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Case Report

A Primary Leiomyosarcoma of the Thyroid Gland: A Case and Literature Review

Mehmet Faik Çetindağ[1*], Ibrahim Gullu[2], Osman Abbasoglu[3], Ipek Pınar Aral[1], Fatih Goksel[4], Yasemin Cihan[5], Atiye Yılmaz Ozsavran[1], Olcay Kandemir[6], and Dincer Yegen[1]

[1] Department of Radiation Oncology Turkish Ministry of Health Ankara Atatürk Training and Research Hospital, Turkey

[2] Department of Medical Oncology, Hacettepe University Faculty of Medicine, Turkey

[3] Department of General Surgery, Hacettepe University Faculty of Medicine, Turkey

[4] Turkish Ministry of Health Dr.A.Y.Ankara Onkoloji Training and Research Hospital, Turkey

[5] Department of Radiation Oncology, Turkish Ministry of Health Kayseri Training and Research Hospital, Turkey

[6] Department of Pathology, Turkish Ministry of Health Dr.A.Y. Ankara Onkoloji Training and Research Hospital, Turkey

Abstract

Introduction: We want to present a rare case of Primary leiomyosarcoma of the thyroid (PLT) gland and review the literature on PLT including the differential diagnoses, pathology, and alternative treatment strategies.

Presentation of Case: A 56-year-old man who underwent left side total thyroidectomy with diagnosis of substernal goiter. On pathologic examination, three different pathology clinics had a common opinion that this was a grade 3 pleomorphic sarcoma of thyroid itself. Positron Emission Tomography (PET/CT) obtained one month after surgery displayed no distant metastases. Loco regional radiotherapy (RT) to the thyroid bed was delivered up to a dose of 59.4 Gray (Gy) in 1.8 Gy daily fractions. PET/CT obtained three months after RT showed bilateral multiple lung metastases without loco regional recurrence. The patient received 6 courses of doxorubicin and cyclophosphamide based chemotherapy. A new PET/CT scan showed only two metabolically active metastases on both lungs. Because of disappearance of small metastases, the patient underwent sequential bilateral metastasectomy in one month interval. Pathology results verified the metastases of PLT. The patient is still alive without any signs of disease 6 years after RT and he is the only long surviving case reported up to now.

Conclusion: The treatment protocols for PLT have not been well established yet, because of their rareness and poor prognosis. We believe that our case may be directive for PLT treatment.

Keywords: thyroid, leiomyosarcoma; radiotherapy; chemotherapy

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***Correspondence to**: Mehmet Faik Çetindağ, Department of Radiation Oncology Turkish Ministry of Health Ankara Atatürk Training and Research Hospital, Turkey; Email: faikcetindag@gmail.com

Introduction

Leiomyosarcoma constitutes %6 of head and neck tumours and they are exceedingly rare in thyroid gland (TG) itself [1]. It is believed that PLT originate from the smooth muscles of blood vessels in TG which has abundant vascularization. To the best our knowledge, there are only 21 well-documented PLT cases in literature. This rare malignant nonepithelial tumour of the TG occurred in older patients with a median age of 65 years old [2, 3]. In our review of the literature we also found the same median age. In hematoxylin-eosin staining, the tumour is composed of characteristic spindle shaped cells with hyperchromatic, blunt-ended nuclei and abundant eosinophilic cytoplasm which are in disordered fascicular pattern [4]. The differential diagnosis includes primary versus metastatic sarcoma, medullary thyroid cancer and anaplastic thyroid cancer [4]. Immunohistochemical analysis is a gold standard for diagnosis. Although the primary treatment of PLT is surgical excision [1] adjuvant RT and chemotherapy should be considered in high grade tumours.

Case presentation

A 56-year-old male referred with a history of hoarseness, and sweating palpitation for three months. He also remarked the changing of his shirt neck size from medium to extra-large in this short period. He has been working in metal industry for 45 years. The medical history was unremarkable and no comorbidities existed. There was no history of radiation exposure. Physical examination revealed a diffuse enlargement of thyroid gland with no palpable cervical or supraclavicular lymph nodes. He was clinically euthyroid. Serum calcitonin, carcinoembryonic antigen (CEA), neuron specific enolase (NSE), thyroglobulin and thyroid hormone assay (thyroid stimulating hormone (TSH), serum triiodothyronine (T_3) and thyroxine (T_4)) results were within normal limits. Ultrasound (US) of the neck showed an ill-defined (7x4 cm) hypoechoic solid mass arising from the left thyroid lobe with no lymphadenopathy. Fine-needle aspiration (FNA) cytologies of the thyroid gland which was performed twice with US guidance were non diagnostic. Contrast computed tomography of the chest exposed a primary retrosternal multinodular goiter which was measured 7x4x5 cm. The mass with necrotic and cystic components encircled and displaced the trachea to the right and caused narrowing of its lumen by %30 (Figure 1). There was no pathologic mediastinal lymphadenopathy. Left lobe total thyroidectomy was performed without neck dissection. The patient was discharged on the third postoperative day without any complication. On gross examination, the necrotic and cystic components of the tumour were well circumscribed and the cut surface was yellowish and hemorrhagic. The gross tumour measurement was 11x7x5 cm (cranial-caudal, median-lateral and anterior-posterior). Histologically, there were well defined and encapsulated tumour cells which had no infiltration to the thyroid parenchyma and no invasion to the thyroid capsule. Vascular invasion was not present. In light microscopy the tumour cells showed a disordered fascicular growth pattern, elongated spindle or round cells with large vesicular nuclei and abundant eosinophilic cytoplasm. Immuno-histochemical staining of the slides with vimentin, desmin, alpha-1antitrypsin, creatine kinase (CK), thyroglobulin, myogenin, epithelial membrane antigen (EMA), CEA, Myo D1, thyroid transcription factor (TTF-1), pancytokeratin, leukocyte common antigen (LCA), smooth muscle actin (SMA), melanoma marker (HMB-45), S 100 protein, cyclin d1, CD 68, CD 21, CD 23 and KI 67 protein was performed. The tumour was

strongly positive for vimentin, SMA, desmin, and negative for pancytokeratin and other epithelial markers except EMA. After excluding anaplastic, follicular, meduller, histiocytic and peripheral nerve tumours, three different pathology clinics had a common opinion that this was a grade 3 pleomorphic leiomyosarcoma of thyroid gland itself. KI 67 score of the tumour was reported as %70.

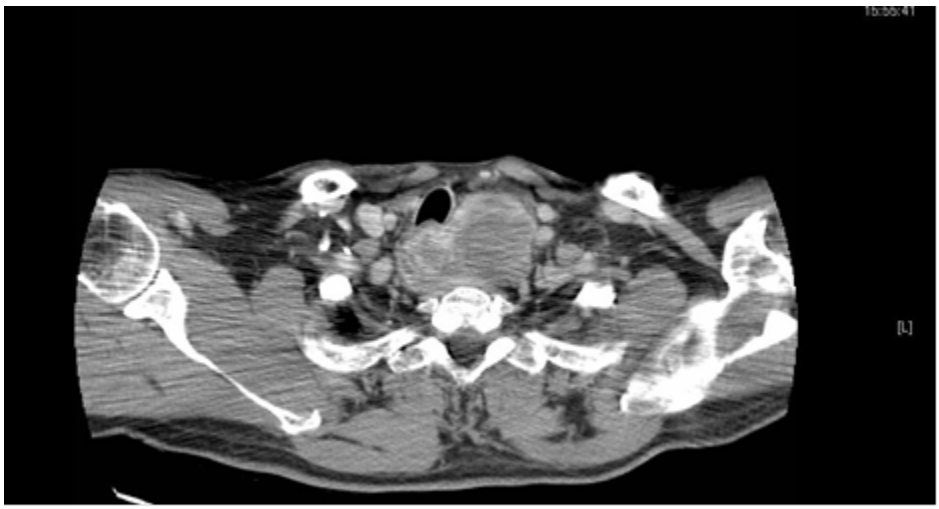

Figure1 Preoperative contrast CT revealed that the retrosternal mass encircled and displaced the trachea to the right

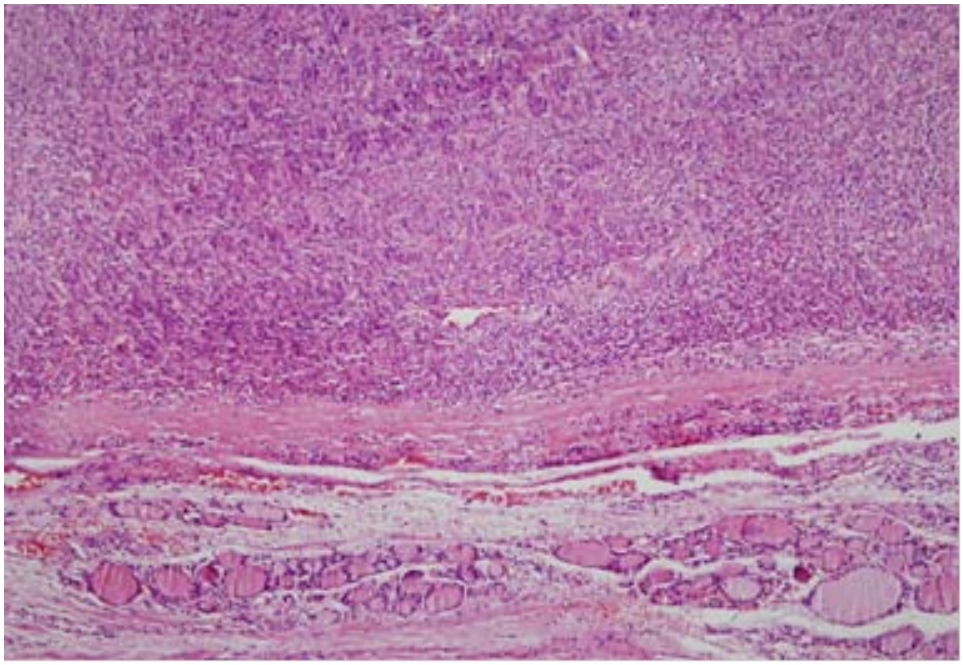

Figure 2 Tumor cells surrounded by fibrous capsule are seen in the thyroid tissue. (H&E x100)

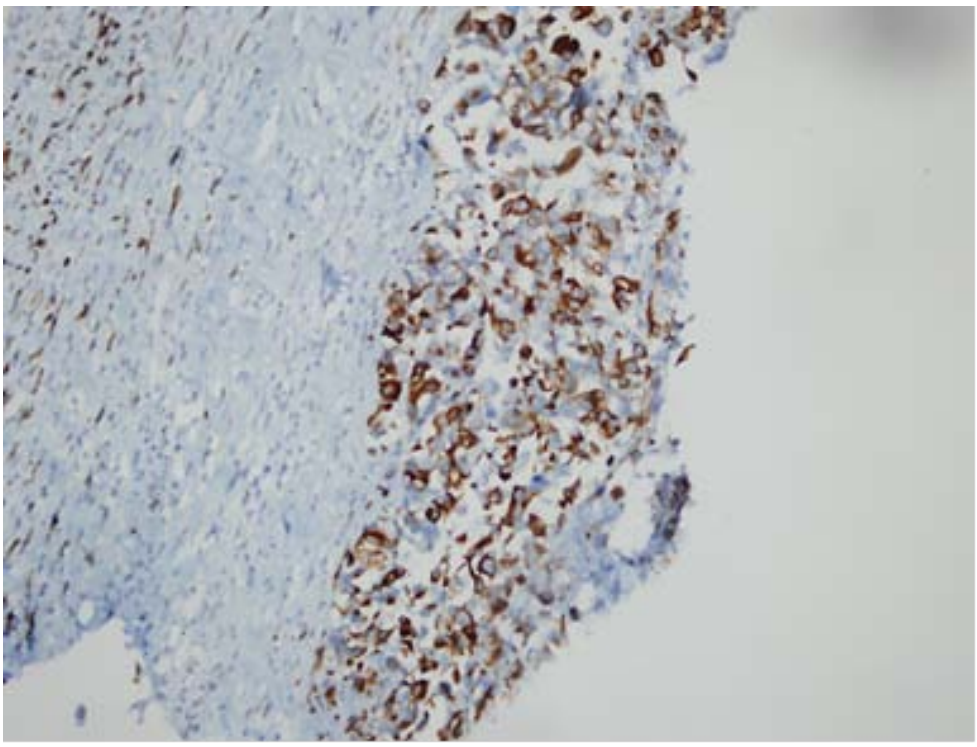

Figure 3 Desmin positive tumor cells (x200)

PET/CT which was performed one month after surgery showed only one paratracheal lymph node with SUV:4.7 and no distant metastases. The lymph node was interpreted as a non-malignant enlargement by nuclear medicine specialist. In multidisciplinary tumour board, it was decided that adjuvant loco regional RT had to be given immediately. After one and half months following the operation, first fraction of the conformal radiotherapy was applied to the surgical bed and upper mediastinal area. Irradiation was performed using linear accelerator 6 MV photon rays with four portals (anterior, posterior, right oblique and left oblique) and wedged based planning was used to get the best possible dose distribution inside the target volume with multileaf collimators. A dose of 59.4 Gy to the %95 of the target volume was applied in 1.8 Gy daily fractions, 5 days a week for 6.5 weeks. There was no grade 3 side effect necessitating interruption for RT schedule. PET/CT which was obtained three months after RT showed bilateral multiple lung metastases without locoregional recurrence. The medical oncology department suggested adjuvant therapy and patient received 6 courses of chemotherapy. Cyclophosphamide (2500 mg/m^2) and doxorubicin (60 mg/m^2) with mesna (2500 mg/m^2) were administered intravenously (IV) over 2 hours on day 1 of a 21-day cycle. The patient tolerated this chemotherapy regime very well and no grade 3 toxicity was reported. A new PET/CT scan showed only two metabolically active metastases on both lungs (left lung inferior lobe median basal, 5.5 cm, standardized uptake value (SUV): max 12.25 and right lung superior lob 2 cm, SUV: max 3.2). Because of disappearance of small metastases, the patient was given a chance of two operations with wedge resections in one month interval. Pathology results verified the metastases of PLT. Low dose maintenance chemotherapy regime with

cyclophosphamide (50 mg/day/1-21days) and etoposide (50 mg/day/1-21days) were administered for one year. He was followed up in six months intervals by thorax and neck tomography thereafter. The only long term complication of therapies was the reactivation of the chronic active hepatitis B. He has been given lamivudine 1x1 for 2.5 years. The patient was still alive with complete remission 6 years after RT. He is the longest surviving case reported up to now.

Discussion

Thyroid cancer represents less than %1 of all malignancies in the world, and most of the cases (%90 to %95) are classified as well-differentiated tumours arising from the follicular cells [4]. Primary smooth muscle tumours of TG (leiomyomas and leimyosarcomas) are rarely seen [5].Together with anaplastic carcinoma they are the most aggressive variant of the thyroid cancers with a very poor prognosis [5] PLT are more often reported in elder individuals and so far only 21 well-documented cases have been reported in the world literature (Table1). Even though women are more prone to benign and malignant lesions of thyroid, PLT are equally seen in both gender [4].
The etiology of PLT is not clear yet. Most of the reports in the literature show that cases are not associated with a benign or malign pre-existing thyroid lesion, and there is not any history of radiation exposure [6]. The PLT usually goes along with fast growing, painless masses and the symptoms of hoarseness and dysphagia [7, 8]. In thyroid isotope scanning, PLT can demonstrate a cold nodule or hyperplasia with increased and decreased uptake of radioactive iodine [1]. Ultrasound can reveal an ill-defined or well-defined hypo-echogenic mass with cystic or calcified components [1]. In most of the thyroid cancer, cross sectional imaging with contrast CT should not be used because it is associated with a delay in radioactive iodine treatment for up to 6 to 8 weeks. But these modalities can be very helpful to assess for local aggressiveness including extra capsular extension and invasion to the airway and esophagus. CT imaging of PLT in most of the thyroid cancer show a low-density mass with calcification and necrosis [1]. The tumor was commonly delineates an isointense mass on T1-weighted MR images and a mass effect of intermediate signal on T2-weighted images. After gadolinium injection, the lesion generally demonstrates a fair enhancement on T1-weighted images [9]. Fine needle aspiration cytology is the most important tool for diagnosis of thyroid diseases [5]. In PLT, it may show malignant spindle-shaped cells which directed someone to consider an unusual tumour of the thyroid [4].

The main differential diagnosis includes anaplastic thyroid carcinomas (ATC), solitary fibrous tumours, spindle cell tumours with thymus-like differentiation, medullary carcinoma and other sarcomas [1]. PLT usually displays smooth muscle cells with histological features characterized by atypical pleomorphism, prominent mitotic activity, necrosis, hemorrhage, and invasive and/or extra thyroidal growth [4]. Leiomyosarcoma is extremely rare in the TG itself. Diagnosis should be clarified by immunohistochemical staining methods when there is a tumour resembling spindle shaped malignant cells [2]. Intermediate filaments are useful markers for diagnosis. The cytokeratins, which are specific of epithelia, are the largest and most diverse class of intermediate filaments. Vimentin is another important intermediate filament protein that is expressed in mesenchymal cells [7]. Carcinoma of the TG usually express both of these markers [7] and anaplastic thyroid carcinoma sometimes stained with vimentin. Desmin is another good marker of muscle origin and carcinoma of the epithelial tumors generally do not express it except lung tumors. In our case, diffuse and strong staining with desmin and vimentin and no reactivity to the Pan CK

were revealed by three different pathology clinics. Anaplastic thyroid carcinoma mimics PLT structurally and functionally and spindle cells of anaplastic thyroid carcinomas generally express Pan CK and vimentin but do not desmin. On the other hand, thyroglobulin, calcitonin, protein S100 and chromogranin are never expressed in PLT [1].

Medullary carcinoma can show variable microscopic features including spindle cells. However, differential diagnosis is easy because tumour cells are positive for chromogranine A, synaptophysine, ACE and calcitonin [1]. Other spindle characteristic, solitary fibrous tumours are usually positive for CD34, BCL2, CD99 and vimentin [1].

Metastatic malign tumours of the thyroid are infrequent [8, 10]. Autopsy series of the patients who died from cancer revealed %2-24 of thyroid metastasis. Lam and Lo have reported 79 patients with metastatic thyroid tumours in 1998 [8]. The most common sites of the primary tumour are the kidneys, stomach, lungs, mammary glands, ovaries, colon and melanomas respectively [8, 10]. The clinical presentations of the metastatic thyroid tumour may be similar to those of primary thyroid tumour, including enlargement of the neck, hoarseness and dysphagia [8]. The presence of known tumor history, clinical examination and imaging studies will assist to diagnosis.

Some authors believed that benign leiomyoma has differentiated leimyosarcoma. Leiomyoma of the thyroid is an extremely rare benign tumour and malignant transformation to another extremely rare leiomyosarcoma is not eventual [2]. Thyroid anaplastic carcinomas can accompany with sarcoma like features (spindle cell) [5] and spindle cell sarcomas arise de novo as a component of anaplastic carcinoma [1]. Chetty et al. have postulated that such smooth muscle differentiation may thus arise as a result of metaplastic modification or by de-differentiation and re-differentiation of anaplastic thyroid carcinoma [11].

Another aspect for the origin of PLT puts forward that it may originate from the smooth muscle component of organ capsule or vascular walls [2]. Adachi et al. in their first report of the autopsy case of PLT stated that PLT originated in the vascular walls, and supported their idea with the evidence that there was no smooth muscle in the thyroglossal tract [2]. Kawahara et al. agreed with this opinion. They also reported the immunohistochemical findings of the PLT for the first time [2]. Thomas and Fine's report supported the idea that leiomyosarcomas might originate in the vascular walls of TG [2]. However it is very difficult to establish precisely whether PLT is originating from the smooth muscles of the TG or from another adjacent muscle organ because in the most cases tumours are in advanced stages at the time of diagnosis.

Consequently, these tumours originate in the tissue elements within the thyroid gland and show invasive growth within the thyroid parenchyma. The tumour often invades into the surrounding thyroid parenchyma and the adjacent structures rather than metastasis to the regional lymph nodes [1, 2]. Despite different and aggressive treatment modalities most patients have got metastatic diseases (lungs, liver, myocardium, kidney, pancreas, small bowel, colon, peritoneum, brain and bones) and die because of metastatic diseases. There is not any specific standard treatment in PLT. Initial treatment generally begins with surgical excision. In high grade patients, 3 different adjuvant chemotherapy regimens take place in literature. The median survival of the metastatic patients who received RT- chemotherapy was 8.5 months (range, 6-11), as compared with 5 months (range, 1-51) for the patients who did not receive these therapy modalities.

Conclusion

The treatment protocols for PLT have not been well established yet, because of their rareness and poor prognosis. We believe that aggressive therapeutic approach is necessary for aggressive cancers. Our case may be directive for PLT treatment.

Consent

Written informed consent was obtained from the patient himself for the publication of this case report and any accompanying images.

References

1. Amal B, Fatemi HE, Souaf I, Moumna K, Affaf A. A rare primary tumor of the thyroid gland: report a new case of leiomyosarcoma and literature review. ***Diagnostic Pathology.*** 2013, 8:36
2. Ozaki O, Sugino K, Mimura T, Ito K, Tamai S, Hosoda Y. Primary Leiomyosarcoma of the Thyroid Gland. ***Japan J Surg.*** 1997, 27:177-180
3. Mansouri H, Gaye M, Errihani H, Kettani F, Gueddari IE. Leiomyosarcoma of the thyroid gland. ***ActaOto-Laryngologica.*** 2008, 128: 335-336
4. Ege B, Leventoğlu S.Primary leiomyosarcoma of the thyroid. ***J Korean Surg Soc***. 2013, 85:43-46
5. Nemenqani D, Yaqoob N, Khoja H. Leiomyosarcoma Metastatic to the Thyroid Diagnosed by Fine Needle Aspiration Cytology. ***J Pak Med Assoc.*** 2010, 60:307-309
6. Thompson LDR, Wenig BM,Adair CF, Shmookler BM, Heffness CS. Primary Smooth Muscle Tumors of the Thyroid Gland. ***American Cancer Society***. 1997, 79:579-587
7. Kawahara E, Nakanıshı I, Terahata S, Ikegaki S.Leiomyosarcoma of the Thyroid Gland: A Case Report With a Comparative Study of Five Cases of Anaplastic Carcinoma. ***Cancer.***1988, 62:2558-2563
8. Lam KY, Lo CY. Metastatic tumors of the thyroid gland: a study of 79 cases in Chinese patients. ***Arch Pathol Lab Med***.1998, 122:37-41
9. Takayama F, Takashima S, Matsuba H, Kobayashi S, Ito N, Sone S.MR imaging of primary leiomyosarcoma of the thyroid gland. ***European Journal of Radiology***. 2001, 37: 36-41
10. Hafez MT, Hegazy MA, Elwahab KA, Arafa M, Abdou I,Refky B. Metastatic rhabdomyosarcoma of the thyroid gland, a case report. ***Head & Neck Oncology***. 2012, 4:27
11. Chetty R, Clark SP, Dowling IP.Leiomyosarcoma of the thyroid: immunohistochemical and ultrastructuralstudy. ***Pathology.***1993, 25:203-205
12. Just PA, Guillevin R, Capron F, Charpentier ML, Naour GL, FabriceMenegau F, Leenhardt L, Simon JM, Hoang C. An unusual clinical presentation of a rare tumor of the thyroid gland: report on one case of leiomyosarcoma and review of literature. ***Annals of Diagnostic Pathology.*** 2008, 12: 50-56
13. Wang TS, Ocal IT, Oxley K, Sosa JA. Primary Leiomyosarcoma of the Thyroid Gland. ***Thyroid.*** 2008, 18:425-428
14. Tanboon J,Keskool P. Leimyosarcoma: A Rare Tumor of the Thyroid. ***Endocrine Pathology.*** 2013, 24:136-143

15. Day AS, Lou PJ, Lin WC, Chou CC.Over-expression of c-kit in a primary leiomyosarcoma of the thyroid gland. ***Eur Arch Otorhinolaryngol*.** 2007, 264:705-708
16. **Hiroko O, Chie W, Hiroko Y, Junko H**. A case of primary leiomyosarcoma of the thyroid. ***The Journal of the Japanese Society of Clinical Cytology***. 2000, 39:258-262

Table 1 Clinical data on 20 reported cases of leiomyosarcoma and on the current case[1,3,4,12,13,14,15,16]

Case	Reference	Age (y)	Location	Gender	Presentation	Size (cm)	Operation	TFT	Adjuvant Chemotherapy	Metastatic Disease	Outcome
1	Thompson et al.[12]	64	Right Lobe	F	Mass multiple nodules	7.5	Excision (rezidü+)	-	-	Post op lung met (2 months); liver-pleural-peritoneal met	DWD, 5 mo
2	Thompson et al.	45	Left Lobe	M	Enlarging mass for 4 weeks; weight loss (13.5 kg)	9	ST	-	Doxorubicin	Lung met	Alive, 11 mo
3	Thompson et al.	68	Left Lobe	M	Mass; hoarseness	1.9	-	-	-	Lung met	DWD, 18 mo
4	Thompson et al.	83	Sub Sternal	M	Enlarging mass; dysphagia	5.5	Excision	-	-	Lung met	DWD, 3 mo
5	Kawahara et al. [12]	82	Right Lobe	M	Mass; hoarseness	5.5	ST + BLND	N	-	Submandibular recurrence	DWD, 4 mo
6	Chetty et al.[12]	54		F	No symptoms	3.5	ST	N	-	-	Alive,15 mo NED
7	Just et.al. [12]	83	Left Lobe	F	Mass, left arm pain	5.7	ST	N	-	Vertebral met	DWD, 2 mo
8	Ozaki et	58	Left Lobe	F	Mass	5	TT +		-	-	Alive,24

	al.[12]						central LND				mo NED
9	Ege et al.[4]	56	Left Lobe	M	Enlarging mass; dysphagia; hoarseness	2.7	TT + central LND	N	-	Pulmonary met (post op 8 mo)	DWD, 8 mo
10	Mansourı et al.[3]	63	Right Lobe	F	Mass; hoarseness	7	TT	N	-	lung met (post op 2 mo) bone-liver-peritoneal met (post op 5 mo)	DWD, 5 mo
11	Amal et al.[1]	72	Left Lobe	F	Mass of the skin fistula	5	ST	N	-		
12	Wang et al.[13]	65	Right Lobe	F	Enlarging Mass; weight loss	8	TT + BLND+ thymectomy		Ifosfamide + Doxorubicin		-
13	Kaur et al.[12]	?	?	?					-	Nodal met	Alive, 12 mo
14	Takayama et al. [12]	66	Left Lobe	F	Enlarging mass	8.5	ST	N	-	Lung met	Alive, 3 mo
15	Tanboon et al. [14]	64		F			TT		-	Lung + liver met	DWD, 3 mo
16	Day et al.[15]	43	Left Lobe	M	Mass; hoarseness	1.8		N	Imatinib	Lung met	DWD, 6 mo
17	Hiroko et	86	Left Lobe	F					-		

	al. [16]										
18	Tulbah et al.[12]	6		M	Upper respiratory tract infections	5	ST		-	?	DWD, 4 mo
19	Tsugawa et al.[12]	90		F	Mass	8	ST		-		DWD, 2 mo, pneumonia
20	Adachi et al.[12]	74		F	Pain; dysphagia weight loss	12			+		DWD, 1 mo
21	Lida et al.[12]	72	Right Lobe	F	Mass	3	ST + BLND		-	-	DWD, 51 mo
22	Current Case	56	Left Lobe	M	Hoarseness; enlarging neck circumferences	11	ST	N	Cyclophosphamide + doxorubicin with mesna; maintenance with cyclophosphamide + etoposide	Bilateral Lung metastasis	Alive, 61 mo, NED

F, female; M, male; TT, total thyroidectomy; ST, subtotal thyroidectomy; BLND, bilateral lymph node dissection; LND, lymph node dissection; TFT, thyroid function test; N, normal; DWD, died with disease; met, metastasis; NED, no evidence of disease.