Anaplastic Thyroid Carcinoma, Thyroid Lymphoma, and Metastases

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Contents

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Case Presentation

Patient is an 80-year-old man who first noted a lump in his neck about 2 years ago. It was initially thought to be infectious and no workup was pursued, but over time became concerning because it began to grow rapidly over the last month prior to presentation. A thyroid ultrasound demonstrated a large right thyroid lobe nodule measuring 7.8 x 5.4 x 5.1 cm. Two weeks following ultrasound, the patient was admitted to the emergency room with hemoptysis. He also complained of cough, fatigue, headaches, and shortness of breath. He reported tolerating a regular diet, but had recent weight loss. A CT scan with contrast of the neck then revealed a large, right thyroid mass measuring 10.3 x 8.9 x 9.3 centimeters with signs of metastatic adenopathy in the neck, including a node in the right carotid sheath measuring 2.4 x 2.6 cm. The mass was shown to be invading the right sternocleidomastoid muscle and abutting the larynx, with infiltration of the thyroid lamina on the right side and into the paraglottic space. There is mass effect noted on the trachea.

Physical examination reveals vital signs within normal range, a well-nourished man in no acute distress. There is an extremely large, fixed mass filling the entire right neck and extending across the midline. It is fixed to the larynx. There is no obvious palpable lymphadenopathy. His voice is hoarse, but he has no dyspnea or stridor. Endoscopic laryngoscopy shows an immobile right vocal cord, edematous pyriform sinus, and right hemilarynx.

Labs are remarkable for calcium 9.2, albumin 3.8, thyroglobulin antibody 1.5, calcitonin <0.5, T3 73, Free T4 1.05, TSH 4.46, Thyroglobulin 50. CBC with WBC 13, platelets 400, neutrophils 80, ANC 10.3.

Questions

1. What diagnoses are most likely in a patient with a rapidly growing thyroid mass?
   1. Anaplastic thyroid carcinoma
   2. Renal cell carcinoma metastasis
   3. Papillary thyroid cancer
   4. Primary thyroid lymphoma
   5. Medullary thyroid cancer
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (4) are correct.
      (d) Only (3) and (4) and (5) are correct.
      (e) All are correct.
2. FNA of a rapidly growing thyroid mass is nondiagnostic. What is the next best step?
   1. Core needle biopsy
   2. Repeat FNA
   3. Open surgical biopsy
   4. Total thyroidectomy
   5. Thyroid lobectomy
      (a) (1)
      (b) (2)
      (c) (3)
      (d) (4)
      (e) (5)

3. Biopsy of a thyroid mass reveals high mitotic activity, bizarre cells, and extensive necrosis. ATC is diagnosed, and early molecular markers are sent for targetable treatment options. Which molecular markers should be studied?
   1. NTRK
   2. RET
   3. BRAF
   4. RAS
   5. Overall high mutational load
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (2) and (3) and (4) are correct.
      (d) Only (1) and (2) and (5) are correct.
      (e) All are correct.
4. What is the most common primary malignancy with metastases to the thyroid gland?
   1. Renal cell carcinoma (RCC)
   2. Prostate cancer
   3. Rhabdomyosarcoma
   4. Colorectal cancer
   5. Breast cancer
      (a) Only (1) is correct.
      (b) Only (2) is correct.
      (c) Only (3) is correct.
      (d) Only (4) is correct.
      (e) Only (5) is correct.
5. Airway management in rapidly enlarging thyroid mass should include the following:
   1. Physical examination
   2. Fiber-optic laryngoscopy
   3. Bronchoscopy
   4. Pulmonary function tests
   5. CT neck with contrast
      (a) Only (1) and (2) are correct.
      (b) Only (1) and (2) and (3) are correct.
      (c) Only (1) and (2) and (3) are correct.
      (d) Only (1) and (2) and (3) and (5) are correct.
      (e) All are correct.
6. Surgical management is most often indicated for the following thyroid pathologies:
   1. Stage IVA + B anaplastic thyroid cancer
   2. Renal cell carcinoma metastasis to the thyroid
   3. Stage IE thyroid lymphoma
   4. Stage IIE thyroid lymphoma
   5. Colorectal cancer metastasis to the thyroid
      (a) Only (1) and (2) are correct.
      (b) Only (1) and (2) and (3) are correct.
      (c) Only (1) and (2) and (5) are correct.
      (d) Only (1) and (2) and (3) and (5) are correct.
      (e) All are correct.

7. Promising targeted therapies for treatment of anaplastic thyroid cancer include the following molecular targets:
   1. BRAF
   2. NTRK
   3. RET fusion
   4. TP53
   5. VEGF
      (a) (1) and (2) and (3) only
      (b) (1) and (2) and (5) only
      (c) (1) and (2) and (4) only
      (d) (1) and (2) only
      (e) (1) and (3) only
8. The preferred chemotherapy regimen for advanced stage thyroid lymphoma is
   1. EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
   2. RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone)
   3. FOLFOX (5-FU, leucovorin, oxaliplatin)
   4. TPF (docetaxel, cisplatin, 5-FU)
   5. GVD (gemcitabine, vinorelbine, doxorubicin)
      (a) (1)
      (b) (2)
      (c) (3)
      (d) (4)
      (e) (5)
9. Mortality in anaplastic thyroid cancer can be related to the following:
   1. Airway obstruction
   2. Catastrophic hemorrhage
   3. Distant metastasis
   4. Circulatory failure due to compression of mediastinal vasculature
   5. Local invasion
      (a) Only (1) and (2) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (2) and (4) and (5) are correct.
      (d) Only (1) and (4) and (5) are correct.
      (e) All are correct.
10. Surgical management of metastases to the thyroid gland most commonly includes
    1. Metastectomy
    2. Thyroid lobectomy
    3. Total thyroidectomy
    4. Total thyroidectomy with central neck dissection
    5. Tracheal resection
       (a) Only (1) and (2) are correct.
       (b) Only (1) and (2) and (3) are correct.
       (c) Only (1) and (2) and (4) are correct.
       (d) Only (1) and (2) and (3) and (4) are correct.
       (e) All are correct.

9.1 Introduction

Thyroid cancer is typically classified based on cell of origin, with the more common cancers being of follicular cell origin, including papillary, follicular, and Hurthle cell cancers. Less common cancers of neuroendocrine origin include medullary thyroid cancer [1]. When presented with a thyroid mass, clinicians must also consider the rarer tumors of the thyroid gland including anaplastic thyroid carcinoma, lymphoma, and metastatic tumors to the thyroid gland.

Anaplastic thyroid carcinoma (ATC) is an aggressive, undifferentiated tumor originating from the follicular epithelium of the thyroid gland [1]. It is postulated this tumor may develop from the dedifferentiation of existing well-differentiated thyroid cancers, but there is evidence that quite often may develop de novo [2]. ATC is quite rare, with approximately one to two cases per one million persons [3]. It is more prevalent in the elderly, with the mean age at diagnosis of 65 years. It is more common in women than men [4, 5]. Although it comprises only 1% of all thyroid cancers, ATC has significant mortality and accounts for up to 35% of all deaths from thyroid cancer in some series [6, 7].

Lymphoma of the thyroid gland is almost always non-Hodgkin's lymphoma; it is very rare to have a Hodgkin's lymphoma arise in the thyroid gland [8]. When considering all extranodal lymphomas, only about 2% occur in the thyroid gland [9]. By subtype, there are two distinct groups of thyroid lymphoma. The more common type, comprising approximately 70% of cases, is diffuse large B-cell lymphoma (DLBCL). This subtype has a more aggressive clinical course with the majority of patients diagnosed with already disseminated disease. Another subtype includes mucosa-associated lymphoid tissue (MALT) lymphoma, only up to 25% of thyroid lymphomas. These have relatively indolent course [10]. Similar to anaplastic disease, the mean age of thyroid lymphoma at diagnosis is 65 years and several series indicate a female predominance [11–14]. Hashimoto's thyroiditis is a known risk factor for thyroid lymphoma, seen in about 50% of patients [15–17].

Metastases of nonthyroid malignancies to the thyroid gland are very uncommon, however, must remain on the differential. It is important to consider metastases in patients who present with a thyroid mass and any history, however remote, of prior malignancy. Nonthyroid malignancies have been reported in 1–3% of all patients who have surgery for suspected cancer in the thyroid gland [18]. The most commonly reported malignancies with metastases to the thyroid are renal cell carcinoma (RCC) and lung, colorectal, and breast carcinoma [19–22]. Metastatic melanoma is also relatively common in this group. The literature reports isolated cases of numerous carcinomas metastasizing to the thyroid gland, including urothelial sarco-

matoid, bladder, endometrial, neuroendocrine, gastrointestinal stromal tumor (GIST), intraductal papillary-mucinous carcinoma of the pancreas, ovarian, testicular seminoma, and uterine [19–25].

Although these rare tumors of the thyroid gland will be seen infrequently, the presentation, diagnosis, and management are clinically significant. Because of clinical parallels in their presentation and the rarity of occurrence, they are addressed together as a group.

9.2 Clinical Presentation

As a classic teaching, patients with anaplastic thyroid carcinoma first present with a rapidly expanding neck mass [26]. Physical examination typically reveals a diffuse, enlarged thyroid. The mass is firm, immobile, and may be tender. There can be multifocal nodules in the gland or one large index nodule, but often ill-defined in nature. At the time of presentation, the diameter of the tumor can be quite large and exceed 5 cm [27]. A rapidly enlarging thyroid mass should also prompt consideration for thyroid lymphoma. Thyroid lymphoma is similarly firm to palpation and possibly tender, and may be fixed to adjacent structures. Substernal extension is common [28].

With both anaplastic thyroid carcinoma and thyroid lymphoma, because of the rapid progression and large size, local invasion is frequently seen at presentation of disease. Nearby structures, including muscles, lymph nodes, esophagus, larynx, and trachea, can be involved and cause clinical symptoms. The most frequent symptoms are hoarseness, dysphagia, dyspnea, and stridor [6, 11–13, 15, 29–32]. When hoarseness is present in either disease, flexible laryngoscopy is indicated and will commonly reveal vocal cord immobility [28].

Some differentiating features between anaplastic thyroid carcinoma and lymphoma may be accompanying symptoms, as well as thyroid function. Classic systemic "B" symptoms associated with lymphomas, such as fever, night sweats, and weight loss, should be elicited in the history of a patient with an enlarging thyroid mass. These "B" symptoms can be seen in about 10% of patients with thyroid lymphoma [33].

Thyroid function tests are usually normal in anaplastic thyroid carcinoma; however, laboratory tests should include electrolytes, serum urea nitrogen, creatinine, glucose, and liver function tests. Thyroid function tests should be obtained because large masses may have compromised thyroid function, and some cases of ATC are associated with significant thyrotoxicosis [34, 35]. In approximately 10% of patients with thyroid lymphoma, thyroid dysfunction can be seen. It is usually related to underlying Hashimoto's, but occasionally secondary

to infiltration of the thyroid gland with lymphoma [33]. Hyperthyroidism has also been described secondary to tumor-induced inflammation or pre-existing Graves' disease [36].

About 50% of thyroid non-Hodgkin's lymphomas have a clinical history of chronic lymphocytic thyroiditis and two-thirds show histology consistent with chronic lymphocytic thyroiditis [37]. It is thought that lymphomas originating in a wide variety of primary sites represent a malignant transformation of lymphocytic tissue during a chronic inflammatory or an autoimmune process [38].

Metastases to the thyroid gland are typically found in routine workup of a new thyroid nodule. The majority of symptoms described in large retrospective studies include new or enlarging thyroid nodule, neck swelling, dysphagia, dysphonia, or cough. It has been described that metastatic disease can also present with a rapidly enlarging mass, however, much less commonly [39, 40]. Up to 25% of cases of metastases to the thyroid gland are incidentally found. The literature describes numerous cases of patients undergoing thyroidectomy for other indications and only after histological examination of the specimen is metastatic disease identified. Routine imaging studies for other indications are commonly the first indicator of metastatic disease [41].

9.3 Diagnosis

In a patient who presents with a new thyroid mass, particularly a rapidly enlarging one, it is critical to obtain a complete history, paying special attention to any known risk factors. For anaplastic thyroid carcinoma, the history may include a patient of older age, history of radiation, established goiter, or family history of thyroid disease [5, 42]. A comprehensive review of symptoms will elicit possible systemic "B" symptoms for patients with lymphoma, as previously described.

Any history of other cancers should be discussed with the patient and, when present, timely consideration to the possibility of metastases. Metastases can be synchronous or metachronous. Thyroid metastases can present many years after initial diagnosis and treatment for another malignancy [43]. In some series, the mean interval of metachronous thyroid metastases is approximately 6 years [20, 24]. The most common synchronous thyroid metastasis is renal cell carcinoma [21].

A full diagnostic physical examination should be performed. Anaplastic carcinoma and lymphoma may reveal a fixed mass indicating local invasion. With large thyroid masses, respiratory symptoms, or hoarseness, careful attention to airway management is warranted. To evaluate the airway and mobility of vocal cords, all patients should undergo fiber-optic laryngoscopy. Local invasion of the larynx may result in an

immobile vocal cord through direct extension to the paraglottic space or paratracheal involvement, damaging the recurrent laryngeal nerve [6].

A bronchoscopy should be planned to evaluate the trachea if the laryngoscopy shows evidence of airway invasion. Bronchoscopy is useful for determining extent of disease, evaluation of the tracheal lumen, luminal obstruction, and resectability of the tumor, if indicated. Similarly, an esophagoscopy should be performed if there is suspected esophageal invasion, particularly when there is dysphagia or odynophagia [44]. A clinical neck exam will often reveal metastatic disease in anaplastic thyroid carcinoma with locoregional spread to lymph nodes noted in over 50% of cases [6].

As with any new clinically evident thyroid nodule, initial workup should include imaging with ultrasound. Thyroid and neck ultrasounds should be performed to evaluate the primary tumor and assess cervical lymph nodes for metastatic disease. The basins of interest include the central and lateral compartments of the neck [44]. On ultrasound, lymphoma will appear hypoechoic and pseudocystic. A series of 46 patients with thyroid lymphoma described the vast majority with a characteristic asymmetrical pseudocystic pattern [45].

The National Comprehensive Cancer Network (NCCN) guidelines recommend fine-needle aspiration biopsy or core biopsy for preoperative diagnosis of ATC and lymphoma. If the FNA results are limited or nondiagnostic, open biopsy should be performed in order to confirm the diagnosis [46]. However, core biopsy with appropriate immunohistochemistry and flow cytometry will help to confirm the diagnosis.

Anaplastic thyroid carcinomas exhibit wide variations of morphology and cytologic patterns, with many tumors manifesting mixed morphology [47, 48]. Cytology from ATC nodules typically reveals multinucleated cells with large, bizarre nuclei and atypical mitotic features, without features of thyroid differentiation [1]. Commonly, the biphasic spindle and giant cell tumor are seen [49]. There is usually extensive necrosis, often so diffuse that that the only viable tumor is preserved around blood vessels. Inflammatory infiltrates are frequently seen with necrosis. Osteoclast-like giant cells may be identified and have been shown by immunohistochemical studies to be of the monocytic or histiocytic lineage [50, 51].

Well-differentiated papillary carcinoma, often the tall cell variant, is the most common coexistent carcinoma with anaplastic thyroid carcinoma, followed by conventional follicular carcinoma or Hürthle cell type [52]. Molecular profiling in anaplastic thyroid carcinoma is fast becoming the most important step in the initial workup. New data on actionable mutations including *BRAF* V600E, *NTRK* gene fusion and *RET* fusion are revolutionizing treatment for ATC. Genomic testing and mutational tumor burden are now imperative recommended

initial diagnostic studies in treating this disease [46]. Exciting new treatments based on molecular profiling will be discussed in the treatment section.

When FNA is obtained in lymphoma, it will likely show a highly cellular sample comprised predominantly of a monomorphic population of lymphoid cells with high nuclear: cytoplasmic (N:C) ratio and scant cytoplasm. Nuclei are typically round to oval with fine chromatin. Centrocytes, mature lymphocytes, macrophages, plasma cells, and occasionally mast cells may be seen in the background [53]. Immunohistochemical staining and flow cytometry are usually necessary to confirm monoclonal populations in lymphoma and characterize surface markers. FNA can suggest lymphoma, but typically is nondiagnostic [45].

Generally, for all lymphomas, including thyroid lymphomas, the addition of flow cytometry yields a sensitivity of 97% and specificity of 87% for the detection of B-cell lymphoma. Inadequate sampling is a limiting factor for performing flow cytometry [54, 55]. A small retrospective study demonstrates that core biopsy can improve the diagnostic accuracy when compared with FNA and flow cytometry alone [56]. Open surgical biopsy is recommended only when less invasive techniques cannot achieve a definitive diagnosis or when identification of the exact subtype is required for specific treatment [32].

In metastases to the thyroid gland, FNA may be inaccurate. In a series of 167 patients with thyroid metastases, FNA was correct in approximately 75% of the cases. However, in the other 25%, the FNA diagnosed primary thyroid malignancy instead of metastatic disease. When there is a history of previous cancer, a high suspicion for metastases must always be maintained [18]. A review and comparison of the previous index tumor pathology will help the pathologist to suspect metastatic tumor.

With large, rapidly enlarging thyroid masses, cross-sectional imaging is appropriate to adequately evaluate the airway at the time of diagnosis. High-resolution cross-sectional imaging is critical for surgical planning, when indicated. Computed tomography (CT) with contrast of the neck and mediastinum provides high-resolution assessment of locoregional involvement and invasion of critical aerodigestive structures. On CT, anaplastic masses appear isodense or slightly hyperdense relative to muscle [57, 58]. These masses are frequently heterogeneous with areas of necrosis and calcifications. Careful attention must be paid to the imaging in cases of surgical resection, as local structures must be clearly delineated from the heterogeneous, poorly defined nature of the mass.

Staging of anaplastic thyroid carcinoma, based on the American Joint Committee on Cancer (AJCC) 8th edition (October 2016), helps to provide stratification of management. As all anaplastic thyroid carcinomas are stage IV tumors, they are subclassified as Stage IVA (intrathyroidal tumor), IVB

[gross extrathyroidal extension (ETE) or cervical lymph node metastasis] or IVC (distant metastasis). The T stage is dependent on tumor size and ETE. T1 disease is less than or equal to 2 centimeters, T2 is 2–4 centimeters, and T3 tumors are greater than 4 centimeters. T3a is disease limited to the thyroid and T3b has gross ETE into strap muscles. T4 disease occurs when there is gross ETE into major neck structures [59, 60]. The staging system can be used to ensure that patients receive the appropriate treatment in order to maximize survival.

The Lugano staging system is used for staging primary thyroid lymphoma [61]. PET/CT can be used for FDG-avid lymphoma staging and CT alone can be used for small lymphocytic lymphomas. Approximately 50% of patients presenting with thyroid lymphoma will have Stage IE disease, defined as being limited to the thyroid gland. Another 45% of patients will have Stage IIE disease with the presence of locoregional nodes. Only the remaining 5% will have distant disease or diffuse organ involvement (Stage IIIE or IV). Almost 80% of patients have limited disease on presentation [15, 28].

9.4 Treatment

Treatment of anaplastic thyroid cancer is largely multimodal, with the most recent NCCN Guidelines recommending surgery, external beam radiation, and chemotherapy/radiosensitizing agents. Different combinations are recommended depending on the characteristics of each particular case [46]. The multidisciplinary approach maximizes survival and provides for a well-balanced treatment plan to optimize quality of life. It is also important in the management of anaplastic thyroid carcinoma to achieve the best balance between quality of life and longevity in a generally fatal disease.

Unlike differentiated thyroid carcinomas, poorly differentiated or undifferentiated tumors cannot concentrate iodine, express TSH receptor, or produce thyroglobulin (Tg). Therefore, 131I imaging and thyroglobulin measurement are not used in anaplastic thyroid carcinoma and radioactive iodine treatment is not effective [44, 62].

Cytogenetics of anaplastic thyroid carcinoma is complex and often shows progressive accumulation of chromosomal alterations (numerical and structural aberrations). The most common mutations are in TP53 (nuclear expression), but BRAF V600E, RAS, PIK3CA, and PTEN are also present in about 10–20% of cases [63, 64]. TP53 gene inactivation plays a role in the progression from differentiated to undifferentiated carcinoma [65].

Groundbreaking data published by Subbiah et al. in 2018 in the *Journal of Clinical Oncology* reported efficacy and safety of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor)

combination therapy in *BRAF* V600E–mutated anaplastic thyroid cancer. This series cites up to 50% of anaplastic thyroid carcinoma cases possessing the *BRAF* V600E mutation. Animal models cited suggest the combined inhibition of BRAF and MEK improves treatment response and can prevent MAPK pathway reactivation, a known resistance mechanism. This combination has previously shown efficacy in melanoma and lung cancer. The overall response rate of dabrafenib and trametinb in ATC was 69% in this series with a 12-month estimate of duration of response of 90%. The Kaplan-Meier 12-month estimate of overall survival was remarkable at 80% [66]. This data led to the FDA approval of this combination for *BRAF* V600E-mutant anaplastic thyroid carcinoma without locoregional treatment options, making it the first newly approved therapy for ATC in approximately 50 years.

Important other new data also emphasizes the utilization of next-generation sequencing (NGS) in thyroid cancer. Neurotrophic receptor tyrosine kinase genes *NTRK1, NTRK2*, and *NTRK3* encode TRK proteins. Fusion events involving these genes have been identified across diverse cancers that occur in children and adults. Animal models suggest TRK fusions may be implicated in up to 1% of all solid tumors [67–70]. Larotrectinib and entrectanib are highly selective small-molecule inhibitors of TRK proteins and have significant and durable therapeutic effects in TRK fusion–positive cancers. This new data underscores the need to routinely test mutations to increase the therapeutic options available for patients who previously suffered from untreatable diseases like anaplastic thyroid carcinoma [71, 72].

RET gene fusions were previously identified in more well-differentiated thyroid cancers, but were absent from anaplastic thyroid carcinoma. However, in newer data, patients with metastatic ATC have identifiable RET fusions that have been treated with lenvatinib and selpercatinib with acceptable partial response [73, 74] New data even suggests that tumors with high mutational burden (≥10 mut/Mb) will be sensitive to pembrolizumab and is recommended as an additional possible treatment [46, 75].

Histological subtype and staging of thyroid lymphoma will guide treatment. Combined chemotherapy and radiation therapy for limited lymphoma is associated with a higher survival rate versus chemotherapy alone [76]. Advanced stage disease is treated with chemotherapy alone. The preferred regimen is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone). Distant disease is the most commonly seen treatment failure. Surgery is generally not recommended with additional benefit compared to chemoradiation therapy [32].

Obstructive symptoms associated with thyroid lymphomas usually improve within hours of initiating R-CHOP because of steroid action. With rapid diagnosis and initiation of treatment, tracheostomy and thyroidectomy can be avoided even in

severe cases. Thyroid hormone replacement is the management strategy for hypothyroidism due to Hashimoto thyroiditis, diffuse thyroid gland infiltration, or radiation-associated dysfunction [32].

Because of possible inaccuracy of FNA in metastatic disease, some authors recommend thyroidectomy as treatment in patients with nodular goiters with a history of malignancy [21, 77]. As an abnormal thyroid gland may increase the likelihood of metastatic deposits, patients with abnormal thyroid lesions should be followed carefully with regular clinical exam and serial ultrasounds. This follow-up is especially important in those patients with nondiagnostic or equivocal FNA who do not undergo thyroidectomy [18].

9.5 Indications for Surgery and Surgical Details

Surgery is a critical component of treatment for anaplastic thyroid carcinoma. Primary surgical resection can be considered for patients with stage IVA or IVB disease, specifically, patients without aerodigestive tract involvement. Primary surgical treatment should be planned when gross resection (R1) is anticipated [44, 78]. There are several studies that have demonstrated survival benefit in patients with ATC if complete resection can be achieved [26, 42]. The ATA guidelines recommended a lobectomy or near-total thyroidectomy with lymph node dissection for patients with intrathyroidal disease (Stage IVA). En-bloc resection is advocated if grossly negative margins (R1) can be achieved for patients with extrathyroidal invasion (Stage IVB) [44].

It is important to note, however, that although most studies do show a survival benefit with R0 or R1 resection, because of the rapidly progressive nature of ATC, very few patients present with fully resectable disease. Ultimately, the surgeon must decide whether a resection can be attempted with acceptable risk and morbidity. Many patients with initially unresectable disease may benefit from external beam radiation (full or partial course) or neoadjuvant chemotherapy to shrink the tumor before undergoing surgical resection [44].

Exciting new data using targeted therapies describes successful outcomes in six patients with a BRAF-V600E mutated ATC using neoadjuvant dabrafenib and trametinib followed by complete surgical resection [79]. By using the combination targeted therapy, this important new data demonstrated that it is possible to achieve complete resection, decrease need for tracheostomy, and provide symptom relief and locoregional control. This type of targeted treatment is changing the paradigm for treating ATC. The 2020 NCCN Guidelines provide a significant focus on multimodal treatment, including this new systemic treatment option for ATC.

Additionally, data published in Thyroid in 2018 by Cabanillas et al. describe another surgical strategy with the use dabrafenib, trametinib, and pembrolizumab ("DTP") in an unresectable, end-stage, *BRAF*-mutated case of anaplastic thyroid carcinoma. Complete surgical resection was only possible after a meaningful clinical response to these agents. Using BRAF- and immune-directed drugs combined with surgical treatment is another approach that is changing the overall landscape of treatment for anaplastic thyroid carcinoma. Survival is significantly improved, patients can avoid tracheostomy, and overall quality of life is greatly enhanced [80]. The new 2020 NCCN Guidelines for thyroid cancer reflect these exciting new developments and recommend targeted and immune-directed therapies in conjunction with surgery in the treatment of anaplastic thyroid carcinoma.

Thyroid lobectomy or total thyroidectomy is usually considered in the cases of thyroid metastases either with the aim of long-term cure or achieving local control [23]. Careful consideration must be given to the balance between the course of systemic disease versus the morbidities associated with uncontrolled local disease. The data regarding those patients with thyroid metastases who should undergo surgery is unclear. Local invasion causing aerodigestive symptoms typically is an indication for surgical intervention to prevent airway compromise. If the metastasis is confined to the thyroid gland without significant extrathyroidal extension, thyroidectomy may be performed with minimal morbidity [18, 81, 82]. When considering thyroid surgery for palliative intent, the burden of disease, overall risk-benefit analysis, and individual patient characteristics should be thoughtfully deliberated [83].

Mean survival after surgical intervention for thyroid metastases is approximately 2 years, with 5-year overall survival of 42%. However, in the majority of those patients who are selected for surgical removal of metastases, long-term control of the central neck can be achieved [84, 85]. A recent meta-analysis suggests that those patients managed with surgery have better outcomes than those managed expectantly. This benefit was most significant for renal cell carcinoma (RCC), where median survival for expectant management was 6 months versus 27 months for surgical treatment [86]. However, this retrospective analysis and inherent biases must be interpreted carefully.

For any patient considered to be candidate for thyroid surgery, regardless of the pathology, the aim should be to ensure removal of all gross disease with an adequate margin. This resectability will dictate the extent of surgery. For any of the pathology discussed, in unilateral disease, most authors favor thyroid lobectomy, when possible, to minimize risk to the contralateral recurrent laryngeal nerve and parathyroid glands. The advantages to total thyroidectomy are improved oncologic margins [83].

Traditionally, in thyroid lymphoma, surgery is indicated for diagnostic biopsy only and debulking surgery has been thought to add no benefit to treatment and may contribute to risk [32]. However, there are always selected cases where there may be a role for surgery depending on the response to treatment and clinical indication. Surgery should be reserved for those situations and at the discretion of the treating surgeon and medical oncology management team.

9.6 Prognosis

Anaplastic thyroid carcinoma historically has a poor prognosis, with high metastatic rate and often rapidly fatal course [87]. Although distant metastases are found in at least 50% of patients at presentation, the immediate cause of mortality in most patients is secondary to local complications, such as airway obstruction. Disease-specific mortality has historically been reported as exceedingly high, often documented as approaching 100% [88]. Older data reports the median survival after diagnosis is between 3 and 7 months and classic publications describe 5-year survival is as low as 5% [87]. Favorable prognostic factors for anaplastic thyroid carcinoma are young age, absence of metastatic disease, small tumors (considered 5–7 centimeters), unilateral tumors, absence of local invasion, and an incidental finding on pathology [89].

With new, promising treatment regimens on the horizon, the survival estimates of anaplastic thyroid carcinoma are greatly changing. As previously mentioned, data shows the combination of dabrafenib and trametinb in ATC has a nearly 70% response rate and 12-month overall survival of 80%. These are dramatically improved outcomes compared to expectations in the past with ATC [66]. Targeted therapies, immune-directed treatments, and radiosensitizing agents are promising new treatments for this previously universally fatal disease. The 2020 NCCN Guidelines for anaplastic thyroid carcinoma reflect these changes and recommend early molecular testing and directed therapy.

Thyroid lymphoma has a variable prognosis depending on the histology, tumor burden, stage, age, performance status, and treatment type. A series of 51 patients with limited (Stage I or II) disease demonstrates a 5-year survival rate of 91% in those who received combined chemotherapy and radiation. The same series has 76% survival for radiation alone and 50% survival for chemotherapy alone. Thyroid lymphoma, in general, has an excellent prognosis [76].

With thyroid lymphoma, the relative prognosis depends on the histological classification of the tumor and the stage. MALT lymphomas, due to a more indolent behavior and more favorable response to therapy, have a better prognosis compared to

DLBCL. The 5-year-survival rate in patients with intrathyroidal disease is 90% and decreases to 35% in patients with extrathyroidal disease. Clinical factors that may predict a worse prognosis include large tumor (>10 cm), advanced stage (greater than stage IE), presence of obstructive local symptoms, rapid growth, mediastinal involvement, elderly patients (>60 years), and elevated LDH and b2microglobulin levels [28].

Although distant metastases are widely considered as a poor prognostic factor, thyroid metastases may be an exception. While metastases to the thyroid show better outcomes than other sites, studies show 35–80% of patients with thyroid involvement present with multiorgan metastases concurrently. The overall prognosis can be most closely linked to the inherent features of the primary tumor [18].

Answers to the Questions

1. (c); 2. (a); 3. (e); 4. (a); 5. (d); 6. (c); 7. (a); 8. (b); 9. (e); 10. (d)

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