akciğerde (5 hasta), akciğer ve kemikte (2 hasta), boyun ve kemikte (1 hasta), boyun, akciğer ve kemikte (1 hasta) olmak üzere toplam 62 tümör odağı saptanmıştır. 6 hastada hiçbir görüntüleme yöntemi ile tiroit tümörü saptanamadı. Ultrason ile 14 hastada boyundaki lenf nodları, bilgisayarlı tomografi ile 15 hastada akciğer, mediastinum ve kemikteki metastatik odaklar gösterildi. 25 hastada tedavi sonrası tarama negatifti ve sadece üç hastada boyunda hafif bir tutulum mevcuttu. FDG-PET ile 18 hastada tümör odağı gösterilebildi; ancak 3 hastada yanlış pozitif sonuç verirken ikisinde servikal adenopati ve birinde metastatik kemik lezyonunu tespit edemedi.

Sonuç: Ultrason servikal adenopati, bilgisayarlı tomografi akciğer ve mediastinumdaki metastatik lezyonları saptamada tanıya katkıda bulunmuştur. Pozitron emisyon tomografisi, mevcut anatomik bulgulara katkıda bulunmuş ve tek bir görüntüleme seansı ile tüm vücudu taramaya imkan vermiştir. Ancak özellikle yüksek serum tiroglobulin düzeyleri ile birlikte olan iyot-negatif diferansiye tiroit kanserlerinin saptanmasında ve uygun tedavinin seçilmesinde faydalıdır.

Anahtar sözcükler: Tiroit kanseri, tiroglobulin, FDG-PET, radyoaktif iyot tarama

Introduction

Thyroid cancer is the most common endocrine tumor, accounting for 1%-3% of all human malignancies (1). Total thyroidectomy followed by radioablation is well established as the initial treatment of differentiated thyroid cancer. The overall prognosis is favorable, even in case of distant metastasis, if the thyroid tumor sites are able to trap radioiodine (2,3); however, in up to 50% of thyroid cancer patients locoregional or distant metastases are detected and about 8% of them eventually die of this disorder (4).

The sequential measurement of serum thyroglobulin (Tg) levels and low-dose diagnostic radioiodine whole-body scanning (dxRIS) are useful for monitoring thyroid cancer patients during the surveillance period after initial treatment. The sensitivity of Tg is as high as 98% under TSH stimulation in the absence of circulating anti-Tg antibodies. The sensitivity of radioiodine scanning tends to be as high as 96%-100%, although its specificity may be as low as 45% because of dedifferentiation of the original tumor cells in up to 30% of patients (40% in patients over 65 years), a process rendering them unable to concentrate radioiodine. (5). Therefore, thyroid cancer patients with elevated serum Tg and negative radioiodine scanning results present a diagnostic dilemma. In the present study we assessed the diagnostic contribution of anatomical and functional imaging procedures, including ultrasound (US) of the thyroid bed and neck, and computerized tomography (CT) of the chest and mediastinum, as compared with those of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in Tg-positive iodine-negative patients.

Materials and methods

The study included 28 patients with proven DTC (20 female, 8 male; age range: 21-85 years; mean age: 56 years). Pathological diagnosis was papillary in 26 patients, (including the tall cell variant in 2), Hurtle-cell carcinoma in 1, and poorly differentiated thyroid cancer in 2. The patients had undergone thyroid surgery and radioablation 3-8 years earlier and the efficiency of the initial treatment was monitored with sequential serum Tg measurement. During the surveillance period 27 patients presented with elevated serum Tg (> 2 ng/mL) and 1 patient (no: 27) had a metastatic lung lesion, although his Tg measurement was below the normal limit (0.5 ng/mL). All patients underwent US of the thyroid bed and neck as the first-line anatomical imaging procedure, and then proceeded to CT of the chest and mediastinum if no cervical adenopathy was delineated. The patients received high-dose radioiodine treatment (100-300 mCi) following a two-week low-iodine diet and cessation of L-thyroxin treatment for approximately 6 weeks. Post-treatment whole-body scanning was performed using a large field gamma camera (Adac, Philips, Eindhoven, the Netherlands) 10 days later. Patients with negative or equivocal radioiodine scan findings had FDG-PET whole-body imaging to determine if a non-iodine avid thyroid tumor was responsible for elevated serum Tg levels in the body. PET imaging was performed using dedicated whole-body PET scanners (Siemens ECAT, EXACT ART scanner; Knoxville, Tennessee, USA) for 8 patients or a dual-head gamma camera with a 5/8-inch (16 mm) thick NaI (Tl) crystal (Siemens, E-Cam+, Knoxville, Tennessee, USA) with coincidence capability. All patients fasted for at least 4 h before undergoing PET. Whole-body PET images were obtained approximately 60 min after the intravenous administration of 8-10 mCi (264 to 370 MBq) of FDG and sequential overlapping scans were acquired to cover the neck, chest, abdomen, pelvis and proximal femora. The images were reviewed by 2 experienced nuclear medicine physicians and the sites of abnormal FDG uptake were noted.

Results

Final diagnostic evaluations showed 63 recurrent or metastatic tumor sites in 22 of the patients (Table). Persistent disease was in the thyroid bed and neck in 7 patients (25%), lung/mediastinum in 6 (21%), both in the neck and lung/mediastinum in 5 (18%), lung/mediastinum and bone in 2, neck and bone in 1, and in the neck, bone, and lung in 1 patient, according to histological and anatomical imaging findings (Figure 1). No persistent tumors were detected in 6 patients and all were assumed to be free of disease. In 14 patients cervical adenopathy suspicious for persistent thyroid carcinoma was observed with US; however, 1 lesion proved to be false-positive and in another patient a metastatic lymph node was not successfully defined. In 15 patients CT provided useful information for final definitive diagnosis, revealing lung deposits, including additional bone involvement in 4 cases; however, 1 proved to be a secondary malignancy (lung carcinoma) based on trans-thoracic aspiration cytology. Of the 21 cases with a positive FDG-PET scan result, 18 were proven to be true-positive. FDG-PET imaging located the diseased sites in the neck (4 patients), lung and mediastinum (5 patients), both in the neck and mediastinum/lung (6 patients), lung/mediastinum and bone (2 patients), and neck and bone (1 patient) (Figure 2). In 3 patients PET was false-positive (i.e. no anatomical lesion corresponding to the focal uptake was defined in the neck and lung in 2 patients, and focal FDG uptake was assumed to be cervical muscle spasm and inflammatory changes, respectively). In the other patient with focal multiple uptake a final diagnosis of lung cancer was made. FDG-PET also missed 2 lymph node metastases in the neck and 1 bone metastasis.

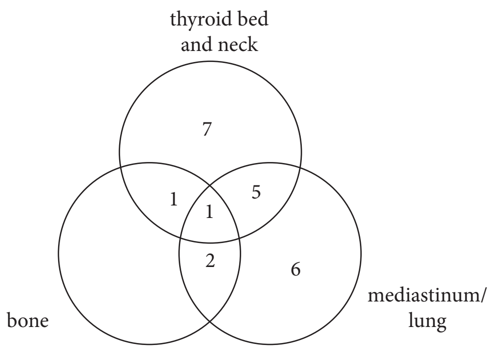

Figure 1. Localization of metastatic lesions in thyroid cancer patients.

Table. Final diagnosis and overall results obtained from all imaging procedures and histopathological diagnoses.

Pt. No.	Sex	Age	Path.	Tg*	Localization	Anatomical imaging	Post-treat. imaging (mCi)	FDG-PET	Confirmation.
1	F	78	P	202	RNeck (3) Lung (3)	Neck (USG), lung (CT)	N (200 mCi)	Lung (3) Rneck (3)	B/Rad
2	F	66	P	3,1	LNeck	Neck (USG)	TB (100 mCi)	LNeck	B
3	M	69	P	82	Lung (2); LNeck (2) L-3 vert.	Lung (CT), Neck (USG), Bone (CT)	N (300 mCi)	Lung(2) LNeck (2)	B/BS/Rad
4	F	70	HC	93	Lung (3); LNeck	Lungs (CT) Neck (USG)	LNeck (faint) (200 mCi)	Lung (2 LNeck	B
5	F	21	P	5,8	-	N	N (150 mCi)	N	FU
6	F	53	P	22,4	-	Lung (CT) LNeck (USG)	Neck (faint) (150 mCi)	Lung (FP)	FU/Rad
7	F	27	P/TC	8,1	LNeck	RNeck (USG, MRI)	Med (thymus, 200 mCi)	RNeck (FP)	H
8	M	34	P/C	6,6	-	N (CT)	N (100 mCi)	N	FU
9	F	78	P	3080	Lung (> 3)	Lungs (CT)	N (250 mCi)	Lung (>3)	Rad
10	M	30	P	26	-	N (CT, USG)	N (150 mCi)	N	FU
11	M	70	F	40	Lung (2);	Lungs (CT)	N (200 mCi)	Lung	FU/Rad
12	F	73	P	400	Lung (2); LNeck (2)	Lung (CT) LNeck (USG)	N (200 mCi)	Lung LNeck	B/Rad
13	F	65	P	305	Lung Bone (4)	Lung (CT)	N (200 mCi)	Lung Bone (3)	Rad/BS/FU
14	F	25	P	25,2	LNeck	LNeck (USG)	N (150 mCi)	N	B
15	F	85	F	42	Lung Med	Lung, med (CT)	N (200 mCi)	Lung Med	B/FU/Rad
16	F	54	P	824	Bone (2) Med (2)	Med,BS (CT, BS)	N (200 mCi)	Bone (2) Med (3)	Rad/BS/FU
17	F	69	P	300	Med, TB	Med (CT), TB (USG)	N (150 mCi)	Med TB	Rad
18	F	60	P	8,8	-	N (CT-chest, USG)	N (100 mCi)	N	FU
19	F	55	PD	56	LNeck (2) Bone (3)	LNeck (USG)	N (150 mCi)	Neck (2) Bone (2)	B/BS
20	F	85	P/T	373	LNeck (2)	LNeck (USG)	N (150 mCi)	LNeck (2)	B
21	F	62	P	98	LNeck (1)	LNeck (USG)	N (150 mCi)	LNeck*	B
22	F	36	P	10,8	-	N (CT-chest, USG)	N (150 mCi)	N*	FU
23	F	26	P	368	Mediast.	Med (CT)	N (200 mCi)	Med	B
24	M	79	P	128	Lung (2); LNeck (2)	Lung, LNeck (CT, USG)	N (200 mCi)	Lung (2)* LNeck (2)	B/FU/Rad
25	F	54	P	149	TB (3)	TB (USG)	N (150 mCi)	TB (2)*	B
26	M	29	P	94.27	TB	TB (USG)	N (250 mCi)	N	B/FU
27	M	69	P	0.5	Lung (2)	Lung (CT)	N (250 mCi)	Lung (2)*	Rad
28	M	62	P	402	Mediast, Lung (2)	Med , Lung (CT)	N (250 mCi)	Med, Lung (2)	Rad

Abbreviations

G: gender; F: female; M: male; Hist.: histology P: papillary; F: follicular; Loc.: localization; L: left; R: right; Med: mediastinum; N: negative; TP: true positive; FP: false positive; B; biopsy: H: histology; F: follow-up; BS: bone scan: Rad: radiology.

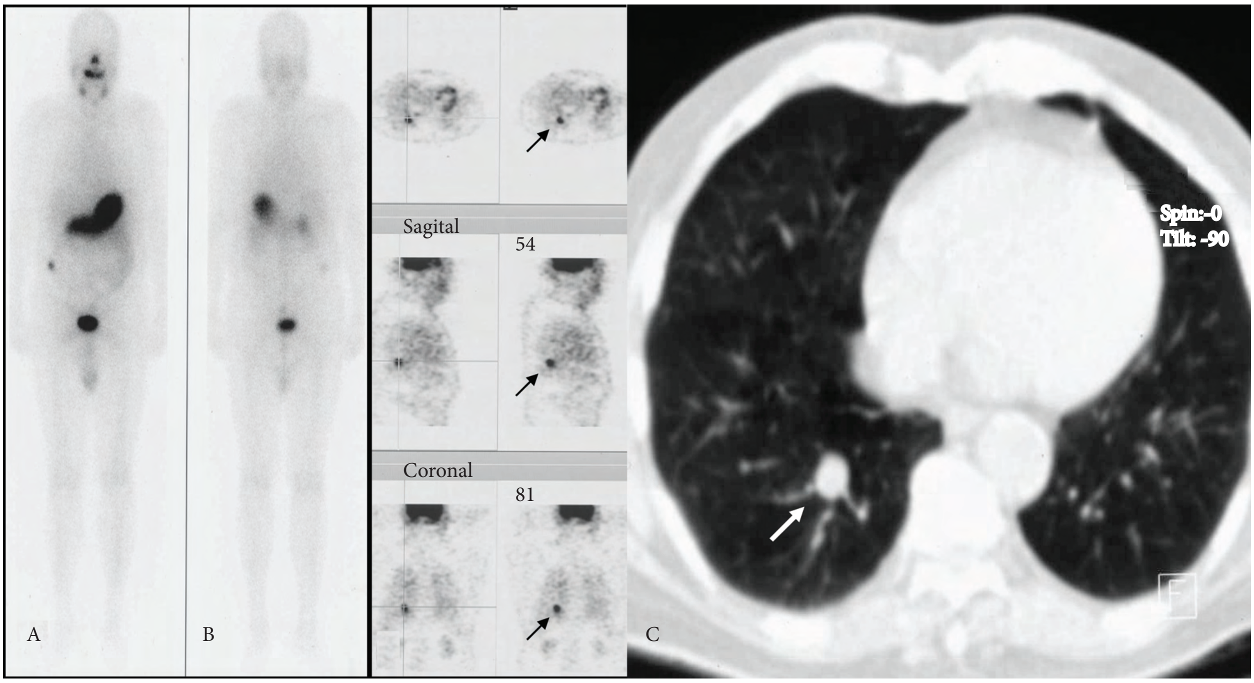

Figure 2. A 79-year-old male with papillary thyroid carcinoma presented with elevated serum Tg. He had undergone thyroid surgery and radioablation 6 years earlier and received a second radioiodine treatment of 250 mCi of I-131. Post-treatment whole-body scanning was negative (A); however, a metastatic lesion in the right lower lung was seen on FDG-PET images (B, arrow) and CT (C, white arrow). The patient also had cervical lymph node involvement (not shown) and was prepared for cervical dissection; however, surgical intervention was canceled because a lung metastasis was observed with PET.

Discussion

Thyroid cancer imaging usually requires multimodality imaging procedures, including several anatomical and functional imaging studies. It was reported that the most frequent sites of persistent thyroid carcinoma were the thyroid bed (28%) and regional lymph nodes (53%). US of the thyroid bed and neck is usually the first-line imaging procedure for the evaluation of the head and neck region for thyroid tumors as small as a few millimeters in diameter (4,6), and has a sensitivity and specificity ranging from 95.3% to 100% and 70% to 85.7%, respectively. US provides anatomical and physiological information with novel technologies, such as color flow and power Doppler (7,8). US-guided fine-needle aspiration cytology from lesions suspected to be malignant is an accurate procedure for establishing a definitive diagnosis (9,10). In the present study all patients underwent US examination and persistent thyroid tumors were detected in 14 patients; however, US is an operator-dependent procedure and its sensitivity decreases because the anatomy of the neck is altered after each surgical intervention. Of the other imaging procedures, CT of the chest and mediastinum was employed in detecting metastatic deposits in the lungs and mediastinum. In our study CT was useful in detecting thyroid cancer metastases to the lungs in 15 patients, and additional bone metastases in 4 of those patients. It was reported that high resolution CT is useful for detecting thyroid cancer metastases in the lungs of iodine-negative patients with elevated Tg levels (11); however, distant metastases are found in up to 18% and 11% of thyroid cancer patients with and without locoregional disease, respectively, and US and CT are useful only for certain parts of the body, such as the neck and lungs. Moreover, the sensitivity of both methods decreases after each surgical procedure because of altered anatomy in the neck and inflammatory lesions in the lungs. Whole-body imaging is more useful as it is possible to scan the body from head to toe.

FDG-PET whole-body scanning was a novel imaging modality for detecting recurrent or metastatic thyroid carcinoma. The clinical use of FDG-PET in differentiated thyroid carcinoma patients with negative radioiodine scanning results and abnormal serum concentration has been reported in previous studies. Feine et al. were among the first to evaluate the role of FDG-PET in the assessment of recurrent or metastatic thyroid carcinoma. In a prospective study that included 41 patients they reported that PET had a sensitivity of 95% and noted an inverse relationship between the uptake of FDG and I-131 by the tumor cells. It was postulated that as tumor cells lose the ability to take up iodine, they exhibit an increase in FDG uptake associated with the dedifferentiation process (12). In a study of 222 patients Grunwald et al. reported that radioiodine scanning was sensitive in well-differentiated thyroid carcinomas, whereas FDG-PET was superior to this technique in patients with poorly differentiated tumors. The overall sensitivity of PET was 75%, but it increased to 85% in the group of patients with negative I-131 scanning results (13). In the present study FDG-PET imaging revealed thyroid tumors in the neck and lungs in 18 patients. FDG uptake and tumor size are important for lesion visualization with PET, as this procedure is a functional imaging modality and has obvious resolution problems. Of note, minimal cervical adenopathy in 2 of our patients and bone involvement in 1 were not detected with FDG-PET scanning. US is recommended for investigating minimal cervical adenopathy due to its true-positive rate of 95.3% and low cost (7).

In 4 patients thyroid cancer metastasized to bone, of which 3 of them were observed on PET scans. The skeleton is the second most common site in patients with thyroid carcinoma, particularly for the follicular subtype. The majority of thyroid cancers with bone involvement were reported to be osteolytic in nature and those lesions were rarely seen on FDG-PET images (14). Therefore, bone scanning remains more sensitive for detecting thyroid cancer metastases to bone, as compared to FDG-PET scanning.

One of the patients in our study presented with multiple solid lesions in the lungs. He had a negative high-dose post-treatment scan and underwent whole-body FDG-PET scanning to observe glucose metabolism in the lesions. All lung lesions exhibited increased FDG uptake; however, his serum Tg concentration of 0.5 ng/mL. It was proven that he had lung malignancy (small cell lung carcinoma) with a cytological investigation following trans-thoracic aspiration biopsy.

Lietzenmayer et al. reported that FDG uptake correlates with dedifferentiation and that FDG uptake with limited I-131 uptake was an indicator of progressive disease and poor prognosis (15,16). Thus, it appears that patients with a positive PET result must be treated more aggressively and that such patients with residual thyroid cancer that present with increased FDG uptake are good candidates for surgical intervention if detected in the neck. Those lesions are relatively radio-resistant and benefit minimally from I-131, even if they have the ability to concentrate radioiodine.

Conclusion

Anatomical imaging procedures, such US and CT, are useful for detecting minimal cervical adenopathy and metastatic lung lesions, respectively. As a whole-body imaging procedure, FDG-PET scanning provides valuable diagnostic information, visualizing distant metastasis, especially in patients with elevated serum Tg levels and negative iodine-scanning results.

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