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Surgical versus non-surgical management of hyperfunctional thyroid metastasis: a case report

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Abstract

Background Hyperthyroidism, caused by metastatic differentiated thyroid cancer, is a rare condition that can be difficult to diagnose. Thyrotoxicosis and metastatic disease regarding functional metastasis increase morbidity and mortality in patients with functional metastasis and need to be treated. This study aims to present a case of hyper-functional metastasis of thyroid cancer to analyze its pathological features, diagnostic procedures, and treatment options and to gather and examine recent cases of hyper-functional metastasis of thyroid cancer.

Case presentation A 26-year-old Iranian woman presenting with hyperthyroidism and a solid cystic nodule measuring 14.5 × 15.7 × 19.6 mm in the left thyroid lobe underwent thyroid surgery revealing papillary thyroid carcinoma. Despite lymph node metastasis, she refused further surgery and opted for lymph node radiofrequency ablation and radioactive iodine therapy. Subsequent follow-ups showed no recurrence of lymphadenopathy, normalized thyroid function, and decreasing triglyceride levels, with the patient under surveillance.

Conclusion Radioactive iodine is a first-line treatment option for patients with hyperactive thyroid cancer presenting with metastatic disease. Another therapeutic option is surgery, which is performed to maximize the reduction of thyroid tissue, lymph nodes, and distant metastasis.

Keywords Thyroid carcinoma, Hyperfunctioning thyroid carcinoma, Thyrotoxicosis, Metastasis, Case report

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Introduction

Differentiated thyroid cancer (DTC) has a 10-year survival rate ranging from 80% to 95%. It usually remains confined to the thyroid, and distant metastases occur in a minority of patients, with reported rates of 4–15%. There are two common forms of DTC: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) [1, 2]. Nearly all patients with thyroid cancer are clinically euthyroid, and the cancer is relatively hypo-functional compared with normal thyroid tissue. Tumor tissue of well-differentiated thyroid cancer maintains much lower levels of iodine uptake than adjacent normal tissue, so scintigraphy usually shows reduced function. However, in rare cases, thyroid cancer can cause clinical hyperthyroidism. One mentioned mechanism is that large tumor masses may secret sufficient thyroid hormones to cause hyperthyroidism. Another possibility is that hyperthyroidism occurs due to thyroid-stimulating antibodies, such as those seen in Graves' disease (GD). Hyper-functional distant metastasis (HFDM) from DTC after total thyroidectomy is rare and can cause hyperthyroidism or euthyroidism. Diagnosis of HFDM due to hormone overproduction by metastatic tissue should be based on the following criteria: (a) presence of hyperthyroidism, subclinical hyperthyroidism, or euthyroidism after total thyroidectomy with levothyroxine withdrawal for at least 3–4 weeks; (b) exclusion of hyper-functioning diffuse or nodular thyroid gland remnants; (c) low or no thyroid radioactive iodine uptake in the residual normal thyroid or no residual thyroid on cervical ultrasound after total thyroidectomy; (d) distant metastases on at least one imaging modality [x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and iodine-131 (^{131}I)-single-photon emission computed tomography (SPECT)/CT)] with high ^{131}I uptake. Serum thyroglobulin (TG) value should also be considered [2].

Functional metastasis (FM) poses a major therapeutic challenge. Both thyrotoxicosis and metastatic disease increase morbidity and mortality in patients with FM and need to be treated [2, 3]. Fatal thyroid storms have been reported in patients with hyperthyroidism secondary to functional metastatic thyroid carcinoma unless the thyrotoxicosis state is controlled with anti-thyroid drugs. In HFDM with thyrotoxicosis, regular doses of beta-blockers and anti-thyroid drugs are generally ineffective. Most patients showed marked improvements in hyperthyroidism after treatment with radioactive iodine; however, thyrotoxicosis persists in some patients whose metastasis is reluctant to treatment [4–7]. A few cases of hyper-functioning, well-differentiated thyroid cancer with metastasis have been reported apart from the simultaneous occurrence of thyroid cancer with hyperthyroidism secondary to Graves' disease, toxic multinodular goiter, or toxic adenoma. About 79 cases of HFDM have been described in the literature from January 1990 to April 2023. Most of the published studies were either single case reports or small series of cases, and present a challenge due to the lack of definitive clinical data [2, 3].

The most probable diagnosis is thyroid remnant in patients with a history of total thyroidectomy who present with thyrotoxicosis. It is challenging to differentiate between thyroid remnant, granulation tissue, or surgical lesions in the thyroid bed after surgery with imaging modalities such as ultrasonography. The final diagnosis can be reached on the basis of the pathology report. If it is negative for thyroid tissue and shows evidence of lymph node or distant metastasis, HFDM from thyroid cancer would be confirmed in a patient with a history of thyroidectomy and remnant tissue in the thyroid bed.

In this study, we presented a case report with HFDM and a systematic review of the relevant articles. We hope that the results from the current study aid us through a better understanding of hyper-functional metastatic thyroid cancer to prevent misdiagnosis and identify the most effective treatment options.

Case report

A 26-year-old Iranian woman presented with hyperthyroidism and a solid cystic nodule measuring 14.5 × 15.7 × 19.6 mm in the left thyroid lobe. A detailed history with emphasis on endocrine organs was taken. She reported no significant family, past medical, and drug history. She underwent a total thyroidectomy in a primary care center with the presumed diagnosis of Graves' disease. Microscopic examination of the surgical specimen revealed a classic type multifocal PTC. The tumor was found scattered throughout both lobes and the isthmus, with no tumor encapsulation, dedifferentiation, lymphovascular or perineural invasion, or microscopic extra-thyroid extension. The tumor abutted painted surgical margins, and its size could not be determined. Non-neoplastic thyroid exhibited diffuse hyperplasia.

The patient's post-surgery course was uneventful, but she reported hot flashes, tremors, hair loss, and unintentional weight loss. Physical examination showed cervical lymphadenopathy on both sides of the neck, and the scar from the thyroidectomy had healed well. Her postoperative blood test revealed a low thyroid-stimulating hormone (TSH) level of 0.002 μIU/mL (normal range: 0.30–4.20 μIU/mL), high free T4 level of 21.4 pmol/L (normal range: 9–19 pmol/L), high free T3 level of 14.6 pmol/L (normal range: 3.1–6.8 pmol/L), and high thyroglobulin level of 829.8 ng/mL (normal range: 1.4–78 ng/mL) despite not taking levothyroxine.

A chest computed tomography (CT) scan 1 month after surgery showed no evidence of lung metastasis. A neck ultrasound revealed central and bilateral lymphadenopathy.

A total of 3 months after the initial operation, the patient underwent interval central and bilateral (complete left-sided and partial right-sided) cervical lymphadenectomy at a tertiary care center. The pathology report showed that, out of the 42 harvested lymph nodes, 13 were positive for cancer, and out of the 11 harvested central lymph nodes, four were positive for cancer. However, the patient declined a second surgery, so an ultrasonography was performed. The results showed an increased number and size of right cervical lymph nodes and a single left paratracheal mass. The mass was confirmed to be positive for metastasis based on fine needle aspiration (FNA) and thyroglobulin (TG) wash. The patient was still hyperthyroidic. Considering the results of the FNA and TG wash, the patient consented to a second surgery. Right cervical lymphadenectomy revealed 9 positive lymph nodes out of the 32 nodes that were harvested. Due to a history of two previous surgeries and severe adhesions, the entrance of the left recurrent laryngeal nerve to the cricoid cartilage was not explored.

1 month later, neck ultrasonography showed one lymph node in zone VI on the left side (left para tracheal). Radiofrequency (RF) waves under color Doppler sonography guidance were used to ablate all the mentioned metastatic lymph nodes successfully. The procedure was performed with local anesthesia using a 5 mm active tip (10 cm length) RF needle after sufficient hydrodissection. There were no complications (Fig. 1). Then she underwent radioactive iodine (^{131}I) therapy for thyroid ablation. In follow-up imaging after 4 and 8 months, there was no evidence of cervical lymphadenopathy. She was euthyroidic, and her TG level showed a decreasing trend. She is currently under surveillance.

Discussion

A PubMed literature search was conducted to identify studies published in English between January 1990 and April 2023. The search terms used were "hyper-functional thyroid metastasis," "hyper-functional metastasis of thyroid cancer," and "hyper-functional metastasis of thyroid carcinoma." A total of 33 articles were found. Additionally, 32 other related articles were retrieved after reviewing the citations of relevant articles referenced in these papers.

Inclusion criteria for studies on metastatic hyperactive thyroid cancer had to meet I, II, and III; or I, II, and IV of the following:

(I) Thyroid carcinomas, such as PTC, FTC, or Hurthle cell carcinoma (HCC), confirmed by biopsy analysis of metastasis or thyroid nodules; (II) hyperthyroidism; (III) persistent or newly developed hyperthyroidism after total thyroidectomy; and (IV) increased uptake of 99mTc, and/or ^{131}I or ^{123}I in the metastatic lesion as confirmed by scintigraphy.

Due to the extremely low occurrence of hyperactive metastatic thyroid cancer, the number of cases identified in PubMed was limited, and in some of the cases had incomplete data. Out of the 65 articles retrieved from PubMed using the search strategy, 2 were duplicates, and 20 did not meet the inclusion criteria. Finally, the remaining 34 articles were included in this study. A detailed flowchart illustrating the study selection process is presented in Fig. 2.

In all, 79 cases of HFMTC were identified through the literature search. The detailed characteristics of each case are presented in Table 1. All patients had

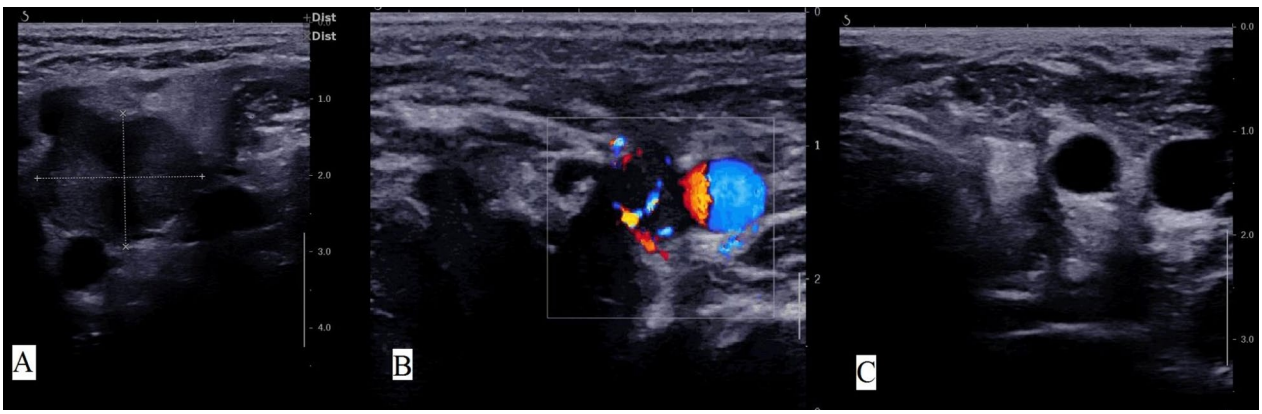

Fig. 1 **A** Primary T4 thyroid nodule. **B** Hyper vascular malignant mass at left thyroidectomy bed. **C** Post-RF ablation echogenic avascular changes

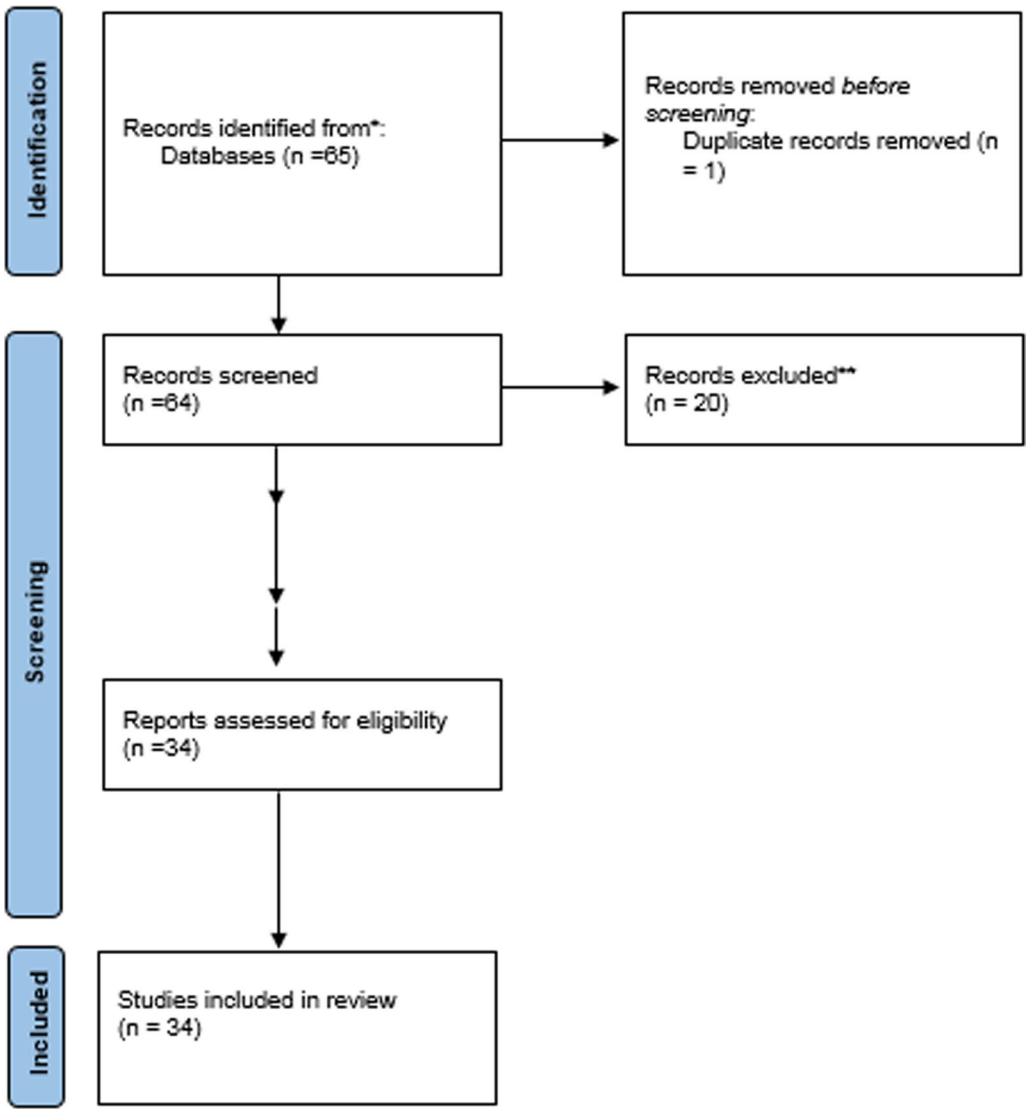

Fig. 2 Study selection flow chart

either clinical thyrotoxicosis with biochemical data indicating hyperthyroidism or had been diagnosed with thyrotoxicosis. Patients presented with multiple or large metastases in the cervical lymph nodes, bone, lung, liver, mediastinum, subcutaneous tissue, small intestines, and gluteal muscles. The average patient's age was 54.07 ± 14.36 years. Females comprised 56 (70%) of the patients, and 24 (30%) of the patients were male. Histopathological examination revealed 55 (68.9%) cases of FTC, 22 (27.5%) cases with PTC (including 1 case of follicular variant of PTC), 1 case of insular thyroid carcinoma (TC), 1 case with an unknown type of DTC, and 1 case that was a mixture of FTC and PTC. Out of the patients with metastatic hyper-functioning thyroid carcinoma, 62 (77.5%) had undergone a total thyroidectomy, 1 had a lobectomy, 2 had a subtotal thyroidectomy, and 2 had other partial thyroidectomies. The remaining 13 (16.3%) patients did not undergo thyroidectomy. All patients received multi-dose radioactive iodine (RAI), except for three patients (3.75%). Following RAI, most patients showed a significant improvement in hyperthyroidism and good cancer control. Of particular note, one patient developed resistance to RAI 4 years after receiving the initial dose. The patient's thyrotoxicosis was caused by pelvic metastasis, which resolved after the surgical removal of the pelvic mass. A total of 18 (22.5%) patients had undergone palliative surgery to remove metastasis.

Table 1 Reported patients with metastatic hyper-functioning thyroid carcinoma

	First author	Year	Age (years); sex	History of thyroidectomy	Thyroid scan	FT3	FT4	TSH	TG	Metastatic location	Pathology	Treatment
1	Girelli [8]	1990	66; F	NO	Cold nodules	650 ng/dL	5.8 ng/dL	0.01↓	5300	Bone	PTC	Total thyroidectomy + RAI
2	Abs [9]	1991	57; F	Partial	Normal	7.7 nmol/L	277 nmol/L	0.6↓	640	Mediastinum	FTC	Rib biopsy + RAI
3	Salvatori [5]	1993	79; F	NO	Cold areas	10.4↑	3.8↑	0.06↓	382	Lung	FTC	Total thyroidectomy + RAI
4	Salvatori [5]	1993	69; F	Partial	Low uptake	3.8↑	10.4↑	0.06↓	48,680	Lung	DTC	RAI
5	Mizukami [10]	1994	64; F	NO	Hot AFTN			↓		Bone	FTC	RAI
6	Kasagi [11]	1994	67; F	Hemithyroidectomy		10.7 pmol/L	↓	0.12 mIU/L	> 4000 pg/L	Femur, lungs, pelvis, and small intestine	FTC	RAI
7	Kasagi [11]	1994	48; F	Total		↑	↑	↓		Lungs, sternum, skull, femur, and humerus	FTC	RAI
8	Lorberboym [12]	1996	67; F	Total		273↑	15.7↑	0.1↓		Hemipelvis	FTC	Pretreatment + EBRT + RAI
9	Gross [13]	1996	50; F	Total		> 12.3 mmol/L	54 mmol/L	< 0.40 mIU/L	310	Bone and lung	FTC	None
10	Gross [13]	1996	56; F	Total		6.4 mmol/L	212 mmol/L	< 0.40 mIU/L	63	Lung	FTC	RAI
11	Gross [13]	1996	64; F	Total		4.2 mmol/L	247 mmol/L	< 0.40 mIU/L		Lung	FTC	RAI
12	Gross [13]	1996	51; F	Total		3.5 mmol/L	141 mmol/L	3.5 mIU/L	90	Subcutaneous tissue, bone, and lungs	FTC	RAI
13	Gross [13]	1996	50; M	Total		3.0 mmol/L	142 mmol/L	< 0.40 mIU/L	290	Subcutaneous tissue, bone, and lungs	FTC	RAI
14	Gross [13]	1996	58; F	Total		1.7 mmol/L	107 mmol/L	2.0 mIU/L	146	Bone	FTC	RAI
15	Ikejiri [14]	1997	59; F	Total						Bone	PTC and FTC	RAI
16	Russo [15]	1997	60; F	NO	Cold areas	2.8↑	N	0.06↓	513	Lung	Insular TC	Subtotal thyroidectomy/1 year total + RAI 2
17	Yoshimura [16]	1997	61; M	Total		46.1↑	105.3↑	0.05↓	329	Pelvis	FTC	RAI + pretreatment
18	Naito [17]	1997	54; M	Total		↑	Normal	↓		Bone	FTC	RAI
19	Guglielmi [6]	1999	58; F	Subtotal		18.4↑	44.5↑	0.1↓	3686	Liver and lung	FTC	ILP + RAI
20	Als [18]	2002	61; M	NO	Hot AFTN					Uncertain	FTC	RAI + surgery + RAI
21	Als [18]	2002	65; F	NO	Hot AFTN					Uncertain	FTC	RAI + surgery + RAI
22	Als [18]	2002	71; F	NO	Hot AFTN	↑	↑	↓		Uncertain	FTC	Surgery + RAI
23	Als [18]	2002	62; F	NO	Hot AFTN	↑		↓		Uncertain	FTC	Surgery + RAI
24	Als [18]	2002	63; M	NO	Hot AFTN		NL	↓		Uncertain	PTC	Surgery + RAI
25	Basaria [19]	2002	74; M	Total		↑	↑	↓	2280	Mediastinum and lung	PTC	Pretreatment + RAI
26	Rosário [20]	2005	68; M	Total		22.0 pg/dL	4.2 ng/dL	0.02 IU/mL	7608 ng/mL	Bone	FTC	RAI
27	HAQ [21]	2005	54; M	Total			41.1 pmol/L	0.05 mIU/L		Lung and bone	FTC	RAI

Table 1 (continued)

	First author	Year	Age (years); sex	History of thyroidectomy	Thyroid scan	FT3	FT4	TSH	TG	Metastatic location	Pathology	Treatment
28	Faivre-Defrance [22]	2007	70; F	Lobectomy		11 ng/L	27 ng/L	0.15 µIU/mL	8500 ng/mL	Bone, liver, and kidney	FTC	RAI + palliative resection
29	Faivre-Defrance [22]	2007	40; F	Total		6.5 ng/L	11.4 ng/L	0.12 µIU/mL	80↑ ng/mL	Lung	FTC	RAI
30	Orsolon [23]	2008	66; M	Total		4.5↑	1.6	< 0.1↓	> 10,000	Bone and lung	FTC	Unknown
31	Sundaraiya [24]	2009	68; M	NO	Cold nodules	42.6↑	100↑	↓		Rib	FTC multifocal	Total thyroidectomy + RAI
32	Tan [25]	2009	39; F	Total		27.9↑	4.41↑	0.01↓	1000	Pelvic mass	FTC	Removal of pelvis mass and partial bone
33	Nishihara [26]	2010	59; F	Total		↑	↑	0.01↓	8000	Multiple bone and lung	FTC	RAI low multiple
34	Damle [7]	2012	65; M	Subtotal		430 ng /dL	15.3 ng /dL	0.03↓	300	Lung and bone	FTC	Subtotal thyroidectomy + RAI
35	Damle [7]	2012	62; M	NO	No uptake	↑	↑	↓	300	Bone	FTC	RAI
36	Lee [27]	2012	49; F	Total		82 ng/dL	1.21 ng/dL	4.51 mIU/L		Cervical LN and lung	PTC	RAI
37	Gardner [28]	2014	66; F	NO	Diffuse reduction	25.1↑	37.9↑	0.006↓		Lung and bone	PTC	Total thyroidectomy + RAI
38	Qiu [2]	2015	29; F	Total		3.71 pmol/l	14.7	3.50		Lung	PTC	RAI
39	Qiu [2]	2015	64; M	Total		4.74 pmol/l	13.28	3.71		Bone and lung	FTC	RAI
40	Qiu [2]	2015	61; F	Total		5.22 pmol/l	17.31	2.49		Lung	FTC	RAI
41	Qiu [2]	2015	28; F	Total		3.94 pmol/l	16.76	1.11		Lung	FTC	RAI
42	Qiu [2]	2015	30; F	Total		5.11 pmol/l	14.17	2.68		Lung	PTC	RAI
43	Qiu [2]	2015	46; M	Total		4.04 pmol/l	13.56	3.64		Lung, bone, and mediastinum	PTC	RAI
44	Qiu [2]	2015	45; M	Total		13.42 pmol/l	33.9	0.04		Bone	FTC	RAI + palliative resection
45	Qiu [2]	2015	57; M	Total		4.67 pmol/l	13.31	2.51		Bone	PTC	RAI
46	Qiu [2]	2015	41; F	Total		4.67 pmol/l	15.10	1.79		Lung	FTC	RAI
47	Qiu [2]	2015	75; M	Total		9.35 pmol/l	27.18	1.79		Lung	PTC	RAI
48	Qiu [2]	2015	32; F	Total		4.09 pmol/l	13.51	1.71		Bone and lung	FTC	RAI + palliative resection
49	Qiu [2]	2015	60; M	Total		4.97 pmol/l	15.32	2.42		Lung	PTC	RAI
50	Qiu [2]	2015	61; M	Total		4.8 pmol/l	19.5	0.26		Bone	PTC	RAI + palliative resection
51	Qiu [2]	2015	46; F	Total		4.5 pmol/l	12.51	3.79		Bone	FTC	RAI + palliative resection
52	Qiu [2]	2015	42; F	Total		5.01 pmol/l	12.65	1.9		Lung	FTC	RAI

Table 1 (continued)

	First author	Year	Age (years); sex	History of thyroidectomy	Thyroid scan	FT3	FT4	TSH	TG	Metastatic location	Pathology	Treatment
53	Qiu [2]	2015	43; F	Total		7.23 pmol/l	29.14	0.22		Bone	FTC	RAI + palliative resection
54	Qiu [2]	2015	51; F	Total		9.51 pmol/l	31.73	0.02		Bone and lung	FTC	RAI + palliative resection
55	Qiu [2]	2015	53; M	Total		4.4 pmol/l	13.15	2.26		Bone and lung	FTC	RAI + palliative resection
56	Qiu [2]	2015	23; F	Total		4.47 pmol/l	13.2	4.19		Bone	PTC	RAI + percutaneous osteoplasty
57	Qiu [2]	2015	57; F	Total		4.22 pmol/l	16.08	4.49		Lung	PTC	RAI
58	Qiu [2]	2015	65; F	Total		4.3 pmol/l	13.5	2.78		Bone and lung	PTC	RAI
59	Qiu [2]	2015	49; F	Total		5.15 pmol/l	19.24	0.13		Bone and lung	FTC	RAI
60	Qiu [2]	2015	43; F	Total		4.3 pmol/l	13.51	4.51		Lung, bone, and mediastinum	FTC	RAI
61	Qiu [2]	2015	48; F	Total		5.4 pmol/l	20.31	1.09		Bone	FTC	RAI + palliative resection
62	Qiu [2]	2015	19; M	Total		5.48 pmol/l	12.49	1.85		Lung, bone, and renal	FTC	RAI
63	Qiu [2]	2015	34; M	Total		4.76 pmol/l	15.18	2.03		Lung	PTC	RAI
64	Qiu [2]	2015	82; F	Total		4.3 pmol/l	17.2	1.78		Bone	PTC	RAI
65	Qiu [2]	2015	52; F	Total		4.9 pmol/l	12.2	7.75		Bone	FTC	RAI
66	Qiu [2]	2015	65; F	Total		5.5 pmol/l	19.6	0.2		Bone	FTC	RAI + palliative resection
67	Qiu [2]	2015	52; F	Total		4.47 pmol/l	12.29	8.53		Bone	FTC	RAI
68	Qiu [2]	2015	37; F	Total		4.79 pmol/l	14.91	3.48		Bone	FTC	RAI + palliative resection
69	Qiu [2]	2015	29; F	Total		3.89 pmol/l	16.13	2.79		Lung and bone	PTC	RAI
70	Qiu [2]	2015	46; M	Total		5.79 pmol/l	19.22	0.17		Lung	FTC	RAI
71	Qiu [2]	2015	49; F	Total		4.32 pmol/l	14.17	4.02		Lung	PTC	RAI
72	Qiu [2]	2015	54; F	Total		7.83 pmol/l	32.15	0.01		Bone	FTC	RAI
73	Qiu [2]	2015	62; F	Total		4.36 pmol/l	15.18	3.19		Lung and bone	PTC	RAI
74	Qiu [2]	2015	67; F	Total		3.89 pmol/l	13.25	3.47		Lung	FTC	RAI
75	Qiu [2]	2015	17; M	Total		3.23 pmol/l	12.11	5.59		Lung	PTC	RAI
76	Kunawudhi [4]	2016	43; F	NO	Cold	32.55↑	6.34↑	0.026↓		Bone and liver	FTC	Total thyroidectomy + right LND + RAI + EBRT
77	Geliebter [29]	2017	79; F	Total			1.92 ng/dL	0.01 mIU/L	1976 ng/mL	Lung and gluteal mass	PTC	Total thyroidectomy + RAI + palliative resection

Table 1 (continued)

	First author	Year	Age (years); sex	History of thyroidectomy	Thyroid scan	FT3	FT4	TSH	TG	Metastatic location	Pathology	Treatment
78	Yan Hu [30]	2019	53; F	Total		12.3 pmol/L	46.7 pmol/L	< 0.005 mIU/mL	> 5000.0 ng/mL	Lung and bone	FTC	Total thyroidectomy + RAI
79	Maria Inês Alexandre [31]	2023	71; F	Total		346 ng/dL	2.22 ng/d	< 0.02 µIU/mL	4524 ng/mL	Multiple bone	FTC	RAI + RT
80	Our study	2023	26; F	Total		14.6 pmol/L	21.4 pmol/L	0.002 µIU/mL	829.8 ng/mL	Cervical LN	PTC	Total thyroidectomy + bila LND + RAI + RFA

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

Patients with thyroid cancer are typically euthyroidic. Different diagnostic possibilities for DTC-related thyrotoxicosis were explored by Salvatori *et al.*, including Graves' disease, toxic multinodular goiter, and even ovarian teratoma [5]. Thyrotoxicosis caused by thyroid cancer is a rare condition. One study showed a 2.8% incidence of hyperthyroidism in patients with thyroid malignancies in areas with iodine deficiency [4, 32]. The reported sites of autonomic hyperactive thyroid cancers are either primary sites in the thyroid bed, which can be seen as hot nodules on thyroid scintigraphy, or metastatic sites [3]. HFDM represents a rare pattern of invasion from DTC with an incidence of 0.71% [2].

In 1946, Leiter *et al.* [33] reported the first case of hyperthyroidism caused by metastatic thyroid cancer. Our literature review has identified a total of 79 reported cases of this syndrome. Thyrotoxicosis due to autonomous functional metastatic thyroid cancer is rare and may present diagnostic challenges. A correct diagnosis is essential for proper treatment to eliminate thyrotoxicosis and address metastatic disease [7, 21]. Hyperfunctioning thyroid cancer requires diagnosis through fine-needle aspiration (FNA) or core needle biopsy, whole-body scan, and confirmation of thyrotoxicosis [3].

Thyroid cancer is a well-differentiated endocrine malignancy, and the metastatic cells, similar to normal thyroid cells, maintain their well-differentiated state and exhibit the physiological characteristics of thyroid cells [7]. The possible mechanisms responsible for HFDM in DTC are unknown. In the rare circumstances in which HFDM produces physiological or supraphysiological levels of thyroid hormone, several possible reasons may be involved. Thyroid-stimulating immunoglobulin can stimulate and increase the thyroid-stimulating hormone receptor (TSHR), promoting the proliferation of DTC cells and ultimately leading to the development of metastatic tumors. It acts autonomously to increase thyroid hormone levels, which in turn causes distant metastases to become functional. Alternatively, some HFDM from FTC may express 5′-iodothyronine deiodinase. In patients with HFDM receiving levothyroxine, there may be an increase in the conversion of levothyroxine to T3 in metastatic tumor tissue. Furthermore, activating mutations in the TSHR or the stimulatory guanine nucleotide-binding protein (Gsa) subunit in primary tumors or metastatic lesions of DTC are associated with clinical and biochemical hyperthyroidism [2]. Russo *et al.* described a 60-year-old female patient with autonomously functioning insular thyroid carcinoma, which resulted in thyrotoxicosis. The tumor contains a somatic gain-of-function mutation in the *TSHR* gene [15].

Some reports have described the mechanism of activated receptors in cancer cells with high levels of TSH-binding inhibitory immunoglobulin and thyroid-stimulating antibodies in the absence of thyroid tissue. This phenomenon occurs at the metastatic site after the completion of radioiodine treatment and can persist for many years [16]. The American Thyroid Association guidelines for the treatment of hyperthyroidism discuss the likelihood of thyrotoxicosis in patients with metastatic thyroid cancer who have undergone multiple injections of rhTSH prior to imaging [34]. Tan *et al.* reported a case of thyrotoxicosis caused by functional metastatic FTC after 12 doses of ^{131}I therapy. In this case, thyrotoxicosis only recovered after surgical removal of the pelvic lesion [25]. In our review, FTC is the most common type of thyroid cancer associated with this form of hyperthyroidism, accounting for 68.9% of cases. The ratio of PTC to FTC is approximately 1:2.5.

DTC cells have functions similar to those of normal thyroid follicular cells, including TSH dependence, iodine absorption, and thyroglobulin secretion. In rare cases, they can also secrete thyroxine [25]. When the autoregulatory mechanism is impaired, such as in Graves' disease, the large DTC can secrete excessive amounts of thyroxine, leading to hyperthyroidism. Therefore, it is suggested that debulking surgery may play a significant role in the management of this rare condition [29]. Tumor size is an important factor in hyperactive thyroid cancer, according to Liu *et al.* [3]. However, this parameter has not been evaluated in this study.

The results of this study have several significances, as explained below. Qiu *et al.* [2] reported that the prevalence of FTC in functional metastatic thyroid cancer was 60.5% (23/38), while Liu *et al.* reported a prevalence of 71.4% [3]. In this study, the prevalence of FTC was found to be 68.4%. In comparison, the Surveillance, Epidemiology, and End Results (SEER) cancer registry program (2013), which categorizes all histological cases of thyroid cancer as a single group, found a prevalence of 10.8% for FTC and 83.6% for PTC [35]. Therefore, the prevalence of FTC is likely to be high in patients with hyperactive thyroid cancer, particularly in those with metastatic disease. This suggests that functional thyroid cancer is more likely to occur in primary or metastatic FTC compared with PTC. The reason for this has yet to be explored. The results presented by Qiu *et al.* suggest that the prognosis of patients with metastatic hyperfunctioning FTC is worse compared with those with PTC. PTC was associated with a better outcome, similar to the outcomes previously reported in DTC patients without HFDM [2].

Treatment of functional thyroid cancer is similar to that of nonfunctioning thyroid cancer, thyroidectomy,

surgical removal of any large accessible metastatic lesions, and radioactive iodine (RAI) therapy. To control hyperthyroidism, patients may require high-dose antithyroid treatment [3, 7, 21]. The ability of functional thyroid carcinoma to concentrate iodine may lead to an improved response to treatment with radioactive iodine (RAI). Previous case reports suggest that functional lung metastases respond particularly well to treatment compared with non-functional lung metastases [25, 29].

Treatment should be directed at both thyrotoxicosis and metastatic disease, as both increase the risk of morbidity and mortality. In patients with hyperthyroidism secondary to functional metastatic thyroid carcinoma, it has been reported that failure to control thyroid toxicity status with anti-thyroid drugs can lead to fatal thyroid storms [5]. In addition, preliminary debulking of large metastases in differentiated thyroid cancer enhances the effectiveness of radioiodine therapy. The metastatic disease in these patients with thyrotoxicosis is often large, bulky, and extensive. The typical daily doses of beta-blockers and anti-thyroid drugs are not effective in controlling symptoms. High doses of thyroid medication are required, such as 60 mg of carbimazole daily and 40 mg of propranolol every 8 hours. Even after treatment with thyroid drugs, hyperthyroidism is not completely controlled, and immediate clinical recovery is usually achieved with radioactive iodine therapy [3, 7, 21].

RAI is necessary for treating hyperfunctioning metastatic lesions in patients with thyroid cancer. It is the first-line treatment option for patients who have undergone thyroidectomy or for those who do not have increased thyroid uptake and cannot undergo resection surgery. Pretreatment with anti-thyroid medications is necessary to avoid potential thyroid storms. Fractionated RAI or minimally invasive local ablation can also be considered. If metastatic lesions are resistant to RAI and functional lesions are resectable, as in our case, surgery is considered a treatment option [2, 3, 7, 27].

Conclusion

The results of our study suggest that the FTC is more likely to be hyperfunctional than the PTC. RAI and surgery are the preferred treatments for metastatic hyperfunctioning thyroid carcinoma, along with new minimally invasive treatments such as RF ablation. However, this study had the following limitations: Considering that the number of hyper-functioning thyroid carcinomas is small and most studies are published as case reports, there is a potential risk of bias, and the results should be interpreted with caution. We hope to raise awareness by sharing our experience of this rare condition and discussing ways to manage it.

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Author contributions
AF, FM, SMT, and MS contributed in study concept and design. AF, FM, and SJ were major contributors in drafting the manuscript. Data extraction was performed by AF, HE, and HC. Critical revision and scientific supervision was performed by MS. All authors read and approved the final manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Since this study is a case report, the study did not require any ethical approval.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
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