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Rare renal metastases from differentiated thyroid carcinoma: early clinical detection and treatment based on radioiodine

Metástases renais raras de carcinoma diferenciado da tireoide: detecção clínica precoce e tratamento com radioiodoterapia

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ABSTRACT

Objective: The aim of this study was to explore the clinical characteristics of renal metastatic cancer, the methods for its detection by radioiodine (^{131}I), and the response to ^{131}I treatment in fourteen patients with renal metastases from differentiated thyroid carcinoma (DTC). **Subjects and methods:** DTC patients (n = 2,955) that received treatment with ^{131}I were retrospectively analyzed. Scans (^{131}I-WBS, ^{31}I-SPECT/CT and/or ^{18}F-FDG-PET/CT) were performed after an oral therapeutic dose of ^{131}I. Therapeutic efficacy was evaluated based on changes inTg and anatomical imaging changes at renal lesions. **Results:** Among these 14 patients, 11 had avidity for ^{131}I, but three patients did not accumulate ^{131}I after ^{131}I treatment. In the 11 ^{131}I-positive renal lesions, 10 cases were detected by ^{131}I-SPECT/CT combined with another imaging modality and one case by ^{131}I-WBS combined with ultrasonography (US). In the three ^{131}I-negative renal lesions, two cases were detected by 18F-FDG-PET/CT and one case by computed tomography (CT). In 11 patients with ^{131}I-avid renal metastases, SerumTg levels in 81.82% (9/11) patients showed a gradual decline, and 18.18% (2/11) of the patients showed a significant elevation.There was no marked difference in serumTg before the last ^{131}I treatment ($Z = 0.157$; $p = 0.875$). Only one patient presented partial response, eight patients exhibited stable disease, and renal metastases progressed in two patients showing progressive disease. No patients reached complete response. **Conclusion:** ^{131}I-SPECT/CT, combined with another imaging modality after ^{131}I-WBS, can contribute to the early detection of renal metastases of DTC. ^{131}I therapy is a feasible and effective treatment for most DTC renal metastases with avidity for ^{131}I. Arq Bras Endocrinol Metab. 2014;58(3):260-9

Keywords
Differentiated thyroid cancer; renal metastases; radioiodine therapy; ^{131}I-SPECT/CT; ^{18}F-FDG-PET/CT

RESUMO

Objetivo: O objetivo deste estudo foi analisar as características clínicas de metástases renais, os métodos para sua detecção por radioiodo (^{131}I) e a resposta ao tratamento com ^{131}I em 14 pacientes com metástases renais de carcinoma diferenciado da tireoide (DTC). **Sujeitos e métodos:** Pacientes com DTC ($n = 2.955$) que receberam tratamento com ^{131}I foram analisados retrospectivamente. ^{131}I-PCI, ^{31}I-SPECT/CT e/ou ^{18}F-FDG-PET/CT foram feitos após uma dose terapêutica oral de ^{131}I. A eficácia terapêutica foi baseada nas alterações daTg e nas imagens anatômicas das lesões renais. **Resultados:** Dos 14 pacientes, 11 apresentaram lesões ávidas por ^{131}I, mas três pacientes não acumularam ^{131}I depois do tratamento com ^{131}I. Nas 11 lesões renais positivas para ^{131}I, 10 casos foram detectados por ^{131}I-SPECT/CT combinado com outra modalidade de exame de imagem e um caso por ^{131}I-WBS combinado com US. Nas três lesões renais negativas para ^{131}I, dois casos foram detectados por ^{18}F-FDG-PET/CT e um caso por tomografia computadorizada (TC). Em 11 pacientes com metástases renais ávidas por ^{131}I, os níveis séricos deTg em 81,82% (9/11) dos pacientes mostraram um declínio gradual e 18,18% (2/11) apresentaram uma elevação significativa. Não houve diferenças marcadas naTg sérica antes do último tratamento com ^{131}I ($Z = 0,157$; $p = 0,875$). Apenas um paciente apresentou resposta parcial, oito pacientes apresentaram doença estável e as metástases renais progrediram em dois pacientes que apresentaram doença progressiva. Nenhum dos pacientes apresentou resposta completa. **Conclusão:** ^{131}I-SPECT/CT, combinada com outra modalidade de diagnóstico por imagem após ^{131}I-PCI, pode contribuir para a detecção precoce de metástases renais de DTC. O tratamento com ^{131}I é passível de ser feito e eficiente para o tratamento da maior parte das metástases renais ávidas por ^{131}I. Arq Bras Endocrinol Metab. 2014;58(3):260-9

Descritores
Carcinoma diferenciado de tireoide; metástases renais; radioiodoterapia; ^{131}I-SPECT/CT; ^{18}F-FDG-PET/CT

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INTRODUCTION

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy and accounts for less than 1% of malignant neoplasms in humans (1). The overall prognosis for DTC patients is one of the best among all types of cancer, with a 10-year survival rate over 85-90%, but its incidence is gradually increasing in different parts of the world (2,3). Although DTC is generally characterized by an indolent course with low mortality, patients with distant metastases have strong prognosis of mortality, and more than 50% of these DTC patients die from distant metastatic disease during follow-up (4). Distant metastases derived from DTC occur in 5-23% of patients at presentation and during follow-up (5,6).

The major sites of distant metastases from DTC are the lungs and bones, while minor sites include the brain, liver, skin, and muscle. In contrast, renal metastases from DTC are extremely rare. Ahmed and cols. (7) reported that from December 1975 to September 2005, only one case of DTC metastasizing to the kidney was found among 3,500 DTC patients at their institution. To the best of our knowledge, only 26 cases have been reported in the literature to date.

^{131}I has been used as a therapy for distant metastases from DTC for over 60 years and has been an important component in the management of DTC. Traditionally, ^{131}I whole-body scans (^{131}I-WBS) have been performed to localize ^{131}I uptake and detect residual (or recurrent) disease and distant metastases after ^{131}I treatment. However, the precise anatomical localization of foci with increased ^{131}I uptake is difficult on planar images because of the lack of anatomical landmarks. By precisely localizing ^{131}I uptake, ^{131}I single photon emission computed tomography/computed tomography (^{131}I-SPECT/CT) might improve the diagnostic accuracy of ^{131}I scanning, thus improving the management of diseases in patients (8,9). Scans based on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) are well established for detecting recurring or metastatic DTC in patients with a negative ^{131}I-WBS and elevated serum Tg (10,11). Moreover, noninvasive imaging tools, including ultrasonography (US), enhanced CT, and magnetic resonance imaging (MRI), are useful for the detection of distant metastases (suspected according to clinical symptoms) in the follow-up of DTC.

Because of its limited and rare appearance, renal metastasis from DTC has only been occasionally reported, mainly as case reports or a small case series. Therefore, the diagnosis and efficacy of ^{131}I therapy have not been clearly defined and need further research. In this study, we retrospectively reviewed 14 patients treated with ^{131}I at Shanghai Sixth People's Hospital in China. We explored their clinical characteristics, as well as methods for ^{131}I-based detection and treatment of renal metastases from DTC.

SUBJECTS AND METHODS

Subjects

A total of 2,955 DTC patients were enrolled in this study at the Department of Nuclear Medicine of Shanghai Sixth People's Hospital, a major referral site in China for ^{131}I treatment. All patients were treated with ^{131}I for the ablation of postsurgical thyroid remnants, or treatment of metastases after total or near-total thyroidectomy from January 1998 to January 2012. Among them, 14 patients had diagnosis of renal metastases from DTC.

Methods for ^{131}I therapy and follow-up

All patients stopped taking thyroid hormone medication and began a low iodine diet 3-4 weeks before radioiodine therapy (thyroid stimulating hormone (TSH) reaching levels of ≥ 30 mIU/L). The patients received an oral administration of ^{131}I after examinations, including FT3, FT3, FT4, TSH, Tg and anti-Tg antibody (TgAb) tests, neck ultrasonography, X-ray, CT, MRI, and whole-body bone scans. ^{131}I-WBS or ^{131}I-SPECT/CT fusion imaging was performed 5 days after ^{131}I administration. The first oral dose of 3.7 GBq of ^{131}I was given to remove thyroid remnants. The oral administration of 7.4 GBq of ^{131}I was then given each time for the treatment of renal metastases. The treatment interval varied from 4 to 12 months, and the treatment was repeated 2-8 times. The time diagnosing renal metastases was established from 0.4 yrs. to 14.3 yrs. with a median time of 5.8 yrs. after the initial thyroid surgical treatment

Detection and diagnosis of renal metastases from DTC

The detection of renal metastases was carried out by means of one of two approaches: (1) if ^{131}I-WBS (with or without SPECT/CT) demonstrates ^{131}I uptake in the renal lesions, an imaging tool (US, enhanced CT, or MRI) can be used to indicate renal metastasis (serum levels of Tg should also be elevated), and (2) if ^{131}I-WBS reveals no ^{131}I uptake, ^{18}F-FDG-PET/CT, enhanced CT, MRI, or US scans that are positive (with elevated serum Tg) may indicate renal metastases from DTC. The diagnosis of renal metastases was confirmed by pathology results and clinical follow-up of renal lesions from DTC.

Evaluation of efficacy

The therapeutic effects of ^{131}I therapy for renal metastases from DTC were evaluated based on changes in serum Tg levels and alterations in the anatomical imaging of renal metastatic lesions. Serum Tg levels were measured with the Immulite chemiluminescent immunoassay system (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum TSH and anti-Tg antibody (TgAb) levels were also measured. The evaluation of anatomical images was performed based on methods established by RECIST 1.1. The responses defined by RECIST 1.1 are as follows: complete response (CR): disappearance of all target lesions, any pathological lesions (target or non-target) must have a reduction in short axis to < 10 mm; partial response (PR): at least a 30% decrease in the diameters of target lesions; progressive disease (PD): at least a 20% increase in the diameters of target lesions, combined with an absolute increase of at least 5 mm in the sum of diameters (in addition, appearance of one or more new lesions was also considered progression); stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increases to qualify for PD.

Statistical analysis

SPSS17.0 was used for statistical analysis. Tg changes were estimated by the Wilcoxon signed rank test. A p value < 0.05 was considered a statistically significant difference.

RESULTS

Demographic features of the patients

Fourteen patients were diagnosed with renal metastases from DTC with multimodality imaging, with an incidence of 0.47% (14/2955). The characteristics of these 14 DTC patients are summarized in table 1. Their ages ranged from 17 to 74 years, with a mean of 43 years. Seven subjects were over 45 years of age, and seven were less than 45 years. Eight subjects were males and six were females (male-to-female ratio of 1.3:1). The distribution of DTC pathological types included nine cases of papillary thyroid cancer and five cases of follicular thyroid cancer. Of the 14 cases, only one (case 14) had a single renal metastasis, whereas 13 cases presented combined metastases to other organs: 11 patients had lung metastases, seven had bone metastases, three had mediastinal metastases, and there was one case each of metastasis to the brain, muscle, liver, and parapharyngeal region. Renal metastases were asymptomatic in nine patients, but found on imaging follow-up studies. Three patients had symptoms of lower back pain, and two had hematuria.

DETECTION OF RENAL METASTASES FROM DTC

Discovery of functional renal metastases

Renal metastases from DTC that were detected with multimodality imaging are shown in figure 1. In the detection of renal metastases from DTC after ^{131}I treatment, ^{131}I-WBS found 21 lesions (indicating abnormal ^{131}I uptake) in the abdomen of 11 DTC patients, suggesting distant metastases from DTC, of which a total of 10 patients with 13 lesions were located in the kidneys after ^{131}I-SPECT/CT. Four cases with four lesions were found in the left kidneys, four cases with four lesions were found in the right kidneys, and two cases with five lesions were bilateral; among them, one case (case 7) with three lesions was found bilateral in the kidneys, one lesion in the left kidney and two lesions in the right kidney. Of those 10 patients with 13 renal metastatic lesions revealed by ^{131}I-SPECT/CT, all patients were SPECT-positive; but only three patients with five lesions (cases 6, 8, and 10) were CT-positive, with the remaining eight lesions of seven DTC patients (cases 2, 3, 4, 7, 9, 11, and 14) presenting equivocal or negative CT, suggesting early or small renal metastases. In these seven patients, three (cases 2, 4, and 7) were synchronous with MRI (Figure 2), three (cases 9, 12, and 14) with US, and one case (case 3) with enhanced CT. Among the remaining eight ^{131}I-uptake foci, one renal metastatic lesion in a DTC patient with lower back pain (case 1) was shown by ^{131}I-WBS combined with US, and others were excluded and identified as five intestinal uptake sites, one liver metastasis, and one erector spinae by ^{131}I-SPECT/CT.

Table 1. Characteristics and related data of patients with renal metastases from differentiated thyroid carcinoma

Patient No	Sex	Age of total thyroidectomy (years)	Age of diagnosing renal metastases of DTC	Years after detection of primary tumor (years)	Histology	Other synchronous distant metastases	Detecting modality	Confirmation modality	Localization of renal metastases	(diameter) cm)	Symptoms	NO. of RIT courses	^{131}I uptake	Cumulative ^{131}I activity (GBq)
1	F	51	65	14.3	F	Lungs, bones, liver	^{131}I-WBS, ultrasonography	FNAB	Left	5.2	Low back pain	8	Yes	59.2
2	F	25	34	9.2	P	Lungs, mediastinum	^{131}I-SPECT/CT, MRI	FNAB	Left	1.2	No	6	Yes	40.7
3	M	29	29	0.4	P	Lungs, erector spinae	^{131}I-SPECT/CT, enhanced CT	Follow-up	Right	0.9	No	5	Yes	35.15
4	M	28	40	12.6	P	Lungs, mediastinum	^{131}I-SPECT/CT, MRI	Follow-up	Left	0.6	No	7	Yes	49.95
5	F	43	51	8.1	F	Lungs and Bones	Biopsy, CT	FNAB	Left	3.1	Low back pain, hematuria	1	No	11.1
6	F	48	52	4.3	F	Lungs, bones	^{131}I-SPECT/CT	FNAB	Right	1.8	No	5	Yes	35.15
7	M	34	35	1.2	F	Lungs	^{131}I-SPECT/CT, MRI	Follow-up	Bilateral	L: 0.4 R: 0.6; 0.4	No	5	Yes	31.45
8	M	11	19	8.6	P	Lungs, bones	^{131}I-SPECT/CT	FNAB	Bilateral	L: 3.2 R: 2.8	Hematuria	3	Yes	22.2
9	M	21	24	3.2	P	Lungs, bone	^{131}I-SPECT/CT, ultrasonography	FNAB	Left	1.1	No	4	Yes	14.8
10	F	63	66	3.7	P	Lungs, bone	^{131}I-SPECT/CT	FNAB	Left	3.3	No	3	Yes	12.95
11	M	57	62	5.4	F	Bones	^{18}F-FDG-PET/ CT,MRI	FNAB	Right	1.9	No	1	No	11.1
12	M	24	25	0.9	P	Mediastinum	^{131}I-SPECT/CT, Ultrasonography	FNAB	Right	2.4	No	4	Yes	18.5
13	M	67	74	7.9	P	Brain, lungs, parapharyngeal, lung mediastinum	^{18}F-FDG-PET/CT	FNAB	Left	2.3	Low back pain	1	No	22.2
14	F	30	31	1.4	P	–	^{131}I-SPECT/CT, ultrasonography	Follow-up	Left	0.5	No	4	Yes	11.1

M: male; F: female; years: years after detection of primary tumor; CT: computed tomography; MRI: magnetic resonance imaging; ^{131}I-SPECT/CT: single-photon emission computed tomography/ computed tomography.

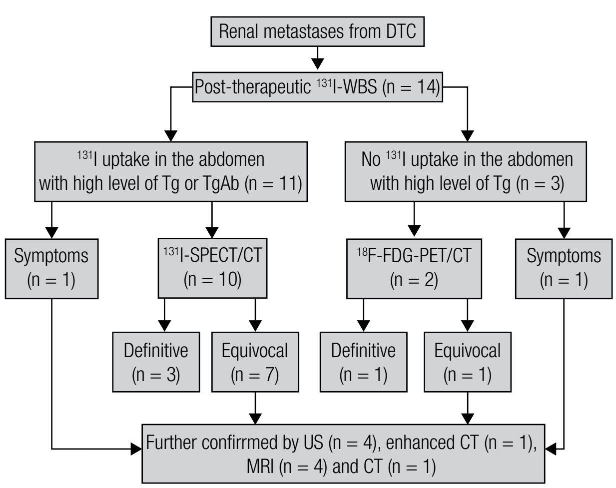

Figure 1. Renal metastases from DTC detected with multimodality imaging.

Discovery of non-functional renal metastases

Of the 14 DTC cases with renal metastases, three patients with three lesions failed to accumulate ^{131}I after ^{131}I treatment. Among them, two DTC patients (cases 11 and 13) with renal metastases were observed with ^{18}F-FDG-FET/CT (Figure 3); one lesion in one patient (case 11) was ^{18}F-FDG-FET–positive but CT-equivocal and confirmed by MRI, and one patient was positive by ^{18}F-FDG-FET and CT (case 13) (Figure 3). The remaining patient (case 5), who had lower back pain and hematuria, but was negative in ^{131}I-WBS with elevated serum Tg, had renal metastasis identified by CT.

Diagnosis of renal metastases from DTC

Among 14 DTC patients with renal metastases, ten cases (71.43%) were diagnosed based on pathological results (cases 1, 2, 5, 6, 8, 9, 10, 11, 12, and 13) and the remaining four cases (28.57%) with renal metastases also should be considered by clinical follow-up because lesions were considered too small for a fine-needle aspiration biopsy. Moreover, ^{131}I-SPECT/CT combined with MRI (cases 4 and 7), enhanced CT (case 3), or US (case 14) showed the existence of renal lesions after several ^{131}I therapy.

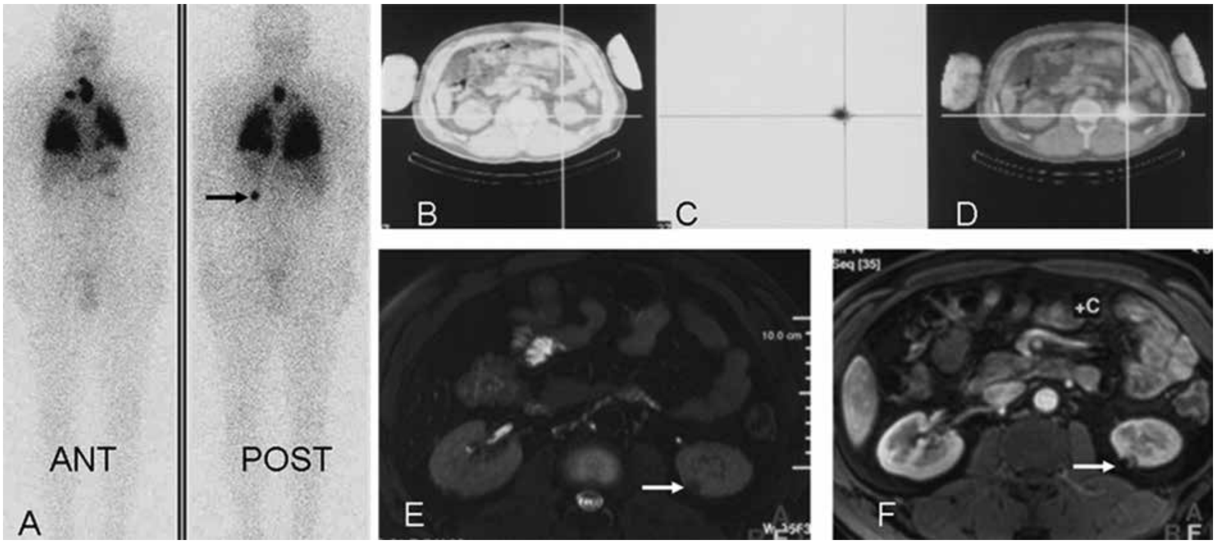

Figure 2. A 40-year-old male patient who presented mediastinal lymph node and pulmonary metastases from papillary thyroid cancer was treated with ^{131}I for postsurgical thyroid remnants and metastases. An unexpected lesion with ^{131}I uptake in the left abdomen, mediastinal lymph node, and lungs (suggesting metastasis) was observed on a ^{131}I-WBS 5 days after an oral therapeutic dose of ^{131}I (**A:** arrow). To localize this unexpected lesion of ^{131}I uptake, a subsequent low-dose ^{131}I-SPECT/CT scan was performed using a GE Hawkeye Millennium. Fusion images showed that the lesion was located in the left kidney (**B-D:** crossing line). Further examination with MRI revealed a solitary metastatic lesion with a diameter of 8 mm in the upper pole of the left kidney (**E-F:** arrow).

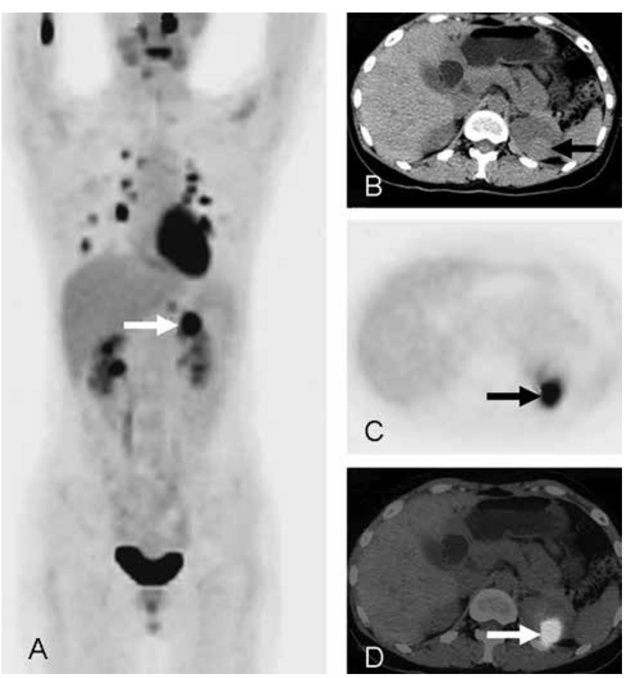

Figure 3. A 74-year-old male patient with lower back pain was given ^{131}I treatment after total thyroidectomy. No abnormal ^{131}I uptake was found in the post-therapeutic ^{131}I-WBS with elevated serum Tg and ^{18}F-FDG-PET/CT was performed to search for potential metastatic lesions. Maximum intensity projections in ^{18}FDG-PET revealed more intense ^{18}FDG uptake lesions in the chest and abdomen (**A:** arrow). ^{18}F-FDG-PET/CT revealed a prominent ^{18}FDG uptake lesion with a diameter of 23 mm in the upper pole of the left kidney (**B-D:** arrow).

Responses to ^{131}I therapy

Among 14 patients, three patients with renal metastases did not accumulate ^{131}I after ^{131}I treatment; therefore, responses to ^{131}I therapy were ineffective for them.

Changes in serum Tg

All eleven ^{131}I-avid patients received approximately three to eight courses of ^{131}I treatment at an interval of 4-12 months. The median stimulated serum Tg level was 4659 ng/mL (range 87-18191 ng/mL) before the first ^{131}I treatment, and 4194 ng/mL (range 31701-19 ng/mL) before the last ^{131}I treatment. There were no marked differences in serum Tg before and after ^{131}I treatments ($Z = 0.157$; $p = 0.875$). Serum Tg levels in 81.82 % (9/11) of the patients showed a gradual decline, while 18.18% (2/11) of the patients showed a significant elevation. In one patient (case 14), serum Tg level was normal and stabilized at about 2.56 and 9.3 ng/mL; however, TgAbs were obviously high and changed from 327 to 92 u/mL after several ^{131}I treatments (Table 2).

Anatomical imaging changes after ^{131}I therapy

Of the 11 cases with renal metastases, only one patient presented PR and eight patients exhibited SD; these findings suggest that the disease remains stable. The renal metastases progressed in two patients showing PD. No patient reached CR (Table 2).

Table 2. Response of DTC patients with renal metastases after ^{131}I treatment

Patient nº	Stimulated Tg before first ^{131}I treatment (ng/mL)	Stimulated Tg before last ^{131}I treatment (ng/mL)	Imaging change after ^{131}I treatment
1	8,752	6,923	PD
2	640.7	289	SD
3	567	19	SD
4	401	123	SD
6	5,463	6,376	SD
7	18,191	602	PR
8	17,016	31,701	PD
9	87	22	SD
10	39.38	22.64	SD
12	94	52	SD
13	13,562	17,817	PD
14	2.56	9.3	SD

PR: partial response; SD: stable disease; PD: progressive disease.

DISCUSSION

Differentiated thyroid cancer (DTC) has been reported to present initially distant metastases in about 4% of cases. During follow-up, distant metastases develop in 2-34% of cases (12). The presence of distant metastases reflects advanced clinical presentation, associated with higher mortality rate, especially in elderly patients (13). However, ^{131}I-WBS combined with elevated serum Tg can contribute to the early detection of distant metastases (at a time when other radiological studies are negative), and the disease is potentially curable by means of ^{131}I therapy (14,15).

The major sites of distant metastases from DTC are the lungs and bones, while other sites infrequently involved include the brain, liver, skin, pleura, and muscle. Metastasis to the kidneys is not an uncommon incidental finding at autopsy; 4.6-7.6% of patients have metastases in the kidneys, with frequencies of bilaterality and multiplicity being as high as 71-81% (16). Metastases to the kidney from papillary and follicular thyroid cancer are found in 2.8-3.8% and 6-20% of cases, respectively (17). However, the clinical detection of DTC metastasis to the kidneys is quite rare; a retrospective review of the literature revealed only 26 case reports of renal metastases arising from DTC. Of the 26 cases of renal metastasis associated with DTC, full-text studies of three patients were not found using the PubMed and EMBASE databases; the other 23 patients are reviewed in table 3 (7,16-36). We previously reported one case of renal metastases from DTC, a 29-year-old man with concomitant metastases to the erector spinae and lungs (case 7) (19). Most subjects were females over 45 years of age; nine cases were FTC, 10 cases PTC, three cases a follicular variant of PTC, and one case of Hurthle cell thyroid cancer. However, because of its limited expression and rarity, renal metastasis from DTC has only been occasionally reported, mainly as case reports or a small case series. Here, a relatively large number of DTC cases from renal metastasis were described in this study. The overall prevalence of renal metastasis from DTC was about 0.47% (14 of 2,955). Similar to our patients, most of the previously reported patients had advanced DTC with metastases to other organs when renal metastases were found. In our study, a 31-year-old female with a single left renal metastasis from DTC was the only case detected by ^{131}I-SPECT/CT and US after ^{131}I treatment.

The ^{131}I-WBS is indispensable for finding distant metastases because of their ability to accumulate ^{131}I through the sodium iodide (Na^+/I^-) symporter after an oral dose of ^{131}I. In our series, most DTC patients (11/14) with renal metastases have the ability to take up ^{131}I. However, the accurate localization of focal activity by ^{131}I-WBS is difficult because of the lack of anatomical markers. Therefore, renal metastases from DTC are easily misinterpreted as an intestinal physiological uptake frequently observed through ^{131}I-WBS in DTC patients. In recent years, ^{131}I-SPECT/CT has emerged in this setting as a useful tool for accurately locating sites of pathological uptake and identifying physiological mimics of disease, thus providing a more accurate staging of prognostic information for risk stratification which, in its turn, tailors management and follow-up regimens (37). ^{131}I-SPECT/CT for anatomic localization of renal metastases has been reported in past reviews (19,20). In our cases, 10 DTC patients with renal metastases were detected by ^{131}I-WBS combined with ^{131}I-SPECT/CT, suggesting that the additional diagnostic information provided by ^{131}I-SPECT/CT over ^{131}I-WBS could detect renal metastases from DTC patients. Patients with renal metastases are usually asymp-

Table 3. Renal metastases from differentiated thyroid cancer previously reported in the literature

No.	Author	Publication (year)	Age/sex	Histopathology	Diagnostic methods	Localization of renal metastases (size, cm)	Other synchronous distant metastases	Years
1	Borde and cols. (16)	2011	56/M	Papillary	^{131}I-WBS, F-FDG PET, SPECT, CT, biopsy	Bilateral (L: 5.5; R: 1.4, 1.5)	–	–
2	Malhotra and cols. (17)	2010	30/M	Papillary	^{131}I-SPECT/CT, biopsy	R (1.5)	Lungs, liver, bones, mediastinum, and adrenal	20
3	Djekidel and cols. (18)	2010	75/M	Hurthle cell	Biopsy	R (5)	Bone	9
4	Luo and cols. (19)	2008	29/M	Papillary	^{131}I-SPECT/CT	R	Erector spinae	–
5	von Falck and cols. (20)	2007	64/F	Follicular	^{131}I-SPECT/CT	L	Lungs and bone	20
6	Ahmed and cols. (7)	2006	24/F	Papillary	Ultrasonography	R (1.3)	–	26
7	Kumar and cols. (21)	2005	66/F	Follicular	^{131}I-WBS, biopsy	L	Adrenal	–
8	Iwai and cols. (22)	2005	76/F	Follicular	CT, MRI, biopsy	R (3)	Muscle, lung	13
9	Liou and cols. (23)	2005	50/F	P/F	CT, biopsy	R (1.9)	Lungs, and bone	-
10	Inahara and cols. (24)	2002	66/M	Papillary	Hematuria, biopsy	Bilateral	–	11
11	Smallridge and cols. (25)	2001	61/F	Papillary	^{131}I-WBS, CT	L (3)	Muscle	–
			53/F	Papillary	CT	R (3.5)	Lungs	–
12	Garcia-Sanchis and cols. (26)	1999	65/F	Follicular	^{131}I-WBS	L (10)	Lungs and bones	–
13	Benchekroun and cols. (27)	1999	56/M	Papillary	Low back pain	L (5.6)	–	3
14	Lam and cols. (28)	1996	91/F	Papillary	–	L (5)	–	-
15	Graham and cols. (29)	1995	75/M	P/F	IVP	L (7.7)	–	< 1
16	Ro and cols. (30)	1995	47/F	Follicular	Hematuria	R (1.2)	–	7
17	Tur and cols. (31)	1994	72/F	P/F	^{131}I-WBS	Bilateral	Liver	3
18	Sardi and cols. (32)	1992	53/M	Papillary	Hematuria	R (12)	Lungs	7
19	Marino and cols. (33)	1991	-/ F	Follicular	^{201}T , ^{123}I scan	R	–	26
20	Johnson and cols. (34)	1982	66/F	Follicular	Hematuria	L	Lungs	37
21	Davis and Corson (35)	1979	49/F	Follicular	–	Bilateral (R: 3.5; L: 4.4)	–	18
22	Takayasu and cols. (36)	1968	44/F	Follicular	IVU	Bilateral	Bone	3

M: male; F: female; P/F: follicular variant of papillary thyroid cancer; years: years after detection of primary tumor; ^{131}I-WBS: ^{131}I-whole body scintigraphy; CT: computed tomography; MRI: magnetic resonance imaging; ^{131}I-SPECT/CT: single-photon emission computed tomography/computed tomography. IVP: intravenous pyelogram; IVU: International Vegetarian Union.

tomatic and most are less than 45 years old, as seen in our cases, also suggesting that avid ^{131}I metastatic foci of renal metastasis could be detected at an early stage by ^{131}I-SPECT/CT scan.

Due to dedifferentiation, about 20-50% of metastatic DTC have no ability to take up ^{131}I. The definitive role of ^{18}F-FDG-PET/CT in DTC patients with serum Tg levels and negative ^{131}I-WBS has been consistently demonstrated (38). The discrepancy between the two imaging tools is attributable to the flip-flop phenomenon of ^{131}I and ^{18}F-FDG (39). Three patients with three lesions did not accumulate ^{131}I after ^{131}I treatment. Among them, two DTC patients had renal metastases discovered on ^{18}F-FDG-FET/CT (originally done to evaluate elevated Tg). Moreover, Borde and cols. also described renal metastases that had no uptake of ^{131}I but were detected by ^{18}F-FDG-FET/CT in a 56-year-old male PTC patient (16). Tumors with ^{131}I non-avidity and FDG uptake suggest their high grade (38).

In clinical settings, most conventional imaging such as US, enhanced CT, and MRI are performed for the evaluation of symptoms, disease staging, or the evaluation of treatment response. Therefore, renal metastases from DTC cannot be considered for these conventional imaging scans without clinical symptoms or clinical suspicion prior to the initiation of various therapies. For example, because of lower back pain and hematuria, a 51-year-old female patient with no avid ^{131}I was found to have a left renal metastasis from DTC by CT combined with biopsy in our study.

Renal metastatic foci from DTC (regardless of ^{131}I avidity) can be accurately localized with ^{131}I-SPECT/CT or ^{18}F-FDG-FET/CT; however, renal lesions less than 1.0 cm are too small for detection by CT scans. Moreover, Blum and cols. (40) reported a sixty-three-year-old woman (with a history of PTC) treated with surgery and then ablation with 100 mCi of ^{131}I. Post-treatment WBS demonstrated an equivocal signal in the upper right abdomen that ^{131}I-SPECT/CT later confirmed as ^{131}I accumulation within a benign renal cyst. These are strong reminders that ^{131}I-SPECT/CT and ^{18}F-FDG-FET/CT images are valuable in finding, but not completely in diagnosing, rare renal metastases from DTC. Thus, other imaging modalities need to be applied for finding renal metastases when metastatic foci are positive in ^{131}I-SPECT or ^{18}F-FDG-FET, but negative or equivocal in CT scans in the follow-up of DTC. These other modalities, including US, enhanced CT, and MRI, are especially useful tools to detect small (< 1 cm) or cryptic renal lesions unseen on CT scans. Of the 14 patients here, four were further identified by MRI scan, four by US, one by enhanced CT, and one by biopsy. Therefore, multimodality imaging is essential to accurately assess the extent of renal metastases from DTC to guide treatment, prevent tumor progression, and improve survival.

Due to the rare occurrence of renal metastases from DTC, the best management for this condition is unclear. Since most cases are associated with metastases at other sites, surgical excision, with its risks and limited efficacy, is not a practical solution. Although external beam radiotherapy can provide local tumor control in a high percentage of cases, its efficacy is transient and dose-dependent. To obtain a longer lasting efficacy, a high dose of irradiation may be required and adverse effects must be considered. In addition, it is usually applied to treat a single metastasis and is unsuitable for the treatment of multiple metastases.

Sorafenib is a multikinase inhibitor that targets several molecular signals involved in the pathogenesis of DTC, and that has been used in the treatment of advanced or metastatic ^{131}I-refractory DTC (41). However, it has only been reported as an anti-cancer drug for DTC with distant metastases, but not avid ^{131}I lung metastases, in recent years. Therefore, these treatments have not been applied in this group of patients. Currently, ^{131}I therapy is the treatment of choice for most DTC patients with distant metastases after thyroidectomy. If renal metastases from DTC have excellent ^{131}I uptake, they can be differentiated from other malignant neoplasms based on this feature, and be treated with ^{131}I. However, there are no data showing the efficacy of ^{131}I for the treatment of renal metastases from DTC due to their rarity. Here, the therapeutic effects of ^{131}I therapy on renal metastases from DTC were evaluated based on changes in serum Tg and alterations in anatomical imaging of metastatic renal lesions. In our study, among the 14 DTC patents with renal metastases, 11 patients showed avidity for ^{131}I.

Serum Tg is a highly sensitive and specific marker of DTC metastasis and recurrence, which also reflects tumor burden. Serum Tg is usually significantly elevated in DTC patients with distant metastases. Thus, the pronounced reduction in Tg (at roughly the same TSH level) indicates that ^{131}I therapy can eliminate some tumor cells after multiple treatments (4). In our study, serum Tg levels in 81.82% (9/11) patients showed a gradual decline and 18.18% (2/11) patients showed a significant elevation, suggesting that ^{131}I is partly effective for the treatment of DTC patients with renal metastases. Because the detection of Tg may be disturbed by TgAbs, we measured serum levels of Tg and TgAbs simultaneously in all patients. In only one patient in this study, serum TgAb levels increased to a certain extent (> 100 ng/mL) but Tg levels were normal and stabilized at about 2.56 and 9.3 ng/mL. After ^{131}I therapy, serum levels of TgAbs decreased markedly.

After ^{131}I therapy, MRI examinations revealed statistically significant shrinking of metastatic renal lesions in only one patient. This improvement may be due to small lesions or those that were at an early stage. The anatomical imaging of renal metastases with excellent avidity for ^{131}I showed insignificant changes in eight patients (72.73%), indicating that those lesions were stable. Though renal metastatic foci accumulated ^{131}I, US still showed PD in a patient, suggesting renal metastasis in this DTC patient may exhibit dedifferentiation (42). Renal metastatic foci in the remaining three patients gradually increased without ^{131}I uptake after ^{131}I treatment. Therefore, ^{131}I treatment is ineffective for patients with a relatively poor prognosis.

CONCLUSION

In summary, renal metastasis is an extremely rare pattern of invasion from DTC with an incidence of 0.47%. ^{131}I-SPECT/CT, combined with other imaging modalities after ^{131}I-WBS, can contribute to the early detection of renal metastases and is essential to accurately assess the extent of renal metastases from DTC to guide treatment and prevent tumor progression. ^{131}I therapy can significantly decrease serum Tg, and shrink or stabilize renal metastatic lesions with excellent avidity for ^{131}I.

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