Hyperfunctioning thyroid carcinoma: A systematic review

JUN LIU[1,2], YE WANG[1,2], DONGZHU DA[1] and MIAO ZHENG[1]

[1]Department of Breast-Thyroid Surgery, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai 201620, P.R. China; [2]Department of Systems Medicine and Bioengineering, Houston Methodist Research Institute, Weill Cornell Medicine, Houston, TX 77030, USA

Received January 31, 2019; Accepted August 6, 2019

DOI: 10.3892/mco.2019.1927

Abstract. Hyperthyroidism may be caused by the development of primary or metastatic thyroid carcinoma. The aim of the present study was to collect recently reported cases of hyperfunctioning thyroid carcinoma in order to analyze its pathological characteristics, diagnostic procedures and treatment strategies. A PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) search was performed for studies published between January 1990 and July 2017. Full-text articles were identified using the terms, 'hyperfunctioning thyroid carcinoma/cancer', 'malignant hot/toxic thyroid nodule', or 'hyperfunctioning papillary/follicular/Hürthle thyroid carcinoma'. Original research papers, case reports and review articles were included. Among all thyroid carcinoma cases included in the present study, the prevalence of follicular thyroid carcinoma (FTC) was ~10%; however, the prevalence of FTC among hyperfunctioning thyroid carcinomas was markedly higher (46.5% in primary and 71.4% in metastatic disease). The size of hyperfunctioning thyroid tumors was considerably larger compared with that of non-hyperfunctioning thyroid tumors, with a mean size of 4.25±2.12 cm in primary hyperfunctioning thyroid carcinomas. In addition, in cases of metastatic hyperfunctioning thyroid carcinoma, tumor metastases were widespread or large in size. The diagnosis of primary hyperfunctioning thyroid carcinoma is based on the following criteria: i) No improvement in thyrotoxicosis following radioactive iodine (RAI) treatment; ii) development of hypoechoic solid nodules with microcalcifications on ultrasound examination; iii) increase in tumor size over a short time period; iv) fixation of the tumor to adjacent structures; and v) signs/symptoms of tumor invasion. The diagnosis of metastatic hyperfunctioning thyroid carcinoma should be considered in patients suffering from thyrotoxicosis who present with a high number of metastatic lesions (as determined by whole-body scanning), or a history of total thyroidectomy. Surgery is the first-line treatment option for patients with primary hyperfunctioning thyroid carcinoma, as it does not only confirm the diagnosis following pathological examination, but also resolves thyrotoxicosis and is a curative cancer treatment. RAI is a suitable treatment option for patients with hyperfunctioning thyroid carcinoma who present with metastatic lesions.

Correspondence to: Dr Jun Liu, Department of Breast-Thyroid Surgery, Shanghai General Hospital, Shanghai Jiaotong University, 650 Xinsongjiang Road, Songjiang, Shanghai 201620, P.R. China
E-mail: liujun95039@163.com

Key words: thyroid carcinoma, hyperfunctioning thyroid carcinoma, malignant hot thyroid nodule, hyperthyroidism, metastasis

Introduction

Thyroid carcinoma coexisting with hyperthyroidism is an uncommon occurrence (1), as low thyroid-stimulating hormone (TSH) levels can suppress the development and growth of differentiated thyroid carcinoma cells. The majority of nodules in patients with low TSH levels are considered to be benign (NCCN, British Thyroid Association) (1); however, an increasing number of thyroid carcinoma cases are diagnosed in patients with Graves' disease, toxic goiter and functioning thyroid adenoma (2). These thyroid carcinomas may be embedded in or adjacent to a larger hot nodule, and the majority are non-functional. However, previous studies have reported that hyperfunctioning thyroid carcinoma may present as autonomous functioning thyroid nodules (AFTN) within the thyroid gland, or as functioning lesions in metastatic foci (3-5). In addition, Als *et al* (3) identified 19 patients with toxic thyroid carcinoma in 2002, while Mirfakhraee *et al* (5) identified a solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma and reported 76 cases of malignant hot thyroid nodules based on a literature search. Hyperfunctioning thyroid carcinomas are capable of absorbing iodine, as well as synthesizing and releasing thyroxine. Patients with hyperfunctioning thyroid carcinomas may therefore present with clinical thyrotoxicosis. It is considered that this type of hyperthyroidism may be caused by hyperfunctioning thyroid carcinoma. However, as the incidence of hyperfunctioning thyroid carcinoma is very low, diagnosis may be delayed and the subsequent choice of treatment may be unsuitable. Therefore, the aim of the present study was to improve our understanding of hyperfunctioning thyroid carcinoma in order to prevent misdiagnosis and to identify the most effective treatment strategies.

Materials and methods

Search strategy and selection criteria. A literature search of PubMed for studies published in English between

January 1990 and July 2017 was performed using the terms, 'hyperfunctioning thyroid carcinoma/cancer', 'malignant hot/toxic thyroid nodule', or 'hyperfunctioning papillary/follicular/Hürthle cell thyroid carcinoma', followed by a review of the identified articles. Hyperfunctioning thyroid carcinoma was divided into primary and metastatic. The inclusion criteria for studies involving primary hyperfunctioning thyroid carcinoma were as follows: i) Thyroid carcinoma, papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) or Hürthle cell carcinoma (HCC); ii) clinical hyperthyroidism with symptomatically or biochemically diagnosed thyrotoxicosis; iii) AFTN, hot or warm nodules (as determined by scintigraphy) and other thyroid tissues with suppressed uptake (^{99m}Tc, and/or ^{131}I or ^{123}I); iv) thyroid carcinomas of an identical size to hot or warm nodules, or the absence of hyperplasia in non-cancerous thyroid tissues on pathological analysis. Studies involving cases where the size of the thyroid carcinoma was not identical to that of the hot or warm nodules on scintigraphy, or those where this information was not included, were excluded from the present study, as these tumors may be embedded in hot benign nodules and be non-functional. The inclusion criteria for studies involving metastatic hyperfunctioning thyroid carcinoma were required to meet aforementioned points i, ii and iii; or i, ii and iv; or a minimum of points i, ii and vi of the following: i) Thyroid carcinoma, PTC, FTC or HCC confirmed by bioptic analysis of the metastatic lesions or thyroid nodule; ii) clinical hyperthyroidism; iii) hyperthyroidism that persists or develops following total thyroidectomy; iv) increased ^{99m}Tc, and/or ^{131}I or ^{123}I uptake in the metastatic lesion as determined by scintigraphy. Studies involving cases of persistent euthyroidism following total thyroidectomy were also excluded, as this may indicate functioning but not hyperfunctioning thyroid carcinoma.

Study selection. Since the incidence of hyperfunctioning thyroid carcinoma is very low, the number of cases found on PubMed was small, and the majority of the cases had incomplete data. Of the 763 articles retrieved from PubMed using our search strategy, 397 were duplicated and 324 did not meet the inclusion criteria. Finally, the remaining 42 articles were included in the present study. A detailed flowchart of the study selection process is presented in Fig. 1.

Results

Primary hyperfunctioning thyroid carcinoma. The literature search identified 43 cases of primary hyperfunctioning thyroid carcinoma between 1998 and 2017 (Table I) that fulfilled the inclusion criteria (3,5-28); the full-text versions of the majority of articles published before 1998 were unavailable. The mean age of patients was 50.1±19.0 years (range, 11-79 years) and the female:male ratio was 2.31 (30:13). All patients presented with clinical hyperthyroidism. Biochemical thyrotoxicosis was confirmed in all patients, apart from 11 cases, 5 of which presented with low TSH and normal T3 and T4 levels, and 6 cases with incomplete information. Thyroid scintigraphy analysis (^{99m}Tc and/or ^{131}I or ^{123}I) was performed in all but 2 patients, and indicated the presence of hot or warm nodules with suppressed uptake in the remainder of the thyroid gland as AFTN. All 43 cases presented with at least one of the following characteristics, indicating that the hyperfunctioning nodule was in fact the thyroid carcinoma: i) Pathological tumor size identical to the size of the nodule as determined by preoperative thyroid scintigraphy analysis; or ii) the thyroid tissue adjacent to the carcinoma was atrophic or normal. The majority of the cases presented with a single hyperfunctioning thyroid carcinoma, apart from 2 cases; patient 23 presented with two hyperfunctioning FTCs, and patient 31 presented with 4 hyperfunctioning PTCs. The mean tumor size was 4.25±2.12 cm. A total of 4.7% of the tumors were ≤1.0 cm in size, 11.6% were >1 to ≤2.0 cm, 39.5% were >2 to ≤4.0 cm and 44.2% were >4.0 cm. Details on the preoperative ultrasound parameters were mostly unavailable; however, based on the available information, there were no characteristic findings indicative of thyroid carcinoma (Table I). The results of fine-needle aspiration (FNA) of the thyroid performed on 15 patients identified differentiated thyroid carcinoma (DTC) or suspected DTC in 10 cases, no diagnosis by cytology in 4 cases, and no malignant characteristics in 1 case. In terms of histological subtype, 20 cases (46.5%) were FTC, 21 cases were PTC [including 7 follicular variant PTC (FVPTC)] and 2 cases were HCC.

Of the 15 patients pretreated with anti-thyroid drugs, the results indicated disease control to euthyroid in 8 patients, unknown outcome for 4 patients, no disease control in 2 patients and drug intolerance in 1 patient. Thyroid surgery was performed in all patients. In all patients with available information on disease outcome (n=9), thyrotoxicosis was well-controlled by surgery. Radioactive iodine (RAI) treatment was performed preoperatively in 3 patients who had been initially diagnosed with benign AFTN, and postoperatively in 20 patients. As long-term follow-up data were absent for the majority of the patients, and as patients were treated with RAI within a short time period following surgery, it was difficult to evaluate the effect of RAI alone on those patients. However, the available data indicated that only few (14 cases in 43 cases) suffered recurrence of thyrotoxicosis or carcinoma within a short follow-up period [44.5 months (6-208 months)] following thyroid surgery and RAI.

Metastatic hyperfunctioning thyroid carcinoma. Following a literature search, a total of 28 cases of metastatic hyperfunctioning thyroid cancer were identified (Table II) (3,4,29-44) according to the aforementioned inclusion criteria. All patients had either clinical thyrotoxicosis with biochemical data indicating hyperthyroidism, or been diagnosed as thyrotoxicosis. In addition, all cases (apart from case 56) had a high ^{99m}Tc, and/or ^{131}I or ^{123}I uptake in distant lesions, as demonstrated by whole-body scanning. All patients presented with multiple or large metastases to the bone, lungs, liver or mediastinum. The largest metastatic lesion was observed in the liver of patient 62 (17.0 cm). The mean patient age was 61.2±10.8 years, and the female:male ratio was 1.8 (18:10). Histopathological examination revealed that 20 cases were FTC, 5 cases were PTC (including 1 FVPTC), 1 case was insular TC, and 1 case was an unknown type of DTC. A total of 14 patients with metastatic hyperfunctioning thyroid carcinoma had undergone thyroidectomy, while the remaining 14 patients had no history of thyroidectomy. Thyroid scans were performed in 13 of the 14 cases with no thyroidectomy history, and the results of

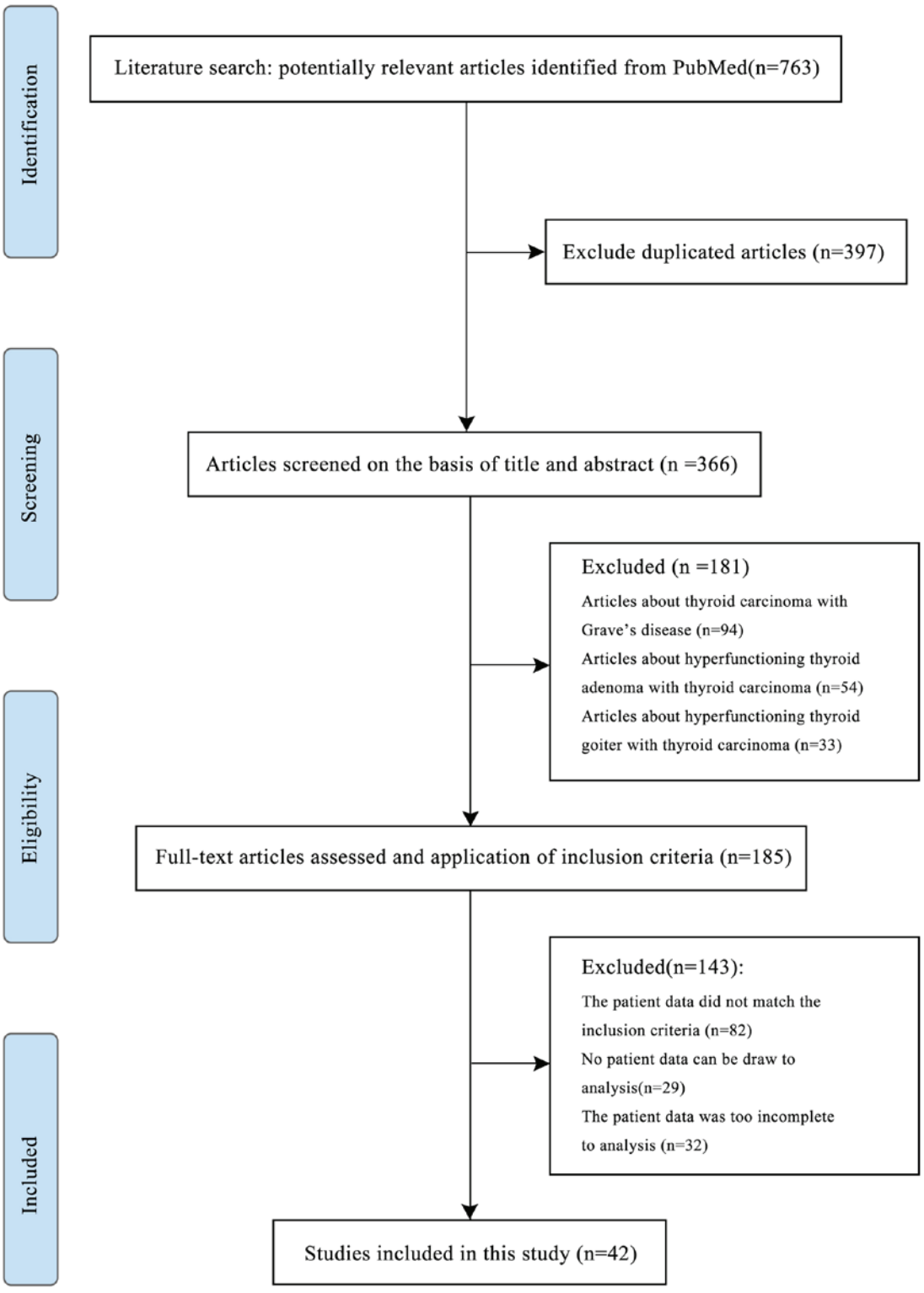

Figure 1. Flow diagram of the screening process for study selection.

6 cases indicated none to normal uptake, cold regions in the thyroid gland and the presence or absence of cold nodules. The remaining 7 cases were diagnosed with AFTN. Thyroid FNAs were performed in 5 cases with no history of thyroidectomy: DTC (1 PTC and 1 FTC) was diagnosed in 2 cases, follicular cells were identified in another 2 cases, and no malignant cells were detected in the remaining case. Biopsies of the metastatic lesions were performed in 3 cases, and the results indicated metastatic DTC. Therefore, of the 14 patients without thyroidectomy, 4 were diagnosed with metastatic hyperfunctioning thyroid cancer, 2 as suspicious and 8 as uncertain.

The results demonstrated that, of the 13 patients who underwent pretreatment with anti-thyroid medication, 6 experienced difficulties or were unable to control thyrotoxicosis, while only 3 patients became euthyroid. The outcome of thyrotoxicosis in the remaining 4 patients was uncertain. Total or subtotal

Table I. Reported cases of primary hyperfunctioning thyroid carcinoma.

A, Study ID, patient characteristics and findings on examination

No.	First author	Year	Age, years	Sex	Tumor growth	Pertechnetate	Chemical thyrotoxicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	AFTN size (cm)	Tumor size (cm)	US	FNA	Pathology	(Refs.)
1	Appetecchia	1998	23	F	3.5→ 4.0 cm	AFTN	Chemical	11.55↑	25.52↑	0.11↓	3.5/4	4	Inhomogeneous nodule		Gross PTC, 4 PTC, 3 microfoci PTC	(6)
2	Mircescu	2000	11	F		Yes, hyperfunctioning nodule	Chemical		75↑	0.03↓	4.5	4	Enlarged with numerous cystic lesions		PTC 4.0 cm, cystic	(7)
3	Bourasseau	2000	47	M		Yes, hot, solitary	Chemical	↑	N	0.05↓	3.5	3.5	Solitary	Suspicious	PTC	(8)
4	Bourasseau	2000	36	M		Yes, hot, solitary	No	N	N	0.025↓	2.5	2.5	Solitary	No diagnostic	FTC	(8)
5	Bourasseau	2000	56	M		Yes, hot, solitary	Chemical		↑	0.03↓	5.5	5.5	Solitary	No	FTC	(8)
6	Bourasseau	2000	39	F		Yes, warm	Chemical	↑	↑	0.004↓	1	1	Multinodular	Suspicious	PTC	(8)
7	Bourasseau	2000	33	F		Yes, hot	No	N		0.005↓	3	3	Multinodular	Not diagnostic	PTC	(8)
8	Camacho	2000	49	F		Yes, Hot, AFTN	Chemical		15.7↑	0.04↓	3.5	3.5		No	FTC with hemorrhagic central portion	(9)
9	Als	2002	54	M		Hot, AFTN	Uncertain				8.5	8.5		No	FTC	(3)
10	Als	2002	62	F		Uncertain	Uncertain							No	PTC	(3)
11	Als	2002	50	M		Hot, AFTN	Uncertain				10	10		No	FTC	(3)
12	Als	2002	62	M		Hot, AFTN	Chemical	↑	N	↓	8	8		No	FTC	(3)
13	Als	2002	71	F		Hot, AFTN	Chemical	↑	↑	↓	4	4		No	FTC	(3)
14	Als	2002	69	F		Hot, AFTN	Chemical	↑	N	↓	6	6		No	FTC	(3)
15	Als	2002	55	F		Hot, AFTN	Uncertain			↓	5.5	5.5		No	FTC	(3)
16	Als	2002	79	F		Hot, AFTN (suppression)	Chemical	↑	↑	↓				No	FTC	(3)
17	Als	2002	65	M		Hot, AFTN	Chemical	↑	N	↓	6.5	6.5		No	FTC	(3)
18	Als	2002	56	M		Hot, AFTN	Chemical	↑	N					No	FVPTC	(3)
19	Als	2002	75	M		Hot, AFTN	Chemical	↑	N	↓	5.5	5.5		No	FTC	(3)
20	Als	2002	77	F		Hot, AFTN	Chemical	↑	N	↓	4	4		No	PTC	(3)
21	Als	2002	71	F		Hot, AFTN	Chemical	↑		↓	6	6		No	FTC	(3)
22	Als	2002	74	F		Hot, AFTN	Chemical	↑	↑	↓	7	7		No	FTC	(3)

Table I. Continued.

No.	First author	Year	Age, years	Sex	Tumor growth	Pertechnetate	Chemical thyrotoxicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	AFTN size (cm)	Tumor size (cm)	US	FNA	Pathology	(Refs.)
23	Fuhrer	2003	59	M		Hot, AFTN right, WBS: no uptake in lung	No	N	N	0.01↓	3.5	3.5	One solid with calcification, one solid	Lung FNA: FTC	FTC x2	(10)
24	Wong	2003	67	F		Yes, hot, AFTN	Chemical		↑	↓	2.5	3		No feature of carcinoma	Hürthle cell carcinoma	(11)
25	Gozu	2004		F		Yes, hot 5.0 cm, 2.0 cm hypoactive	Chemical	9.11↑	1.89↑	0.005↓	5	5		No	PTC (intracystic)	(12)
26	Majima	2005	59	F		AFTN	Chemical	4.4↑	2.7↑	0.01↓	1.5	1.5	Hypoechoic with cystic degeneration, calcification	PTC	PTC	(13)
27	Bitterman	2006	57	F		Hot in right, cold in left	Possibly	?	?	?	6	6	Multinodular	Not diagnostic	FTC	(14)
28	Bitterman	2006	59	F		Hot, 5 cm AFTN	Possibly	?	?	?	5	5	Solitary nodule	No	FTC	(14)
29	Niepomniszcze	2006	64	F		Yes, AFTN	Chemical			0.02↓	6	6		no	FTC	(15)
30	Uludag	2008	36	M	1.4→ 1.8 cm (11 months)	AFTN	No	N	N	0.05↓	1.4	1.5	Hypoechoic nodule	PTC	PTC	(16)
31	Nishida	2008	62	F		4 hot AFTN in both lobes	Chemical	5.2↑	2.39↑	0.007↓	2.0, 1.5, 0.6,1.5	2.0	Multinodular	PTC	PTC x4	(17)
32	Bommired-dipalli	2010	63	M	Enlarging (5 months)	Yes, AFTN right	Chemical	N	2.1↑	0.01↓	4	4	Solid mass	FVPTC?	FVPTC, LN, FVPTC	(18)
33	Azevedo	2010	47	F	Enlarging (2 years)	Yes, high iodine uptake AFTN	Chemical		2.75↑	0.05↓	2.6	3	Solid nodule	PTC suggestive	FVPTC	(19)
34	Giovanella	2010	68	F		AFTN, no cold area in nodule	Chemical	7.6↑	N	0.006↓	5.3	5.3	Hypoechoic nodule	No	FTC	(20)
35	Tfayli	2010	11	F		Yes, predominant AFTN	Chemical		1.14	↓	3.5	3	Non-homogenous nodule	Not, diagnostic TC not excluded	PTC	(21)

Table I. Continued.

No.	First author	Year	Age, years	Sex	Tumor growth	Pertechnetate	Chemical thyrotoxicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	AFTN size (cm)	Tumor size (cm)	US	FNA	Pathology	(Refs.)
36	Karanchi	2012	43	F		AFTN	Chemical	12.7↑	3.1↑	0.01↓	6.5		Solid nodule	No	Hürthle cell carcinoma	(22)
37	Nair	2012	38	M		Hot, AFTN right lobe whole	Chemical	6.12↑	2.9↑	0.003↓	3.8	3	Hypoechoic with scattered microcalcification	NO	PTC with multifocal microPTC	(23)
38	Ruggeri	2013	15	F	2.5→ 3.5 cm (6 months)	Yes, AFTN	Chemical	5.0↑	20.15↑	0.001↓	3.5	3.5	Isoechoic, peripheral halo, blood flow, regular margin	No	FVPTC	(24)
39	Mirfakhraee	2013	29	F	2.4→ 2.7 cm (2 years)	Yes, AFTN	No	N	N	0.005↓	2.7	2.5	Solid, isoechoic, internal Hypervascularity	No	FTC	(5)
40	Gabalec	2014	15	F		Hot, AFTN	Chemical		30.4↑	0.01↓	4.5	4	Heterogenous, well-demarcated nodule	Follicular neoplasia?	FVPTC	(25)
41	Kuan	2014	60	F	No mention	Hot, AFTN right lobe whole	Chemical	7.71↑	7.75↓	0.005↓	8	8	Hypoechoic, avascular, nodule	Follicular neoplasia, FTC?	FVPTC	(26)
42	Rees	2015	16	F		Yes, 2.6 cm uptake	Chemical	14.3↑	39.4↑	0.03↓	4	4	Hyperechoic, hypervascular nodule	DTC?	FVPTC	(27)
43	Kadia	2016	37	F	Enlarging (3 months)	-	Chemical		23.3↑	0.13↓	3.6	3	Isoechoic, well-defined homogeneous solid nodule	NO	PTC encapsulated variant	(28)

B, Treatment and outcome

No.	First author	Treatment	Pretreatment effect	Surgery outcome	RAI effect and prognosis	Metastatic	(Refs.)
1	Appetecchia	Thyroidectomy + bilateral neck dissection + RAI	Triamazole to euthyroid	Hypothyroid, but anterior cervical tumor residual	No thyrotoxicosis or recurrence		(6)

Table I. Continued.

B, Treatment and outcome

No.	First author	Treatment	Pretreatment effect	Surgery outcome	RAI effect and prognosis	Metastatic	(Refs.)
2	Mircescu	Right loboisthmectomy/total (2 months) + RAI	Methimazole + blocker	No mention	8 months, no residual uptake		(7)
3	Bourasseau	Thyroidectomy	No mention	No mention	No		(8)
4	Bourasseau	Thyroidectomy	No mention	No mention	No		(8)
5	Bourasseau	Thyroidectomy	No mention	No mention	No		(8)
6	Bourasseau	Thyroidectomy	No mention	No mention	No		(8)
7	Bourasseau	Thyroidectomy	No mention	No mention	No		(8)
8	Camacho	Thyroidectomy + RAI	No mention	No mention	3 years, no thyrotoxicosis or recurrence		(9)
9	Als	Surgery + RAI	Uncertain	Uncertain	117 months	Yes	(3)
10	Als	Surgery + RAI + PR	Uncertain	Uncertain	82 months	Yes	(3)
11	Als	Surgery + RAI + PR	carbimazole	Uncertain	18 months	Yes	(3)
12	Als	Surgery + RAI	Uncertain	Uncertain	190 months	Yes	(3)
13	Als	RAI + surgery + RAI	Uncertain	Uncertain	68 months	Yes	(3)
14	Als	Surgery + RAI + PR	Uncertain	Uncertain	28 months	Yes	(3)
15	Als	Surgery + RAI + PR	Uncertain	Uncertain	93 months	Yes	(3)
16	Als	RAI + surgery + RAI	Uncertain	Uncertain	46 months	Liver and sacrum	(3)
17	Als	Surgery + RAI + PR	Uncertain	Uncertain	107 months	Yes	(3)
18	Als	Surgery + RAI	Uncertain	Uncertain	208 months alive	No	(3)
19	Als	Surgery + RAI	Uncertain	Uncertain	181 months	No	(3)
20	Als	Surgery + RAI	Uncertain	Uncertain	45 months	Uncertain	(3)
21	Als	Surgery + RAI + PR	Uncertain	Uncertain	44 months	Yes	(3)
22	Als	Surgery + RAI	Uncertain	Uncertain	76 months alive	Yes	(3)
23	Fuhrer	Total thyroidectomy + RAI - thoracic surgery (8 months)	Euthyroid	Hypothyroid with RAI	Hypothyroid, 8 months thyrotoxicosis control good	Yes	(10)
24	Wong	Lobectomy/total thyroidectomy + RAI	No mention	No mention	No mention		(11)
25	Gozu	Lobectomy/total thyroidectomy + RAI	Euthyroid	Hypothyroid (6 weeks)	1 year, no thyrotoxicosis or recurrence		(12)
26	Majima	Lobectomy	No mention	Hypothyroid (3 months)	No		(13)

Table I. Continued.

B, Treatment and outcome

No.	First author	Treatment	Pretreatment effect	Surgery outcome	RAI effect and prognosis	Metastatic	(Refs.)
27	Bitterman	Loboisthmectomy + nodule excision/total thyroidectomy	PTU, no clinical improve	Disease-free 1.5 years	No		(14)
28	Bitterman	Left lobectomy	PTU, intolerance several months	No mention	No		(14)
29	Niepomniszcze	Lobectomy/total thyroidectomy + RAI	No mention	No mention	6 months, no thyrotoxicosis or recurrence		(15)
30	Yazici	RAI→total thyroidectomy + CND	No mention	No recurrence or residual disease	Thyrotoxicosis control, but size increase		(16)
31	Nishida	Total thyroidectomy	Thiamazole, 5 months to euthyroid	No recurrence and residual disease (1 year)	No		(17)
32	Bommireddipalli	Total thyroidectomy + RAI	No	No mention	1 year, TG↑LN + , 1.5 year, LN biopsy +	Yes	(18)
33	Azevedo	Total thyroidectomy + RAI	Methimazole 2 months to euthyroid	True hypothyroidism (2 months) then RAI	3 years + 2 years no thyrotoxicosis or recurrence		(19)
34	Giovanella	Right loboisthmectomy + RAI	No	Hypothyroid	3.4 years, negative		(20)
35	Tfayli	Lobectomy/total thyroidectomy + RAI	No mention	No mention	1 year, no thyrotoxicosis or recurrence		(21)
36	Karanchi	Hemithyroidectomy/total thyroidectomy (1 year) + RAI	No control	Euthyroid (2 weeks)	No		(22)
37	Nair	Total thyroidectomy + CND + LND + RAI (4 weeks + 6 months)	Carbimazole to euthyroid	No mention	TG 1 year high, LN metastases	Yes	(23)
38	Ruggeri	Surgery	Methimazole to euthyroid	No mention	No		(24)
39	Mirfakhraee	Left lobectomy	No mention	Euthyroid (6 months) with no recurrence of cancer	No		(5)
40	Gabalec	Hemithyroidectomy/total thyroidectomy + CND + RAI	Triamazole	No mention	To hypothyroid state		(25)
41	Kuan	Total thyroidectomy	No mention	No mention	No		(26)
42	Rees	Left lobectomy + RAI	Carbimazole to euthyroid	No mention	Wel-controlled		(27)
43	Kadia	Left lobectomy	methimazole + blocker	Euthyroid (2-4 weeks)	No		(28)

M, male; F, female; AFTN, autonomous functioning thyroid nodule; US, ultrasound; FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; FVPTC, follicular variant papillary thyroid carcinoma; LN, lymph node; RAI, radioactive iodine; PR, preoperative radioactive iodine; CND, central neck dissection; LND, lateral neck dissection; TG, thyroglobulin; WBS, whole-body scanning.

Table II. Reported cases of metastatic hyperfunctioning thyroid carcinoma.

A, Study ID, patient characteristics and findings on examination

No.	First author	Year	Age, years	Sex	Thyroid-ectomy history	Thyroid scan	Whole body scan	Thyroto-xicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	TG (ng/ml)	Metastatic location	Thyroid FNA	Biopsy on metastasis	Pathology	(Refs.)
44	Girelli	1990	66	F	No	Normal, uptake cold nodules	High uptake in distant lesions	Clinical			0.01↓	5,300	Bone	PTC	Metastatic	PTC PTC	(29)
45	Mizukami	1994	64	F	No	Hot AFTN 4.0	High uptake in distant lesions	Clinical			↓		Bone	Microfo-llicular	No	FTC	(30)
46	Russo	1997	60	F	No	Hot AFTN two	High uptake in distant lesions (after surgery)	Clinical	2.8↑	N	0.06↓	513	Lung	No	No	Insular TC	(31)
47	Salvatori	1993	79	F	No	Cold areas	High uptake in distant lesions	Clinical	10.4↑	3.8↑	0.06↓	382	Lung	FTC	No	FTC	(32)
48	Als	2002	61	M	No	Hot AFTN	High uptake in distant lesions	Clinical					Uncertain	No	No	FTC	(3)
49	Als	2002	65	F	No	Hot AFTN	High uptake in distant lesions	Clinical					Uncertain	No	No	FTC	(3)
50	Als	2002	71	F	No	Hot AFTN	High uptake in distant lesions	Clinical		↑	↓		Uncertain	No	No	FTC	(3)
51	Als	2002	62	F	No	Hot AFTN	High uptake in distant lesions	Clinical			↓		Uncertain	No	No	FTC	(3)
52	Als	2002	63	M	No	Hot AFTN	High uptake in distant lesions	Clinical		N	↓		Uncertain	No	No	PTC	(3)
53	Sundaraiya	2009	68	M	No	Cold nodule	High uptake in distant lesions	Clinical	42.6↑	100↑	↓		Rib	No	Rib FTC	FTC multifocal	(33)
54	Damle	2012	65	M	No	-	High uptake in distant lesions	Clinical			0.03↓	300	Lung, bone	Follicular neoplasm	No	FTC	(34)
55	Damle	2012	62	M	No	No uptake	High uptake in distant lesions	Clinical	↑	↑	↓	300	Bone	No	Metastatic FTC		(34)
56	Gardner	2014	66	F	No	Diffuse reduction	No WBS	Clinical	25.1↑	37.9↑	0.006↓		Lung, bone	No malignant cells		FVPTV	(35)
57	Kunawudhi	2016	43	F	No	Cold	High uptake in distant lesions	Clinical	32.55↑	6.34↑	0.026↓		Bone, liver	No	No	FTC	(36)

Table II. Continued.

No.	First author	Year	Age, years	Sex	Thyroid-ectomy history	Thyroid scan	Whole body scan	Thyroto-xicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	TG (ng/ml)	Metastatic location	Thyroid FNA	Biopsy on metastasis	Pathology	(Refs.)
58	Abs	1991	57	F	Partial thyroid-ectomy	Normal	High uptake in distant lesions	Clinical			0.6↓	640	Mediasti-num			FTC	(37)
59	Lorberb-oym	1996	67	F	Total thyroid-ectomy		High uptake in distant lesions	Clinical	273↑	15.7↑	0.1↓		Hemipelvis			FTC	(38)
60	Yoshimura	1997	61	M	Total thyroidectomy + RAI + hip replacement		High uptake in distant lesions	Clinical	46.1↑	105.3↑	0.05↓	329	Pelvis			FTC	(39)
61	Salvatori	1993	69	F	Partial thyroidectomy	Low uptake	High uptake in distant lesions	Clinical	3.8↑	10.4↑	0.06↓	48,680	Lung			DTC	(32)
62	Guglielmi	1999	58	F	Subtotal thyroidectomy		High uptake in distant lesions	Clinical	18.4↑	44.5↑	0.1↓	3,686	Liver, lung		Liver FTC	FTC	(40)
63	Basaria	2002	74	M	Total thyroidectomy 8 years		High uptake in distant lesions	Clinical	↑	↑	↓	2,280	Mediastinum and lung			PTC	(41)
64	Orsolon	2008	66	M	Total thyroidectomy		High uptake in distant lesions	Clinical	4.5↑	1.6	<0.1↓	>10,000	Bone, lung			FTC	(42)
65	Tan	2009	39	F	Total thyroidectomy + hip replacement + RAI		High uptake in distant lesions (FDG)	Clinical	27.9↑	4.41↑	0.01↓	1,000	Pelvic mass			FTC	(43)
66	Nishihara	2010	59	F	Total thyroidectomy + EBRT		High uptake in distant lesions	Clinical	↑	↑	0.01↓	8,000	Multiple bone and lung			FTC	(44)
67	Qiu	2015	45	M	Total thyroidectomy		High uptake in distant lesions	Clinical	13.42↑	33.9↑	0.04↓		Bone			FTC	(4)
68	Qiu	2015	75	M	Total thyroidectomy		High uptake in distant lesions	Clinical	9.35↑	27.18↑	0.24↓		Lung			PTC	(4)

Table II. Continued.

No.	First author	Year	Age, years	Sex	Thyroid-ectomy history	Thyroid scan	Whole body scan	Thyroto-xicosis	FT3 (pmol/l)	FT4 (pmol/l)	TSH (uIU/ml)	TG (ng/ml)	Metastatic location	Thyroid FNA	Biopsy on metastasis	Pathology	(Refs.)
69	Qiu	2015	43	F	Total thyroidectomy		High uptake in distant lesions	Clinical	7.23↑	29.14↑	0.22↓		Bone			FTC	(4)
70	Qiu	2015	51	F	Total thyroidectomy		High uptake in distant lesions	Clinical	9.51↑	31.73↑	0.02↓		Bone, lung			FTC	(4)
71	Qiu	2015	54	F	Total thyroidectomy		High uptake in distant lesions	Clinical	7.83↑	32.15↑	0.01↓		Bone			FTC	(4)

B, Treatment and outcome

No.	First author	Pretreatment antithyroid drug	Treatment	Surgery outcome	Response to RAI	(Refs.)
44	Girelli	Thyrotoxicosis to subhyperthyroidism	Total thyroidectomy + RAI	Persistent	Hyperthyroidism persisting 6 months after RAI	(29)
45	Mizukami	Unknown	RAI	-	Persistent after 2 RAI	(30)
46	Russo	Unknown	Subtotal thyroidectomy/1 year total + RAI 2	Mild hyperthyroidism	Hypothyroid, TG remains high (2 years)	(31)
47	Salvatori	Effect not shown	Total thyroidectomy + RAI	Improved only 1 month	Hyperthyroidism persisting 4 months after RAI	(32)
48	Als	Unknown	RAI + surgery + RAI	Persistent	27 months, died	(3)
49	Als	Unknown	RAI + surgery + RAI	Persistent	39 months, died	(3)
50	Als	Unknown	Surgery + RAI	Persistent	229 months, died	(3)
51	Als	Unknown	Surgery + RAI	Persistent, possible improvement	10 months, died	(3)
52	Als	Unknown	Surgery + RAI	Persistent	71 months, died	(3)
53	Sundaraiya	Effect not shown	Total thyroidectomy + RAI	Persistent	3 months RAI hypothyroid with tumor control	(33)
54	Damle	Thyrotoxicosis difficult to control	Subtotal thyroidectomy + RAI	Improved only 2 months	5 years of no recurrence of thyrotoxicosis	(34)
55	Damle	Thyrotoxicosis difficult to control	RAI	-	3 years of no recurrence of thyrotoxicosis	(34)
56	Gardner	Thyrotoxicosis difficult to control	Total thyroidectomy + RAI	Died of thyroid storm 12 days postoperatively	-	(35)
57	Kunawudhi	Effect not shown	Total thyroidectomy + right LND + RAI + EBRT	Persistent	2 years, progressive disease	(36)
58	Abs	Thyrotoxicosis difficult to control	Rib biopsy + RAI, good		RAI 9 years, no metastases	(37)

Table II. Continued.

No.	First author	Pretreatment antithyroid drug	Treatment	Surgery outcome	Response to RAI	(Refs.)
59	Lorberboym	Pretreatment to euthyroid +EBRT to hypothyroid	Pretreatment + EBRT + RAI		4 weeks RAI hypothyroid	(38)
60	Yoshimura	No mention	RAI + pretreatment		Rapid improvement 1.5 years survival	(39)
61	Salvatori	Effect not shown	RAI		Hyperthyroidism persisting 6 months after RAI	(32)
62	Guglielmi	Failure to control thyrotoxicosis	ILP + RAI		1.5 years good control	(40)
63	Basaria	Good control	Pretreatment + RAI		3 months hypothyroid	(41)
64	Orsolon	Unknown	Unknown		Unknown	(42)
65	Tan	Worsening	Removal of pelvis mass and partial bone	Thyrotoxicosis disappeared	Resistant to RAI	(43)
66	Nishihara	Unknown	RAI low multiple		10 months after RAI, toxicosis control, but tumor progression, 8 years of survival	(44)
67	Qiu	Unknown	RAI + palliative resection		Effect not clearly shown	
68	Qiu	Unknown	RAI		Effect not clearly shown	(4)
69	Qiu	Unknown	RAI + palliative resection		Effect not clearly shown	(4)
70	Qiu	Unknown	RAI + palliative resection		Effect not clearly shown	(4)
71	Qiu	Unknown	RAI		Effect not clearly shown	(4)

M, male; F, female; RAI, radioactive iodine; EBRT, external beam radiation therapy; AFTN, autonomous functioning thyroid nodule; FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; FVPTC, follicular variant papillary thyroid carcinoma; TC, thyroid carcinoma; DTC, differentiated thyroid carcinoma; LND, lateral neck dissection; ILP, interstitial laser photocoagulation; TG, thyroglobulin; LN, lymph node.

thyroidectomy was performed in 12 of 14 cases without a history of thyroidectomy. One patient succumbed to thyroid crisis at 12 days post-surgery. Following surgery, thyrotoxicosis persisted in 8 patients, while a transient improvement was observed in 3 patients. All patients underwent multi-dose RAI, apart from 2 patients (patient 56 succumbed to the disease and the outcome of patient 64 is unknown). Following RAI, the majority of the patients exhibited a significant improvement in hyperthyroidism and good cancer control; however, thyrotoxicosis in patient 44 persisted for up to 6 months. Patients 55 and 58 experienced no recurrence of thyrotoxicosis or cancer during a follow-up period of 3 or 9 years, respectively following RAI treatment. Of particular note, patient 65 developed RAI resistance 4 years after the first dose of RAI. This patient's thyrotoxicosis was caused by pelvic metastasis, which was cleared following surgical removal of the pelvic mass.

Discussion

Thyroid carcinoma coexisting with hyperthyroidism is rare and is more commonly encountered among younger, female patients (5). Diagnosis relies on clinical and histopathological correlation. On histopathological examination, the lack of hyperplastic thyroid tissue often suggests a hyperfunctioning thyroid cancer (28).

The results of the present study have several implications, as discussed below. First, the prevalence of different histological subtypes of hyperfunctioning thyroid carcinoma was investigated in the present study. The results indicated that 46.5% of primary hyperfunctioning thyroid carcinomas and 71.4% (20/28) of metastatic hyperfunctioning thyroid carcinomas were of the FTC subtype. Mirfakhraee *et al* (5) reported that 36.4% (28/77) of solitary hyperfunctioning thyroid nodules harboring a thyroid carcinoma, in which the majority are primary hyperfunctioning thyroid carcinomas, were of the FTC subtype. Qiu *et al* (4) reported that the prevalence of FTC in functioning metastatic thyroid carcinoma was 60.5% (23/38), of which 5 cases were hyperfunctioning. By comparison, the Surveillance, Epidemiology and End Results (SEER) cancer registry program (1974-2013) (45), which records all histological thyroid cancer cases as a single group, indicates that the prevalence of FTC is 10.8% and that of PTC is 83.6%. Therefore, there appears to be a higher prevalence of FTC among patients with hyperfunctioning thyroid carcinoma, and a particularly high prevalence among patients with metastatic disease. This suggests that hyperfunctioning thyroid carcinoma may be more likely to occur in either primary or metastatic FTC when compared with PTC. The reason for this is unknown. The results presented by Qiu *et al* (4) indicate that the prognosis of patients with metastatic hyperfunctioning FTC is worse compared with that for patients with PTC.

Tumor size is an additional important factor to consider for hyperfunctioning thyroid carcinoma. In the present study, the mean tumor size of primary hyperfunctioning thyroid carcinoma was observed to be 4.25±2.12 cm. These results are consistent with those presented by Mirfakhraee *et al* (5), who reported a mean tumor size of 4.13±1.68 cm in malignant hot nodules (the majority of which were hyperfunctioning thyroid carcinomas). By comparison, the SEER cancer registry program (1974-2013) (45) reports that 28.6% of thyroid carcinomas are ≤1.0 cm in size, 26.0% are >1.0 to ≤2.0 cm, 23.0% are >2.0 to ≤4.0 cm, 9.6% are >4.0 cm and 13.0% are unknown. Pazaitou-Panayiotou *et al* (2) conducted a well-organized review, which demonstrated that the majority of non-functioning thyroid carcinomas that coexist with Graves' disease, toxic nodule goiter or hyperfunctioning adenoma, are microcarcinomas (35.0-88.0%). In addition, similar characteristics were observed in these metastatic hyperfunctioning thyroid carcinoma patients. It is considered that large primary or metastatic tumors may synthesize excessive thyroid hormones more readily, which may cause hyperthyroidism. Somatic mutations in TSH receptor genes may explain the hyperthyroidism caused by thyroid cancer. These mutations activate the intracellular cAMP cascade, induce hormone production and, ultimately, lead to hyperthyroidism (28,46). Pringle *et al* (47) observed that thyroid-specific knockout of *PrkarIa* leads to hyperthyroidism and thyroid cancer in mice. Moreover, they suggested that another genetic mutation may be implicated in metastasis, apart from *PrkarIa* mutation in the thyroid (47). As DTC cells have similar functions to normal thyroid follicular cells, such as TSH-dependence, absorption of iodine and secretion of thyroglobulin, DTC cells may also secrete thyroxine. When autoregulation mechanisms are impeded, such as in Graves' disease, large DTCs may secrete excessive amounts of thyroxine resulting in hyperthyroidism. These results also indicate that debulking surgery may play a key role in the treatment of this rare disease.

As regards the diagnosis of hyperfunctioning thyroid carcinoma, it is difficult to distinguish malignant from benign AFTN, as they share common characteristics, such clinical thyrotoxicosis with hot nodules on thyroid scintigraphy. However, the following factors may help determine whether thyrotoxicosis is the result of primary hyperfunctioning thyroid carcinoma: i) No improvement in thyrotoxicosis following RAI treatment (patient 30 in the present systematic review) (16); ii) ultrasound results indicating the presence of hypoechoic solid nodules with microcalcifications (patients 23 and 37 in the present systematic review) (10,23); and iii) tumor growth over a short time period (patient 32 and 43 in the present systematic review) (18,28). Additional risk factors for malignancy were also reported, such as age (<20 or >60 years), male sex, a family history of DTC, a previous history of head or neck irradiation, tumor fixation to adjacent structures and symptoms of tumor invasion (3,5). Most importantly, AFTN should not be considered to rule out the possibility of malignant thyroid tumor. The applicability of thyroid FNA in differentiating malignant from benign AFTN is limited. This is because ~50% of primary hyperfunctioning thyroid carcinomas are FTCs, which are difficult to distinguish from follicular adenoma by FNA. However, if follicular neoplasms in the thyroid nodule are detected by FNA, combined with high uptake in distant lesions on whole-body scan images and thyrotoxicosis, a diagnosis of metastatic hyperfunctioning thyroid carcinoma, FTC or FVPTC should be considered. Of the 5 metastatic hyperfunctioning thyroid carcinoma patients who underwent FNA, 2 cases were DTC (1 PTC and 1 FTC) and 2 cases were follicular neoplasms; therefore, these 4 patients were diagnosed with metastatic hyperfunctioning thyroid carcinoma. FNA may therefore facilitate the diagnosis

of hyperfunctioning metastatic thyroid carcinoma. In 13 of 14 patients with no history of thyroidectomy who underwent thyroid scans, 6 cases demonstrated no increased uptake in the thyroid gland. For these patients, and for patients who develop thyrotoxicosis following total/subtotal thyroidectomy, a diagnosis of metastatic hyperfunctioning thyroid carcinoma should be considered and a whole-body scan should be performed with other additional imaging methods in order to identify metastatic lesions. Core needle aspiration and pathological analysis by H&E staining may also facilitate the diagnosis of primary or metastatic thyroid carcinoma. Hyperfunctioning thyroid carcinoma will require diagnosis by FNA or core needle aspiration and whole-body scanning, as well as confirmation of clinical thyrotoxicosis.

Drug management is considered more suitable for primary hyperthyroidism with Graves' disease. However, based on our clinical experience, favorable clinical benefits may be achieved with early surgery in cases with secondary hyperthyroidism caused by nodular goiter or thyroid adenoma. Furthermore, surgery can effectively cure patients with hyperthyroidism with non-functioning thyroid carcinomas. For the treatment of hyperfunctioning thyroid carcinoma, the primary aim is to control hyperthyroidism, as well as the cancer itself. Therefore, surgery, particularly total thyroidectomy, is the first-line treatment option for patients with primary hyperfunctioning thyroid carcinoma, as it does not only confirm the diagnosis following pathological examination, but also resolves thyrotoxicosis and cures the cancer. Of the 43 patients in the present study, all except 4 patients diagnosed preoperatively by FNA, were diagnosed with thyroid carcinoma following thyroid surgery. In addition, all 43 patients developed euthyroidism/hypothyroidism within a short time-period following surgery. However, total thyroidectomy may not be the optimal first-line treatment option for patients with hyperfunctioning metastatic lesions with non-functioning primary thyroid carcinoma (as indicated by no increased uptake on thyroid scintigraphy). This is because a total thyroidectomy is unable to control thyrotoxicosis and may even lead to deterioration, as the majority of hormones are produced by metastatic lesions. Of the 5 cases who had undergone total or subtotal thyroidectomy, postoperative thyrotoxicosis persisted in 3 patients, transient improvements were observed in 1 patient, and the remaining patient succumbed to thyroid crisis 12 days after surgery. In addition, the significance of total thyroidectomy in terms of ^{131}I therapy was markedly lower in patients with low thyroid bed ^{131}I uptake and intense ^{131}I uptake in distant metastatic lesions. However, for patients with functional primary and metastatic tumors, total thyroidectomy may be the optimal primary treatment option, as it eliminates the hot primary thyroid carcinoma, which produces a certain amount of thyroid hormones, removes the thyroid gland and reduces the ^{131}I dose required to treat the metastatic lesions. In addition, total thyroidectomy and subsequent pathological diagnosis may be particularly useful for patients who have not undergone a preoperative FNA.

RAI is necessary for treating hyperfunctioning metastatic lesions in patients with thyroid carcinoma (4); it is a first-line treatment option for patients with a history of thyroidectomy or for those with no increased uptake in the thyroid gland. To avoid a possible thyroid storm, pretreatment with antithyroid medication is required. Fractionated RAI (as for patient 66 in the present systematic review) (44), or minimal invasive local ablation may also be considered (as for patient 62 in the present systematic review) (40). If the metastatic lesion is resistant to RAI and the functioning lesion resectable, surgery may be considered as a treatment option. This was demonstrated in patient 65 (43), whose thyrotoxicosis disappeared following surgical removal of the functioning pelvic mass. However, it is difficult to evaluate the efficiency of RAI following surgery in patients with primary functioning thyroid carcinoma without metastasis. As the majority of primary hyperfunctioning thyroid tumors were large, and metastasis was reported during follow-up post-surgery, RAI was considered as a treatment option following surgery in patients with primary hyperfunctioning thyroid carcinoma (12,19).

In conclusion, the results of the present study indicated that the size of hyperfunctioning thyroid tumors is markedly larger, and primary or metastatic FTC is more commonly hyperfunctioning compared with PTC. FNA or core needle aspiration together with whole-body scanning may play a key role in the diagnosis of clinical thyrotoxicosis. In addition, surgery and RAI are the preferred treatments for primary and metastatic hyperfunctioning thyroid carcinoma, respectively. However, there were certain limitations to the present study: We evaluated studies using the Newcastle-Ottawa Scale and the scores of the studies ranged 2-4. Considering that the number of hyperfunctioning thyroid carcinomas is small and most studies are published as case reports, a risk of bias may exist and the results must be interpreted with caution.

Acknowledgements

JL gratefully acknowledges the support of Shanghai Jiao Tong University K.C. Wong Medical Fellowship Fund (2017) and Program of Foreign Visiting Studies of Young Teachers in Shanghai Colleges and Universities (2017). The authors would like to thank Xiaoyun Xu for proofreading the article.

Funding

The present study was funded by the Shanghai Jiao Tong University K.C. Wong Medical Fellowship Fund (2017) and the Program of Foreign Visiting Studies of Young Teachers in Shanghai Colleges and Universities (2017).

Availability of data and materials

All the datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JL conceived the study and drafted and wrote the manuscript, YW and DD collected the data, MZ analyzed and interpreted the data and provided the clinical suggestion. All the authors have read and approved the final version of this manuscript for publication.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests to disclose.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, *et al*: 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 26: 1-133, 2016.
2. Pazaitou-Panayiotou K, Michalakis K and Paschke R: Thyroid cancer in patients with hyperthyroidism. Horm Metab Res 44: 255-262, 2012.
3. Als C, Gedeon P, Rösler H, Minder C, Netzer P and Laissue JA: Survival analysis of 19 patients with toxic thyroid carcinoma. J Clin Endocrinol Metab 87: 4122-4127, 2002.
4. Qiu ZL, Shen CT and Luo QY: Clinical management and outcomes in patients with hyperfunctioning distant metastases from differentiated thyroid cancer after total thyroidectomy and radioactive iodine therapy. Thyroid 25: 229-237, 2015.
5. Mirfakhraee S, Mathews D, Peng L, Woodruff S and Zigman JM: A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: Review of the literature. Thyroid Res 6: 7, 2013.
6. Appetecchia M and Ducci M: Hyperfunctioning differentiated thyroid carcinoma. J Endocrinol Invest 21: 189-192, 1998.
7. Mircescu H, Parma J, Huot C, Deal C, Oligny LL, Vassart G and Van Vliet G: Hyperfunctioning malignant thyroid nodule in an 11-year-old girl: Pathologic and molecular studies. J Pediatr 137: 585-587, 2000.
8. Bourasseau I, Savagner F, Rodien P, Duquenne M, Reynier P, Guyetant S, Bigorgne JC, Malthièry Y and Rohmer V: No evidence of thyrotropin receptor and G(s alpha) gene mutation in high iodine uptake thyroid carcinoma. Thyroid 10: 761-765, 2000.
9. Camacho P, Gordon D, Chiefari E, Yong S, DeJong S, Pitale S, Russo D and Filetti S: A Phe 486 thyrotropin receptor mutation in an autonomously functioning follicular carcinoma that was causing hyperthyroidism. Thyroid 10: 1009-1012, 2000.
10. Führer D, Tannapfel A, Sabri O, Lamesch P and Paschke R: Two somatic TSH receptor mutations in a patient with toxic metastasising follicular thyroid carcinoma and non-functional lung metastases. Endocr Relat Cancer 10: 591-600, 2003.
11. Wong CP, AuYong TK and Tong CM: Thyrotoxicosis: A rare presenting symptom of Hurthle cell carcinoma of the thyroid. Clin Nucl Med 28: 803-806, 2003.
12. Gozu H, Avsar M, Bircan R, Claus M, Sahin S, Sezgin O, Deyneli O, Paschke R, Cirakoglu B and Akalin S: Two novel mutations in the sixth transmembrane segment of the thyrotropin receptor gene causing hyperfunctioning thyroid nodules. Thyroid 15: 389-397, 2005.
13. Majima T, Doi K, Komatsu Y, Itoh H, Fukao A, Shigemoto M, Takagi C, Corners J, Mizuta N, Kato R and Nakao K: Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J 52: 309-316, 2005.
14. Bitterman A, Uri O, Levanon A, Baron E, Lefel O and Cohen O: Thyroid carcinoma presenting as a hot nodule. Otolaryngol Head Neck Surg 134: 888-889, 2006.
15. Niepomniszcze H, Suárez H, Pitoia F, Pignatta A, Danilowicz K, Manavela M, Elsner B and Bruno OD: Follicular carcinoma presenting as autonomous functioning thyroid nodule and containing an activating mutation of the TSH receptor (T620I) and a mutation of the Ki-RAS (G12C) genes. Thyroid 16: 497-503, 2006.
16. Uludag M, Yetkin G, Citgez B, Isgor A and Basak T: Autonomously functioning thyroid nodule treated with radioactive iodine and later diagnosed as papillary thyroid cancer. Hormones (Athens) 7: 175-9, 2008.
17. Nishida AT, Hirano S, Asato R, Tanaka S, Kitani Y, Honda N, Fujiki N, Miyata K, Fukushima H and Ito J: Multifocal hyperfunctioning thyroid carcinoma without metastases. Auris Nasus Larynx 35: 432-436, 2008.
18. Bommireddipalli S, Goel S, Gadiraju R, Paniz-MondolFi A and DePuey EG: Follicular variant of papillary thyroid carcinoma presenting as a toxic nodule by I-123 scintigraphy. Clin Nucl Med 35: 770-775, 2010.
19. Azevedo MF and Casulari LA: Hyperfunctioning thyroid cancer: A five-year follow-up. Arq Bras Endocrinol Metabol 54: 78-80, 2010.
20. Giovanella L, Fasolini F, Suriano S and Mazzucchelli L: Hyperfunctioning solid/trabecular follicular carcinoma of the thyroid gland. J Oncol 2010, 2010.
21. Tfayli HM, Teot LA, Indyk JA and Witchel SF: Papillary thyroid carcinoma in an autonomous hyperfunctioning thyroid nodule: Case report and review of the literature. Thyroid 20: 1029-1032, 2010.
22. Karanchi H, Hamilton DJ and Robbins RJ: Hürthle cell carcinoma of the thyroid presenting as thyrotoxicosis. Endocr Pract 18: e5-e9, 2012.
23. Nair CG, Jacob P, Babu M and Menon R: Toxic thyroid carcinoma: A new case. Indian J Endocrinol Metab 16: 668-670, 2012.
24. Ruggeri RM, Campenni A, Giovinazzo S, Saraceno G, Vicchio TM, Carlotta D, Cucinotta MP, Micali C, Trimarchi F, Tuccari G, *et al*: Follicular variant of papillary thyroid carcinoma presenting as toxic nodule in an adolescent: Coexistent polymorphism of the TSHR and Gsα genes. Thyroid 23: 239-242, 2013.
25. Gabalec F, Svilias I, Plasilova I, Hovorkova E, Ryska A and Horacek J: Follicular variant of papillary carcinoma presenting as a hyperfunctioning thyroid nodule. J Pediatr Hematol Oncol 36: e94-e96, 2014.
26. Kuan YC and Tan FH: Thyroid papillary carcinoma in a 'hot' thyroid nodule. QJM 107: 475-476, 2014.
27. Rees DO, Anthony VA, Jones K and Stephens JW: Follicular variant of papillary thyroid carcinoma: An unusual cause of thyrotoxicosis. BMJ Case Rep 2015, 2015.
28. Kadia BM, Dimala CA, Bechem NN and Aroke D: Concurrent hyperthyroidism and papillary thyroid cancer: A fortuitous and ambiguous case report from a resource-poor setting. BMC Res Notes 9: 369, 2016.
29. Girelli ME, Casara D, Rubello D, Pelizzo MR, Busnardo B and Ziliotto D: Severe hyperthyroidism due to metastatic papillary thyroid carcinoma with favorable outcome. J Endocrinol Invest 13: 333-337, 1990.
30. Mizukami Y, Michigishi T, Nonomura A, Yokoyama K, Noguchi M, Hashimoto T, Nakamura S and Ishizaki T: Autonomously functioning (hot) nodule of the thyroid gland. A clinical and histopathologic study of 17 cases. Am J Clin Pathol 101: 29-35, 1994.
31. Russo D, Tumino S, Arturi F, Vigneri P, Grasso G, Pontecorvi A, Filetti S and Belfiore A: Detection of an activating mutation of the thyrotropin receptor in a case of an autonomously hyperfunctioning thyroid insular carcinoma. J Clin Endocrinol Metab 82: 735-738, 1997.
32. Salvatori M, Rufini V, Corsello SM, Saletnich I, Rota CA, Barbarino A and Troncone L: Thyrotoxicosis due to ectopic retrotracheal adenoma treated with radioiodine. J Nucl Biol Med 37: 69-72, 1993.
33. Sundaraiya S, Dizdarevic S, Miles K, Quin J, Williams A, Wheatley T and Zammitt C: Unusual initial manifestation of metastatic follicular carcinoma of the thyroid with thyrotoxicosis diagnosed by technetium Tc 99m pertechnetate scan: Case report and review of literature. Endocr Pract 15: 458-462, 2009.
34. Damle NA, Bal C, Kumar P, Soundararajan R and Subbarao K: Incidental detection of hyperfunctioning thyroid cancer metastases in patients presenting with thyrotoxicosis. Indian J Endocrinol Metab 16: 631-636, 2012.
35. Gardner D and Ho SC: A rare cause of hyperthyroidism: Functioning thyroid metastases. BMJ Case Rep 2014: pii: bcr2014206468 2014.
36. Kunawudhi A, Promteangtrong C and Chotipanich C: A case report of hyperfunctioning metastatic thyroid cancer and rare I-131 avid liver metastasis. Indian J Nucl Med 31: 210-214, 2016.

37. Abs R, Verhelst J, Schoofs E and De Somer E: Hyperfunctioning metastatic follicular thyroid carcinoma in Pendred's syndrome. Cancer 67: 2191-2193, 1991.
38. Lorberboym M and Mechanick JI: Accelerated thyrotoxicosis induced by iodinated contrast media in metastatic differentiated thyroid carcinoma. J Nucl Med 37: 1532-1535, 1996.
39. Yoshimura Noh J, Mimura T, Kawano M, Hamada N and Ito K: Appearance of TSH receptor antibody and hyperthyroidism associated with metastatic thyroid cancer after total thyroidectomy. Endocr J 44: 855-859, 1997.
40. Guglielmi R, Pacella CM, Dottorini ME, Bizzarri GC, Todino V, Crescenzi A, Rinaldi R, Panunzi C, Rossi Z, Colombo L and Papini E: Severe thyrotoxicosis due to hyperfunctioning liver metastasis from follicular carcinoma: Treatment with (131)I and interstitial laser ablation. Thyroid 9: 173-177, 1999.
41. Basaria S and Salvatori R: Thyrotoxicosis due to metastatic papillary thyroid cancer in a patient with Graves' disease. J Endocrinol Invest 25: 639-642, 2002.
42. Orsolon P, Giachetti M, Lupi A, Salgarello M, Malfatti V and Zanco P: Pre-therapy hyperfunctioning follicular thyroid carcinoma evaluation with I-131 whole-body scan and with F-18 FDG PET/CT. Clin Nucl Med 33: 882-886, 2008.
43. Tan J, Zhang G, Xu W, Meng Z, Dong F, Zhang F, Jia Q and Liu X: Thyrotoxicosis due to functioning metastatic follicular thyroid carcinoma after twelve I-131 therapies. Clin Nucl Med 34: 615-619, 2009.
44. Nishihara E, Amino N and Miyauchi A: Fractionated radioiodine therapy for hyperthyroidism caused by widespread metastatic follicular thyroid carcinoma. Thyroid 20: 569-570, 2010.
45. Lim H, Devesa SS, Sosa JA, Check D and Kitahara CM: Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. JAMA 317: 1338-1348, 2017.
46. Salih AM, Kakamad FH and Nihad H: Hyperfunctioning papillary thyroid carcinoma: A case report with literature review. Int J Surg Case Rep 26: 202-204, 2016.
47. Pringle DR, Yin Z, Lee AA, Manchanda PK, Yu L, Parlow AF, Jarjoura D, La Perle KM and Kirschner LS: Thyroid-specific ablation of the Carney complex gene, PRKAR1A, results in hyperthyroidism and follicular thyroid cancer. Endocr Relat Cancer 19: 435-446, 2012.