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Management of Rare Thyroid Malignancies

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Abstract

The purpose of this chapter is a focused analysis and review of rare thyroid malignancies including anaplastic thyroid cancer (ATC), medullary thyroid cancer (MTC), primary thyroid lymphoma (PTL), and primary thyroid sarcoma (PTS). The focus will be on the epidemiology, risk factors, workup, and a contemporary review of management of these rare entities.

Keywords: anaplastic thyroid cancer, medullary thyroid cancer, thyroid lymphoma, thyroid sarcoma

1. Introduction

The majority of thyroid neoplasms are well-differentiated lesions that have been extensively studied and reported in the literature with regard to diagnosis and management [1, 2]. While most patients with thyroid malignancy typically fall in to the above-mentioned category, few patients may carry diagnoses of rare thyroid cancers that are not as widely researched. Owing to the dearth of literature on these rare thyroid malignancies, the consensus for management is often unclear and highly debated. As head and neck oncologists should be well versed in the treatment options for these uncommon malignancies, this chapter seeks to coalesce the literature in hopes of providing practitioners with an overview of these challenging pathologies. The chapter will focus on the analysis of anaplastic thyroid cancer (ATC), medullary thyroid cancer (MTC), primary thyroid lymphoma (PTL), and primary thyroid sarcoma (PTS). In the following sections, each of these entities will be discussed beginning with epidemiology and risk factors progressing to work up and management.

2. Anaplastic thyroid cancer

ATC is among the most aggressive and uniformly fatal malignancies afflicting the human species. It is extremely rare, comprising approximately 2–5% of all thyroid malignancies [3–5]. The annual incidence of ATC is one to two cases per million. The majority of patients, greater than 90%, are over the age of 50 [5–7]. Females are more commonly affected than males, with a comparison ratio of approximately 1.5:1 [6, 8]. A large majority of ATC occurs in conjunction with other thyroid cancers and is theorized to be a degeneration of well-differentiated carcinomas [1, 8].

Few patients survive beyond 6 months after initial presentation, with a median survival of 2–12 months [1, 3, 4, 6, 9]. At present, it is reported that more than 50% of patients with ATC have distant metastases [10]. Patients typically present with a rapidly enlarging neck mass, often stating that the neck mass was stable for a significant period of time before the period of rapid growth. Not uncommonly, patients complain of pain, dysphonia, and difficulty breathing as the mass grows and begins to invade the laryngopharyngeal framework [2]. Death from ATC is typically caused by compression of the great vessels, namely the superior vena cava, or asphyxiation from airway compromise [2].

As with any rapidly enlarging neck mass, airway stability is of primary importance and a stable airway should be established even prior to diagnosis if the patient is unstable. In the event the patient has a stable airway, following thorough examination including nasopharyngolaryngoscopy, imaging should be obtained to evaluate the extent and radiographic characteristics of the mass. Computed tomography (CT) is typically the initial imaging study of choice, however, magnetic resonance imaging (MRI) can be obtained to determine the extent of soft tissue and cartilage involvement. Following imaging, tissue diagnosis can be established with fine-needle aspiration (FNA); however, at times a larger tissue sample may be needed to rule out lymphoma [2]. Pathology of ATC typically shows gross macroscopic involvement of surrounding tissue along with areas of florid necrosis. A population of undifferentiated cells is typically seen, along with a heterogeneous population of polygonal, spindle, and giant cells. As cells are poorly differentiated, no thyroglobulin production or thyroid hormone receptors are found on further evaluation [1]. After a diagnosis of malignancy is established, practitioners may opt to pursue a fludeoxyglucose (^{18}F -FDG) positron emission tomography (PET) scan or whole body CT scan to evaluate for metastases. Staging of ATC is based on its extension from the thyroid gland and distal metastases. All lesions are considered stage 4; stage 4A for lesions within the thyroid gland without distal spread, stage 4B for lesions that have grown outside the thyroid without distal spread, and stage 4C for any lesion that has distal metastases [11].

The management of ATC poses a number of challenges for the practitioner owing to the advanced nature of the malignancy at diagnosis, short survival time, and often severe functional impairment. Of paramount importance is an understanding of the patient's desires and the goals of care. Treatment options include radiation, surgery, chemotherapy, or a combination. Commonly, patients require tracheostomy and enteral feeding support with a gastrostomy tube [2, 6]. Routine tracheostomy is not advocated and the decision is highly based on the patient's desire to undergo a surgical airway procedure in lieu of potential

changes in the quality of life [12, 13]. Chemotherapeutic regimens have not been uniformly accepted and as such, there is no standard regimen. In recent studies, however, there have been promising results with newer drug modalities. The combination of carfilzomib, a proteasome inhibitor, and CUDC-101, a histone deacetylase, have been shown to induce apoptosis in anaplastic thyroid cancer cells [14]. Another recent study has shown positive results through the use of doxorubicin nanospheres combined with extracorporeal shock wave therapy [15].

The role of surgery is controversial. In conjunction with the American Thyroid Association, Smallridge et al. report that surgery can be considered with locoregional disease; however, given the lack of survival benefit, they recommend against tumor debulking [16]. Disease extending beyond the thyroid gland has typically represented unresectable disease [17–22].

In a recent study by Brown and Ducic, 16 patients with extrathyroidal ATC were evaluated for long-term survival following complete surgical resection. These patients had stage 4B ATC without evidence of distal metastases, and no disease extension beyond the carotid arteries. Twelve patients required total laryngectomy, four required tracheal resection, and six required cervical esophagectomy. Twelve out of 16 patients also required bilateral complete neck dissection for clinically evident disease. Postoperatively, surgical patients underwent external beam radiation. Of the 16 patients that underwent surgery with adjuvant radiation, 50% had long-term disease free survival ranging from 9 months to 8 years. Six patients died from metastatic disease while one died from a myocardial infarction. Based on their findings, Brown and Ducic believe that specific patients with extrathyroidal ATC that does not extend lateral to the carotid artery and without distal metastases may be suitable surgical candidates for complete resection followed by radiation therapy [23].

Regardless of treatment modality chosen, resectability of locoregional cancer, localized intrathyroidal disease, and absence of distal metastases are associated with a more favorable prognosis [24–26].

Anaplastic thyroid cancer is an aggressive disease with a high mortality rate. Early detection with thoughtful planning involving the patient's family is the cornerstone of managing this challenging malignancy.

3. Primary thyroid sarcoma

PTS is an extremely rare entity with an incidence no higher than 1.5% [27–29]. The rarity of PTS has led to a substantial dearth of literature and the majority of information is based on scattered case reports in the literature, along with several review papers. PTS is a general term for all types of thyroid sarcoma; however, specific entities include angiosarcoma, heman-gioendothelioma, fibrosarcoma, leiomyosarcoma, fibrous histiocytoma, and several others.

Patients are typically between the ages of 60 and 80 years and do not possess any other specific risk factors for this entity. Presenting complaints center on a thyroid nodule without any specific signs or symptoms unless they have advanced disease [29]. Diagnosis for PTS is similar

to other thyroid nodules, centered on ultrasound imaging followed by FNA. On ultrasound, these lesions have a hypohyperechoic pattern in comparison to normal thyroid tissue. As the pattern is nonspecific, it may raise suspicion for PTS but by no means is pathognomonic [30]. It is important for the practitioner to realize that certain subsets of sarcoma, such as angiosarcoma, can often have similar pathologic findings as other thyroid malignancies. In a study by Bayir et al., it was reported that angiosarcoma can be mistaken as ATC due to similar pathologic findings; however, angiosarcoma tends to bleed more significantly than ATC and often leaves a hematoma at the FNA site [31]. Although treatment is based on surgery with postoperative radiation for advanced disease, there is no standard protocol for treatment given the rare nature of this disease.

In a contemporary review, Surov et al. examined the PTS literature and evaluated the cases of 142 patients with PTS. They reported a slight male preponderance and found that the majority of patients, approximately 70%, did not present with distal metastases at presentation. Patients typically had a painless goiter, and a small subset of patients had dyspnea and dysphagia indicating advanced disease [30]. Of their population, approximately 20% of lesions were angiosarcoma, 15% were malignant hemangioendothelioma, followed by smaller percentages of fibrous histiocytoma, leiomyosarcoma, and fibrosarcoma. Leiomyosarcoma and malignant histiocytoma were reported to be more likely to infiltrate the trachea or esophagus compared to the other subtypes [30].

Fibrosarcoma patients were more likely to present with regional disease while leiomyosarcoma and angiosarcoma patients were more likely to present with distal disease. Patients with distal metastases primarily involved the lung [30]. In their review, 75 patients were treated with surgery as single modality, while 53 had surgery with adjuvant chemo-radiation. One patient had only radiation, two had just chemotherapy, and four had chemo-radiation without surgery. During the follow-up period of 0.5–120 months (median 7 months), 31% of patients were living while the remainder died or were lost to follow-up [30].

As mentioned previously, due to the lack of cohesive literature, there have been no studies reporting the overall 5-year survival or disease free survival of PTS as a group. One study reported a 33% 5-year survival for angiosarcoma of the thyroid and noted that patients present at a late stage [32]. While this statistic may not be applicable to other subtypes of sarcoma, the practitioner must understand that given the possibility of this rare malignancy and its tendency for locally aggressive behavior, any thyroid nodule with suspicious features should be imaged and biopsied in a timely fashion.

4. Primary thyroid lymphoma

PTL comprises 1–5% of all thyroid malignancies with women more commonly affected than men [33, 34]. The disease typically affects individuals between the ages of 50 and 80, and is rarely found in those younger than 40 years of age [35, 36]. Carrying a diagnosis of Hashimoto's thyroiditis is a major risk factor for PTL. Studies by Holm and Kato report a 67–80-fold

increased risk of PTL in patients with Hashimoto's thyroiditis [37, 38]. In a 2015 study by Chai et al., 87% of patient with PTL had Hashimoto's [39].

Patients typically present with a painless enlarging neck mass, often in the setting of a known autoimmune thyroiditis. Adenopathy can be associated with the primary complaints as well [40]. Complaints of dysphagia, dyspnea, and hoarseness are uncommon, and signify advanced disease with compressive symptoms or invasion of the recurrent laryngeal nerve [2]. Only an estimated 10% of patients present with constitutional symptoms such as fever, weight loss, and night sweats [5]. Following thorough history and physical examination, thyroid studies can be obtained followed by ultrasound and fine needle aspiration if indicated. FNA by itself may yield inconclusive information and as such, either ultrasound guided FNA or open biopsy is recommended [2, 41, 42].

PLT is a broad term encompassing multiple pathologies. B-cell non-Hodgkin's lymphoma (NHL) is by far the most common cell line in PTL; T-cell lymphoma, plasmacytoma, and Hodgkin's lymphoma have been reported but are exceedingly rare [42, 43]. The three main subtypes of B-cell NHL are mucosal associated lymphoid tissue (MALT) lymphoma, diffuse large B-cell lymphoma (DLBCL), and a mixed variant of DLBCL and MALT [39]. MALT lymphoma is generally of low grade and indolent growth while DLBCL is high grade with aggressive growth. The mixed variant behaves more similarly to DLBCL than MALT [33, 35, 42, 44, 45]. Staging of PTL is based on extension from the thyroid gland. Stage 1 disease is localized to the thyroid gland; stage 2 disease is localized to the thyroid gland but also involves regional lymph nodes; stage 3 disease involves spread to lymph nodes on both sides of the diaphragm; stage 4 disease has spread to distant sites of the body [36].

The management of PTL is primary through chemotherapy and radiation; surgery is reserved for early stage MALT localized to the thyroid gland or for patients suffering from compressive symptoms [5, 46]. The chemotherapeutic regimen commonly utilized, CHOP, consists of cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone [47, 48].

Chai et al. examined 38 patients with PTL, 92% early stage, treated with a combination of surgery, chemotherapy, radiation, or a combination. Few patients received single modality therapy, while the majority were treated with multimodality therapy. Treatment outcomes were followed from 3 to 156 months with the median follow up being 56 months. They reported a 100% 5-year disease specific survival for MALT lymphoma, 100% for mixed, and 87.5% for DLBCL [39]. This concurs with previous studies reporting a 96–100% 5-year disease specific survival for MALT lymphoma, and shows an improvement in survival compared to the previously reported 71–75% 5-year disease specific survival for DLBCL [35, 36, 49]. Stratifying survival by stage, a surveillance, epidemiology, and end results (SEER) database study by Graff Baker reported 86% 5-year disease-specific survival for stage 1 PTL, 81% for stage 2, and 64% for stages 3 and 4 [36].

As overall prognosis is highly dependent on the subtype of primary thyroid lymphoma and the stage at presentation, the practitioner must have a high suspicion for lymphoma especially in a patient with a history of Hashimoto's presenting with enlarging neck mass. Establishing

a diagnosis with sufficient cell volume to perform flow cytometry is crucial in categorizing the subtype of lymphoma and quickly beginning treatment with a multidisciplinary team.

5. Medullary thyroid cancer

MTC is a malignancy that arises from the calcitonin producing parafollicular cells and comprises 3–5% of thyroid malignancies [2, 50]. It is important to note that the parafollicular c-cells also produce carcinoembryonic antigen (CEA), prostaglandin, and serotonin of which excess levels could lead to symptoms [10]. Males and females are equally affected, typically over the age of 50 [51, 52].

The majority of MTC, approximately 75%, occurs in a sporadic fashion and generally are unilateral and unifocal [50, 52]. The remaining MTC is derived from an autosomal dominant hereditary pattern associated with the *RET* proto-oncogene. Hereditary MTC is more likely to be multifocal and bilateral in nature [53–59]. Thirty percent of MTC affects patients younger than 50 and can have a familial inheritance pattern including the association with multiple endocrine neoplasia (MEN) syndromes. MTC in MEN2A is associated with pheochromocytoma and hyperparathyroidism, while MTC associated with MEN2B is associated with mucosal neuromas, Marfanoid habitus, or pheochromocytoma [53, 54, 60, 61].

Patients commonly present with a painless thyroid nodule that can be accompanied by palpable cervical adenopathy [50]. Pain, dyspnea, and dysphagia are worrisome symptoms that can indicate invasion of local structures or compression from mass effect [2]. Symptoms of serotonin production can also be present such as diarrhea or flushing [50]. Initial regional spread can be found in the central neck, lateral neck, or superior mediastinum. Fifty percent of MTC patients have distal metastases on diagnosis, typically involving the mediastinum, liver, bone, or lung [62].

Diagnosis is based on ultrasound, fine needle aspiration, and appropriate testing of serum markers. FNA of MTC shows infiltrating neoplastic cells with marked heterogeneity. Occasionally, amyloid deposits resulting from polymerized calcitonin will be found, strongly indicative of MTC [63]. Following FNA diagnosis of MTC, patients should have calcitonin and CEA levels evaluated, as they are both diagnostic and important for surveillance [2]. Calcitonin strongly correlates with tumor volume and progression while CEA is a predictor of survival. Often, the doubling of calcitonin can be followed to determine the rate of tumor progression. A doubling time of greater than 6 months is associated with a 5-year survival of 92% while a doubling time less than 6 months is associated with a 5-year survival of 25% [64, 65]. CT imaging of the neck and mediastinum can be pursued to evaluate for radiographic evidence of spread. As the uptake of fluorodeoxyglucose is low in MTC, PET scanning is not routinely recommended. However, the use of other radionuclide tracers such as ^{18}F -DOPA can be useful, as ^{18}F -DOPA has been reported to have a sensitivity of 81%, much greater than FDG for metastatic disease [66]. To evaluate for metastases, CT of the chest, abdomen, and head is recommended along with MRI of the liver and brain due to the increased accuracy [50].

Prior to undertaking treatment, the patient should also be evaluated for *RET* mutations and a thorough screening for MEN syndrome should be completed. Genetic testing is becoming more common with these patients and their families as early detection and treatment of family members may lead to favorable prognoses. The workup of MEN syndrome includes evaluation of hyperparathyroidism by checking calcium and parathyroid hormone levels. More importantly, patients should have a 24-h urine screen for catecholamines and metanephrines along with an abdominal MRI to evaluate for the presence of a pheochromocytoma. An undiagnosed or poorly managed pheochromocytoma could result in an intraoperative catastrophe leading to a significant increase in mortality [2, 50].

Initial treatment of MTC is total thyroidectomy and bilateral central neck dissection. Family members with MEN2B or MEN 2C are recommended to have a prophylactic total thyroidectomy [2, 50]. If the patient has positive central neck adenopathy or palpable lateral neck disease, a neck dissection of levels two through six should be performed along with dissection of the superior mediastinal lymph nodes on the ipsilateral side or bilaterally if indicated. If the primary MTC lesion is greater than 1 cm, there can be a greater than 50% chance of occult metastases to the ipsilateral neck and a lateral neck dissection should be performed in that scenario as well [67–69]. As MTC is from parafollicular cells, it does not respond to radioactive iodine therapy [70]. Following surgery, patients should be followed with serial calcitonin and CEA levels to evaluate for recurrence or persistent disease [69]. External beam radiation can be considered for resections with positive margins or unresectable tumor [2]. Serum calcitonin greater than 150 pg/ml signifies residual or metastatic disease [64, 71].

Advanced MTC can be potentially treated with surgery and postoperative radiation, but often patients with extensive local disease or distal metastases are not surgical candidates. Chemotherapy in MTC, often times involving a combination of doxorubicin, dacarbazine, or cisplatin, is indicated only in rapidly progressive metastatic disease, but the response rates have not been reported higher than 20% [72–75]. Currently, molecular therapies targeting kinases of VEGFR2 and *RET* are in clinical trials but reserved for a very specific subset of patients given the adverse risk profile [76]. The overall prognosis of MTC is related to disease stage. Ten-year survival for all MTC is 61–75%; however, the presence of cervical adenopathy decreases survival to 45% [70].

MTC can be an aggressive malignancy with limited treatment options. Early intervention and close surveillance with imaging and serum markers are vital. As this malignancy has the possibility of being associated with concomitant endocrine maladies and familial inheritance, a thorough assessment of the patient and family alike can allow for safe treatment and the prevention of disease progression.

6. Conclusion

Anaplastic thyroid cancer, primary thyroid lymphoma, primary thyroid sarcoma, and medullary thyroid cancer are all extremely rare malignancies that make up a small portion of all thyroid malignancies. The literature available for guiding management is often limited as

the small number of cases precludes adequate investigation in clinical trials. Although these rare malignancies are not frequently encountered, they have the potential of being aggressive with poor outcomes if not managed in a timely fashion. Patients with any of the above malignancies should be encouraged to be vigilant in the care and follow up of these conditions. Practitioners should make every attempt to rapidly establish a diagnosis for thyroid nodules and initiate treatment in an expedited fashion while keeping the patients and their families closely involved in the decision making process.

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References

- [1] LiVolsi VA, Merino M. Pathology of Thyroid Tumors. Philadelphia: Saunders; 1987.
- [2] Lai S, Mandel S, Weber R. Management of thyroid neoplasms. In Flint P, editor. Cummings Otolaryngology, 6th ed.; 2015. p. 1901–1928 [Chapter 123].
- [3] Nel CJ, Van heerden JA, Goellner JR, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 82 cases. Mayo Clin Proc. 1985;60(1):51–58.
- [4] Nagaiah G, Hossain A, Mooney CJ, Parmentier J, Remick SC. Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment. J Oncol. 2011;2011:542358.
- [5] Green LD, Mack L, Pasioka JL. Anaplastic thyroid cancer and primary thyroid lymphoma: a review of these rare thyroid malignancies. J Surg Oncol. 2006;94:725–736.
- [6] Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. Endocrinol Metab Clin North Am. 2008;37(2):525–538, xi.
- [7] Chiacchio S, Lorenzoni A, Boni G, Rubello D, Elisei R, Mariani G. Anaplastic thyroid cancer: prevalence, diagnosis and treatment. Minerva Endocrinol. 2008;33(4):341–357.
- [8] Kapp DS, Livolsi VA, Sanders MM. Anaplastic carcinoma following well-differentiated thyroid cancer: etiological considerations. Yale J Biol Med. 1982;55(5–6):521–528.

- [9] Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. *Ann Surg Oncol*. 2006;13(4):453–464.
- [10] Demeter JG, De Jong SA, Lawrence AM, Paloyan E. Anaplastic thyroid carcinoma: risk factors and outcome. *Surgery*. 1991;110(6):956–961.
- [11] American Joint Committee on Cancer. How is thyroid cancer staged? (2015). <http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-staging>.
- [12] Kebebew E, Greenspan FS, Clark OH, Woeber KA, Mcmillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer*. 2005;103(7):1330–1335.
- [13] Shaha AR. Airway management in anaplastic thyroid carcinoma. *Laryngoscope*. 2008;118(7):1195–1198.
- [14] Zhang L, Boufraquech M, Lake R, Kebebew E. Carfilzomib potentiates CUDC-101-induced apoptosis in anaplastic thyroid cancer. *Oncotarget*. 2016;7(13):16517–16528.
- [15] Marano F, Argenziano M, Frairia R, et al. Doxorubicin-loaded nanobubbles combined with extracorporeal shock waves: basis for a new drug delivery tool in anaplastic thyroid cancer. *Thyroid*. 2016;26(5):705–716.
- [16] Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012;22(11):1104–1139.
- [17] Mciver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery*. 2001;130(6):1028–1034.
- [18] Venkatesh YS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA. Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer*. 1990;66(2):321–330.
- [19] Haigh PI. Anaplastic thyroid carcinoma. *Curr Treat Options Oncol*. 2000;1(4):353–357.
- [20] Grant CS, Thompson G. Anaplastic thyroid carcinoma: hope on the horizon?. *Surgery*. 2011;150(6):1220–1221.
- [21] Passler C, Scheuba C, Prager G, et al. Anaplastic (undifferentiated) thyroid carcinoma (ATC). A retrospective analysis. *Langenbecks Arch Surg*. 1999;384(3):284–293.
- [22] Cobin RH, Gharib H, Bergman DA, et al. AACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. American Association of Clinical Endocrinologists. American College of Endocrinology. *Endocr Pract*. 2001;7(3):202–220.
- [23] Brown RF, Ducic Y. Aggressive surgical resection of anaplastic thyroid carcinoma may provide long-term survival in selected patients. *Otolaryngol Head Neck Surg*. 2013;148(4):564–571.

- [24] Voutilainen PE, Multanen M, Haapiainen RK, Leppäniemi AK, Sivula AH. Anaplastic thyroid carcinoma survival. *World J Surg.* 1999;23(9):975–978.
- [25] Tan RK, Finley RK, Driscoll D, Bakamjian V, Hicks WL, Shedd DP. Anaplastic carcinoma of the thyroid: a 24-year experience. *Head Neck.* 1995;17(1):41–47.
- [26] Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995 [see comments]. *Cancer.* 1998;83(12):2638–2648.
- [27] Buła G, Waler J, Niemiec A, Trompeta J, Stepievska K, Gawrychowski J. Unusual malignant thyroid tumours—a clinical study of 20 cases. *Acta Chir Belg.* 2008;108(6):702–707.
- [28] Thompson LD, Wenig BM, Adair CF, Shmookler BM, Heffess CS. Primary smooth muscle tumors of the thyroid gland. *Cancer.* 1997;79(3):579–587.
- [29] Surov A, Holzhausen HJ, Machens A, Dralle H. Imaging findings of thyroidal sarcoma. *Clin Imaging.* 2014;38(6):826–830.
- [30] Surov A, Gottschling S, Wienke A, Meyer HJ, Spielmann RP, Dralle H. Primary thyroid sarcoma: a systematic review. *Anticancer Res.* 2015;35(10):5185–5191.
- [31] Bayır Ö, Yilmazer D, Ersoy R, et al. An extremely rare case of thyroid malignancy from the non-Alpine region: angiosarcoma. *Int J Surg Case Rep.* 2015;19:92–96.
- [32] Kalitova P, Plzak J, Kodet R, Astl J. Angiosarcoma of the thyroid. *Eur Arch Otorhinolaryngol.* 2009;266(6):903–905.
- [33] Widder S, Pasiaka JL. Primary thyroid lymphomas. *Curr Treat Options Oncol.* 2004;5(4):307–313.
- [34] Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. *Semin Oncol.* 1999;26(3):316–323.
- [35] Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, Abbondanzo SL. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *Am J Surg Pathol.* 2000;24(5):623–639.
- [36] Graff-baker A, Roman SA, Thomas DC, Udelsman R, Sosa JA. Prognosis of primary thyroid lymphoma: demographic, clinical, and pathologic predictors of survival in 1,408 cases. *Surgery.* 2009;146(6):1105–1115.
- [37] Holm LE, Blomgren H, Löwhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. *N Engl J Med.* 1985;312(10):601–604.
- [38] Kato I, Tajima K, Suchi T, et al. Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. *Jpn J Cancer Res.* 1985;76(11):1085–1090.

- [39] Chai YJ, Hong JH, Koo DH, et al. Clinicopathological characteristics and treatment outcomes of 38 cases of primary thyroid lymphoma: a multicenter study. *Ann Surg Treat Res.* 2015;89(6):295–299.
- [40] Kumar R, Khosla D, Kumar N, et al. Survival and failure outcomes in primary thyroid lymphomas: a single centre experience of combined modality approach. *J Thyroid Res.* 2013;2013:269034.
- [41] Matsuda M, Sone H, Koyama H, Ishiguro S. Fine-needle aspiration cytology of malignant lymphoma of the thyroid. *Diagn Cytopathol.* 1987;3(3):244–249.
- [42] Alzouebi M, Goepel JR, Horsman JM, Hancock BW. Primary thyroid lymphoma: the 40 year experience of a UK lymphoma treatment centre. *Int J Oncol.* 2012;40(6):2075–2080.
- [43] Salhany KE, Pietra GG. Extranodal lymphoid disorders. *Am J Clin Pathol.* 1993;99(4):472–485.
- [44] Tsang RW, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol.* 2003;21(22):4157–4164.
- [45] Thieblemont C, Mayer A, Dumontet C, et al. Primary thyroid lymphoma is a heterogeneous disease. *J Clin Endocrinol Metab.* 2002;87(1):105–111.
- [46] Sakorafas GH, Kokkoris P, Farley DR. Primary thyroid lymphoma (correction of lypoma): diagnostic and therapeutic dilemmas. *Surg Oncol.* 2010;19(4):e124–e129.
- [47] Devine RM, Edis AJ, Banks PM. Primary lymphoma of the thyroid: a review of the Mayo Clinic experience through 1978. *World J Surg.* 1981;5(1):33–38.
- [48] Rasbach DA, Mondschein MS, Harris NL, Kaufman DS, Wang CA. Malignant lymphoma of the thyroid gland: a clinical and pathologic study of twenty cases. *Surgery.* 1985;98(6):1166–1170.
- [49] Oh SY, Kim WS, Kim JS, et al. Primary thyroid marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type: clinical manifestation and outcome of a rare disease – consortium for improving survival of lymphoma study. *Acta Haematol.* 2012;127(2):100–104.
- [50] Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. *Lancet Diabetes Endocrinol.* 2016;4(1):64–71.
- [51] Hazard JB. The C cells (parafollicular cells) of the thyroid gland and medullary thyroid carcinoma. A review. *Am J Pathol.* 1977;88(1):213–250.
- [52] Chong GC, Beahrs OH, Sizemore GW, Woolner LH. Medullary carcinoma of the thyroid gland. *Cancer.* 1975;35(3):695–704.

- [53] Delellis RA. Multiple endocrine neoplasia syndromes revisited. Clinical, morphologic, and molecular features. *Lab Invest.* 1995;72(5):494–505.
- [54] Raue F, Frank-raue K, Grauer A. Multiple endocrine neoplasia type 2. Clinical features and screening. *Endocrinol Metab Clin North Am.* 1994;23(1):137–156.
- [55] Wells SA, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid.* 2015;25(6):567–610.
- [56] Elisei R, Cosci B, Romei C, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab.* 2008;93(3):682–687.
- [57] Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. *J Clin Endocrinol Metab.* 2011;96(5):E863–E868.
- [58] Boichard A, Croux L, Al Ghuzlan A, et al. Somatic RAS mutations occur in a large proportion of sporadic RET-negative medullary thyroid carcinomas and extend to a previously unidentified exon. *J Clin Endocrinol Metab.* 2012;97(10):E2031–E2035.
- [59] Agrawal N, Jiao Y, Sausen M, et al. Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS. *J Clin Endocrinol Metab.* 2013;98(2):E364–E369.
- [60] Moley JF. Medullary thyroid cancer. *Surg Clin North Am.* 1995;75(3):405–420.
- [61] Goodfellow PJ, Wells SA. RET gene and its implications for cancer. *J Natl Cancer Inst.* 1995;87(20):1515–1523.
- [62] Ellenhorn JD, Shah JP, Brennan MF. Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland. *Surgery.* 1993;114(6):1078–1081.
- [63] Stepanas AV, Samaan NA, Hill CS, Hickey RC. Medullary thyroid carcinoma: importance of serial serum calcitonin measurement. *Cancer.* 1979;43(3):825–837.
- [64] Laure Giraudet A, Al Ghulzan A, Aupérin A, et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times. *Eur J Endocrinol.* 2008;158(2):239–246.
- [65] Barbet J, Champion L, Kraeber-bodéré F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. *J Clin Endocrinol Metab.* 2005;90(11):6077–6084.
- [66] Beheshti M, Pöcher S, Vali R, et al. The value of ^{18}F -DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with ^{18}F -FDG PET-CT. *Eur Radiol.* 2009;19(6):1425–1434.

- [67] Sherman SI, Angelos P, Ball DW, et al. Thyroid carcinoma. *J Natl Compr Cancer Netw*. 2007;5(6):568–621.
- [68] Block MA. Surgical treatment of medullary carcinoma of the thyroid. *Otolaryngol Clin North Am*. 1990;23(3):453–473.
- [69] Donovan D, Gagel RF. *Medullary Thyroid Carcinoma and Multiple Endocrine Neoplasia Syndromes*, 2nd ed., Philadelphia: Lippincott-Raven; 1997.
- [70] Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. *Medicine (Baltimore)*. 1984;63(6):319–342.
- [71] Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *J Clin Endocrinol Metab*. 2005;90(4):2029–2034.
- [72] Shimaoka K, Schoenfeld DA, Dewys WD, Creech RH, Deconti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. *Cancer*. 1985;56(9):2155–2160.
- [73] Williams SD, Birch R, Einhorn LH. Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. *Cancer Treat Rep*. 1986;70(3):405–407.
- [74] Nocera M, Baudin E, Pellegriti G, Cailleux AF, Mechelany-corone C, Schlumberger M. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. *Groupe d'Etude des Tumeurs à Calcitonine (GETC). Br J Cancer*. 2000;83(6):715–718.
- [75] Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE. Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. *The Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer*. 1995;71(2):363–365.
- [76] Dunna NR, Kandula V, Girdhar A, et al. High affinity pharmacological profiling of dual inhibitors targeting RET and VEGFR2 in inhibition of kinase and angiogenesis events in medullary thyroid carcinoma. *Asian Pac J Cancer Prev*. 2015;16(16):7089–7095.

