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THYROID CARCINOMA

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Summary of Literature Review

Introduction/Background

Thyroid cancer is the most common endocrine malignancy in the United States, where the annual incidence is approximately 37,000 and increasing due to the more frequent diagnosis of early well-differentiated thyroid carcinoma (WDTC) [1]. Annually, approximately 1,600 people die from thyroid malignancies [2]. Women represent approximately 75% of newly diagnosed thyroid carcinoma cases. Risk factors for thyroid cancer include exposure to ionizing radiation and a family history of the disease [3,4]. Thyroid cancer spans a spectrum of disease entities from the often curable, well-differentiated histologies (papillary, follicular/Hürthle cell, and medullary) to the aggressive anaplastic histology that represents only 2% of all thyroid cancer cases but 50% of thyroid cancer-related deaths. Guidelines for the management of thyroid carcinoma have been promulgated and are widely used [5,6]. The overwhelming majority of patients with WDTC will do well with appropriate treatment. The high long-term survivorship and relative rarity of the disease have frustrated efforts to execute randomized trials, so management recommendations are not guided by conventional modern standards in oncology.

Anatomy and Physiology of the Thyroid Gland

The thyroid gland is a bilobed organ joined at the isthmus, which is located just inferior to the cricoid cartilage and surrounds the anterior portion of the trachea. The recurrent and superior laryngeal nerves pass near the thyroid gland on their way to the larynx. Four parathyroid glands are usually located near the thyroid gland as well.

The physiology of the thyroid gland is unique. Thyrotropin-releasing hormone, produced within the hypothalamus, signals the anterior pituitary to release thyroid-stimulating hormone (TSH). TSH then stimulates the follicular cells within the thyroid gland to release thyroxine, which in turn modulates the body's metabolic rate. Iodine is required for the production of thyroxine. The production of TSH and thyroxine is tightly regulated by a negative feedback loop within the hypothalamic-thalamic-thyroid axis. TSH can stimulate both normal thyrocytes and WDTC cells. Therefore, TSH suppression is a vital component of treatment for WDTC. The thyroid gland also contains parafollicular C cells that secrete calcitonin, a hormone that helps regulate, but is not mandatory for, calcium homeostasis. Primary lymphatic drainage of the thyroid is to the central neck compartment (level VI), with secondary echelons including the internal jugular chain (levels II–IV), posterior neck (level V), and superior mediastinum (level VII). However, this drainage pattern is inconsistent, and skip metastases directly to the lateral neck compartment have been reported in ≤20% of cases [7].

Presentation of Thyroid Carcinoma

A thyroid carcinoma most often presents as a localized palpable nodule, although the disease is increasingly detected as an incidental finding resulting from imaging studies conducted to evaluate other conditions. The cancer may present with lateral cervical lymphadenopathy from metastatic disease, compressive symptoms (including respiratory embarrassment and dysphagia), and hoarseness with recurrent laryngeal nerve injury. Fine

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needle aspiration biopsy represents the appropriate initial diagnostic maneuver, and it readily distinguishes many papillary thyroid carcinomas (PTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) from benign nodular thyroid disease. A benign follicular adenoma cannot be distinguished from a follicular carcinoma without examination of the lesion margin for vascular or capsular invasion. Hence, a thyroidectomy is required to confirm follicular thyroid cancer (FTC), which represents only about 20% of follicular neoplasms. The follicular variant of papillary carcinoma may also present with what appears to be a follicular neoplasm. The molecular mechanisms of malignant transformation include activating mutations in the RAS-RAF-MEK-ERK pathway in PTC [8], mutations in the RET proto-oncogene in MTC [9], and protein 53 defects in ATC [10].

Thyroid cancers typically spread to distant sites in a characteristic fashion, depending on the histology—PTC to lymph nodes, lungs, and bones; FTC to bones and lungs; and ATC to lymph nodes, lungs, bones, brain, and other sites. As many as 50% of patients with apparently localized PTC harbor lymph node metastases. Few develop a clinically significant progression in nodes. Unlike other FTC, Hürthle cell carcinomas (HCC) may spread to regional lymph nodes. PTC often afflicts children and young adults, but it is a far more threatening malignancy in older individuals. Mortality rises with patient age.

Treatment of Thyroid Carcinoma

Surgery is the mainstay of treatment for WDTC, and the overwhelming majority of patients who undergo complete resection of their clinical disease will do well. Adjuvant treatment with radioactive iodine (RAI) using iodine-131 (^{131}I) is frequently used for diagnostic and therapeutic purposes. MTC, arising from C cells, is characterized by the early dissemination to lymph nodes and does not concentrate iodine. Resection should include a lymphadenectomy, the extent of which remains subject to debate. Most ATCs are unresectable at presentation. Surgical maneuvers (including tracheotomy) are controversial. Distant metastases are common, and chemoradiotherapy alone represents the usual management strategy.

WDTC includes PTC (the most common variant of thyroid cancer), FTC (which includes HCC), and MTC. The primary treatment modality for WDTC is surgery. For most WDTCs, a total thyroidectomy is recommended, although there is strong support for a total lobectomy for a substantial group of patients with low-risk disease (age 15–45 years, with no prior radiation, no distant metastases, no cervical nodal disease, no clinical or radiographic extrathyroidal extension, cancer <4 cm in diameter, and no aggressive variant). Although multiple studies have suggested improved outcomes with a total thyroidectomy compared with a partial thyroidectomy [11-14], controversy persists because the morbidity of bilateral thyroidectomy is higher (particularly with respect to parathyroid injury) even in experienced hands. A series of 1,355 patients with PTC or FTC showed a 30-year recurrence rate of 40% after a subtotal thyroidectomy versus 26% after a total or near-total thyroidectomy [13]. Furthermore, a total thyroidectomy is advantageous for several reasons: 1) follow-up screening for recurrence or metastasis is simplified if there is no residual thyroid tissue; 2) postoperative RAI is more effective when there is no residual normal thyroid tissue; and 3) completion thyroidectomy for recurrent disease has a high associated morbidity (due to the resulting total thyroidectomy, with increased risks to the laryngeal nerves and parathyroid glands).

Papillary microcarcinoma (<10 mm) is managed on a clinical spectrum from a subtotal thyroidectomy and no adjuvant treatment to a total thyroidectomy followed by RAI. In autopsy studies, an occult papillary microcarcinoma has been detected in ≤35% of specimens [15], indicating that this disease entity is unlikely to progress to clinically symptomatic PTC. Given the risks of a second malignancy and other toxicity associated with RAI, a total lobectomy or subtotal/total thyroidectomy without RAI is adequate treatment for papillary microcarcinoma.

Following surgery for WDTC, all patients should begin thyroxine supplementation with the goal of suppressing TSH production, as this can stimulate residual disease and/or metastatic progression. Some advocate for thyroxine supplementation even for microcarcinomas, although this method is controversial. Recommended goals for TSH suppression are <0.01–0.1 mU/L for high-risk patients and <0.1–0.4 mU/L for low-risk patients, with risk based on the aforementioned factors. Serum thyroglobulin should be monitored for evidence of recurrence or metastasis. Serial neck ultrasound and RAI diagnostic scans may be used to assess for recurrence [16]. Postoperatively, risk factors should be assessed to determine whether the patient may benefit from RAI and external beam radiotherapy (EBRT).

Multiple prognostic systems have been developed, using factors that include patient age, tumor grade, extracapsular extension, tumor size, distant metastases, DNA aneuploidy, completeness of resection, and extent of resection to determine the prognosis and possible benefit of adjuvant therapy [17-20]. These prognostic systems are applicable in both PTC and FTC/HCC. Any imaging studies within 6 weeks of a planned RAI treatment should be done without intravenous contrast.

Well-Differentiated Thyroid Cancer—Iodine Avid

Indications for postoperative adjuvant RAI are: 1) tumor >1–1.5 cm; 2) patient age >45 years; 3) capsular, vascular, or soft-tissue invasion; 4) multifocal, residual, or recurrent disease; 5) lymph node metastasis; 6) distant metastasis; and 7) intermediate or high-risk disease based on a prognostic system. RAI is usually administered 4–12 weeks after a thyroidectomy. RAI without a known residual disease can ablate the microscopic local or distant disease. The RAI dose is usually 30 mCi for low-risk or 75–100 mCi for intermediate-risk disease. Higher doses of 150–200 mCi are administrated for patients at high risk for local recurrence, death from macroscopic disease, or with gross distant metastases. Because ^{131}I is cleared by the kidneys, the dose should be reduced for patients with impaired renal function or end-stage renal disease [21]. RAI may be safely administered on an outpatient basis [22]. RAI should not be given to pregnant women due to the theoretical risk to the fetus.

There are no randomized controlled trials investigating the use of RAI when there is no gross residual disease. Multiple retrospective studies [13,14,23] and 1 meta-analysis [24] have shown that ^{131}I ablation improves outcomes. However, other studies have failed to show a benefit. The Mayo Clinic [25] found no difference in mortality or recurrence when it compared a cohort of patients treated in the era before ^{131}I use with a later cohort that received RAI in 50% of cases. Additionally, a more recent systematic review [26] and meta-analysis [27] failed to show a benefit for RAI in reducing recurrence or improving disease-specific mortality in low-risk patients. However, as the definition of low-risk patients frequently changes between studies, it is often difficult to identify groups that truly will or will not benefit from RAI. One multi-institutional series risk-stratified close to 3,000 patients as low risk (stage I), intermediate risk (stage II), and high risk (stages III–IV). In this study, a benefit of RAI use was seen in stages II–IV, but not stage I [28]. Multiple studies have demonstrated a benefit of RAI use in patients with residual or high-risk disease [11,13,23,29]. In 1 series, the treatment of residual tumor after surgery was associated with an approximately 50% decrease in local recurrence and disease-specific mortality [13]. Based on these results, RAI should be considered in patients at stage II or higher or possibly in patients with any risk features at stage I.

In 1 review of a large experience after a subtotal thyroidectomy, radioactive remnant ablation (RRA) at 30 years was shown to decrease recurrence rates (16% versus 38%) and death (3% versus 9%) when controlling for prognostic factors [13]. However, multiple other studies have failed to show a benefit. A meta-analysis of >4,000 patients treated in 23 nonrandomized studies failed to show a benefit in overall survival; however, it did show an improvement in 10-year locoregional recurrence (relative risk 0.31) and an absolute 3% reduction in distant metastases with the addition of RRA [24].

Prior to RAI, administration of recombinant human thyrotropin or thyroid hormone withdrawal should be implemented to improve uptake of ^{131}I in remnant thyroid tissue or residual disease. Patients should also be given instructions for a low-iodine diet. Two recent, large, randomized trials demonstrated similar ablation rates after thyrotropin administration or thyroid hormone withdrawal, with 1 trial suggesting a trend toward increased adverse events with thyroid hormone withdrawal (30% versus 23%, P=.11) [30] and the other trial showing a significantly higher proportion of patients with symptoms of hypothyroidism, deterioration of quality of life, and higher rates of lacrimal gland dysfunction after thyroid hormone withdrawal [5]. Based on these 2 studies, the use of recombinant human thyrotropin should be considered the preferred method to improve uptake of ^{131}I.

If a diagnostic scan is performed prior to therapy, ^{123}I should be administered to prevent stunning (the reduced uptake of subsequent RAI administration due to sublethal radiation damage) of thyroid tissue or residual disease. Alternatively, an empiric treatment dose of ^{131}I can be administered, making sure to obtain a post-treatment diagnostic scan. This should not be done if the results of the scan would change the therapeutic dose, per the American Thyroid Association (ATA) guidelines [31].

The dose for postoperative RAI remains controversial. Most centers use a fixed dose between 30 mCi and 100 mCi, depending on risk factors. A systematic review of 41 retrospective studies, 12 prospective studies, and 6 randomized studies compared the low dose (30 mCi) with the high dose (100 mCi) and found a trend toward improved ablation with the higher dose, although this did not reach significance [32]. Multiple guidelines and

recommendations have been released in recent years suggesting the use of ablative doses ranging from 30 mCi to 150 mCi [33]. A recent study of patterns of care in North America showed that approximately 50% of centers treat with 100 mCi, 20% treat with 30–99 mCi, and 14% treat with ≤29.9 mCi for low-risk PTC [33]. Two recent, large, randomized trials that included patients with pT1-3 and node-negative or -positive disease demonstrated equivalent rates of remnant ablation with 30 mCi and 100 mCi [5,30]. ATA and National Comprehensive Cancer Network guidelines recommend 30 mCi–100 mCi for patients without residual gross disease and 100 mCi–200 mCi for patients with a high risk of local recurrence, residual gross disease, or distant metastases [6,31]. These doses are similar to those used at large tertiary referral centers, including lower risk patients (age <45 years with intrathyroidal tumors <2 cm) receiving 30 mCi–50 mCi, while intermediate-risk patients receive 75 mCi–100 mCi for the initial therapy. Only patients with a high risk of local recurrence, residual gross disease, or distant metastases are treated with 130 mCi–200 mCi. Whole body and blood dosimetry studies are rarely performed for routine RAI ablation, as the standard ^{131}I doses are well below a dose that may cause toxicity. Hospitalization is no longer required in most states following ^{131}I administration.

Toxicity associated with RAI includes transient parotitis, nausea, emesis, and bone marrow suppression. In 2 recent, large, randomized trials [5,30], longer post-treatment hospitalization stays, higher rates of adverse events, and decreased quality of life were significantly associated with a dose of 100 mCi compared with 30 mCi ^{131}I. Bone marrow suppression after a dose of 100 mCi for RRA has been shown to depress white blood cell and platelet counts at 1 year [34]. There is no significant increased risk of infertility, spontaneous abortion, premature delivery, or congenital anomalies in children of women who receive RAI prior to pregnancy [35,36]. To mitigate the potential adverse salivary effects of RAI, the use of pilocarpine [37] and amifostine [38] have been investigated. However, due to the cost and associated side effects, they are not used in standard practice. Most patients are advised to eat hard candies the day following RAI treatment to prevent accumulation of ^{131}I in the salivary glands. In the treatment of extensive metastatic disease, rare side effects include pulmonary fibrosis and an increase in malignancies, including leukemia and solid tumors.

Recent evidence shows an increase in RAI use for early-stage (pT1N0) thyroid cancer, with no evidence to support a survival outcome [39]. This trend is of concern, given the known risk for second malignancies, particularly leukemia and salivary gland tumors [39].

Elderly patients should receive aggressive surgery (near-total or total thyroidectomy) followed by RAI if their performance status will tolerate it. A recent analysis of the Surveillance Epidemiology and End Results registry showed that elderly patients are less likely to be treated with surgery or RAI, although multivariable analysis associated both treatment modalities with improved survival [40].

External Beam Radiotherapy

The use of EBRT for thyroid cancer has not been tested in well-designed, randomized, controlled trials and should, therefore, be considered on a case-by-case basis following surgery and RAI. Indications for use of EBRT postoperatively can include gross residual disease, extracapsular or extrathyroidal extension, recurrent disease or ^{131}I failure, poor iodine avidity, multiple pathologically involved lymph nodes, HCC histology, patient age >45 years, or high risk on prognostic systems [41]. There has been no report of successfully completed, randomized, controlled trials investigating the role of postoperative adjuvant EBRT. One trial attempted to randomize patients treated with surgery, ^{131}I, and TSH-suppression for pT4 FTC to EBRT for observation [42]. Due to poor accrual, the trial became a prospective cohort study after only 45 of 311 patients had consented to randomization. Of the 47 randomized patients, 26 received EBRT. This trial failed to show a statistically significant local control benefit for EBRT, although there was a trend toward improved complete remission rates (96% versus 86%) and local control (100% versus 97%) with the addition of EBRT. Although there is a lack of prospective randomized data, retrospective evidence supports the use of EBRT in high-risk patients. A retrospective study of 169 patients with pathologic T4 disease who received RAI and TSH suppression therapy found a benefit with EBRT, which improved failure-free survival from 45% to 90% [43]. However, this benefit was limited to patients >40 years of age with lymph node–positive disease. A similar benefit was not seen with FTC. Another study, in which 105 of 842 patients received EBRT, showed a benefit of EBRT use, with a relative risk of locoregional failure of 0.35 [44]. Although other studies failed to show a benefit to adjuvant EBRT after surgery and RAI, the groups receiving EBRT had unfavorable characteristics [45-48]; therefore, selection bias may have played a role in this outcome. Based on the totality of the evidence, EBRT should be considered particularly for older patients (>40 years) with high-risk PTC or HCC (pathologic T4 or with pathologically involved lymph nodes) after surgery and RAI [49,50].

When administered postoperatively, EBRT treatment volumes for these patients usually include levels II–VII (including upper mediastinal lymph nodes) extending from the angle of the mandible to the tracheal bifurcation with or without the retropharyngeal lymph nodes at a dose of 45–50 Gy. The coverage of elective nodal regions is often recommended, based on small retrospective studies of locoregionally advanced nonanaplastic thyroid cancer that demonstrated significantly improved 5-year locoregional control (89% versus 40%) with the addition of elective field irradiation in the recurrent or postoperative setting with gross residual disease [51]. No difference was seen in acute or late toxicities between the groups. High-risk microscopic regions (ie, tumor bed, initial thyroid gland volume, adjacent primary nodal group, level VI, or any pathologically involved lymph node levels) are often treated with 60 Gy, while areas of positive margins are treated with 66–70 Gy. When treated, gross residual disease is often treated at 70 Gy or higher.

Conventional treatment fields traditionally consisted of anterior or anteroposterior/posteroanterior fields to below cord tolerance followed by anterior electrons or opposed lateral/oblique fields to the final dose. Interest is being directed at developing techniques to reduce EBRT-related toxicity, in particular intensity-modulated radiotherapy (IMRT). Recent publications have demonstrated the feasibility of using IMRT to treat patients with thyroid cancer [52,53]. One group showed equivalent survival outcomes with reduced severe late morbidity (2% versus 12%) for ^{131}I postoperative patients when comparing 57 patients treated with IMRT to 74 patients treated with conventional radiotherapy [54].

When gross residual disease is present, some studies have suggested that EBRT may improve locoregional tumor control. For patients with an incomplete surgical resection, the addition of EBRT was shown to improve the 15-year local control from 77% to 89%, although the patients treated with EBRT had larger and more extensive tumors [55]. Another study showed equivalent local control in patients treated with EBRT regardless of the extent of resection [56]. Together, these studies demonstrate the potential effectiveness of EBRT. Risk factors that have been shown to predict for worse response to EBRT include high-risk histologic features [54], gross residual disease [54,57], and lack of iodine avidity [58].

Systemic Therapy

Chemotherapy plays a minimal role in the management of WDTC. Doxorubicin is currently the only FDA-approved agent for noniodine avid disease [59]. Studies are now elucidating the common genetic alterations in thyroid cancer such as the BRAF gene V600E mutation [60], which may represent targets for novel biologic agents. Similarly, vascular endothelial growth factor (VEGF) is overexpressed in WDTC, which has prompted the study of small molecule tyrosine kinase inhibitors over the past few years. Sorafenib has demonstrated response rates of 15%–23% in 3 phase II studies [61-63]. Axitinib and pazopanib have also been evaluated with similar results [64,65]. In a multi-institutional phase II study, levantinib demonstrated a response rate of 50%, with a median progression-free survival (PFS) rate of 13 months, and recently it was compared to a placebo in a large, randomized, phase III trial, the results of which are pending. The results of the DECISION trial—a multi-institutional, randomized, placebo-controlled, phase III trial comparing sorafenib with a placebo—were presented at the 2013 American Society of Clinical Oncology Annual Meeting. In evaluation of the primary endpoint of this study, sorafenib demonstrated an improvement over the placebo in the PFS rate by 5 months, and the majority of adverse events were manageable and nonlife threatening. The objective response rate for sorafenib was 23%, and survival was not improved due to the cross-over effect in the placebo arm. Interestingly, at 400 days 25% of the placebo arm patients did not demonstrate disease progression, begging the question of whom to treat and when. In 1 series of WDTC patients, who were iodine-refractory and FDG-negative, the median PFS rate was 41 months without treatment [66]. Deciding when and to whom to administer targeted therapy may become more evident as data from a subset analysis of this study and future randomized studies evolve. Additional data suggest that targeting molecular phenotypes may also be reasonable. A recent study by Ho et al [67] demonstrated that radioiodine uptake could be enhanced by selumetinib in advanced thyroid cancer patients. Similarly, vemurafenib may induce clinical responses in patients harboring BRAF mutations. (See Variant 1, Variant 2 and Variant 3.)

Well-Differentiated Thyroid Cancer—Medullary Thyroid Cancer

MTC is a neuroendocrine tumor of the parafollicular C cells, which produce calcitonin. Approximately 80% of MTC cases are sporadic, although some are familial, arising from multiple endocrine neoplasia type 2 (MEN2) syndrome. The management of patients with MEN2 syndrome should include familial screening and evaluation for aprophylactic thyroidectomy. Further discussion is beyond the scope of this review. At the time of diagnosis, approximately 50% of patients with MTC have clinically detectable cervical lymph node metastases. All patients

with sporadic MTC should be offered germline RET oncogene testing, given that approximately 6%–7% of unselected patients with MTC have a germline mutation [68,69].

The primary management for MTC is surgical resection with a lymphadenectomy. Prior to surgery, all patients with MTC should be evaluated for pheochromocytoma, or, to rule out pheochromocytoma, they should be tested for a negative RET proto-oncogene mutation and have a negative family history for MTC. Staging is based on size, extrathyroidal extension, lymph node status, and metastases. There is no role for RAI, as MTC is not iodine avid. Thyroxine should be started immediately following surgery with the goal of maintaining euthyroidism. There is no role for suppression of serum thyrotropin, because parafollicular C cells do not respond to TSH. EBRT is recommended postoperatively for patients with gross residual disease to obtain local control. In a series of 21 patients treated postoperatively with gross residual disease, local control was 20%, which is poor but demonstrates that local control can be achieved in a subset of patients [70]. The use of adjuvant EBRT for microscopic disease is less clear. There have been no reports of a consistent survival benefit with the use of adjuvant EBRT, likely due to microscopic disease outside of the neck. However, local control improves with the use of EBRT [70-73]. In 1 series of 40 patients with high-risk features, including gross residual disease, positive lymph nodes, or extracapsular extension, the use of postoperative adjuvant EBRT (median 40 Gy) significantly improved 10-year local-regional control (86% versus 52%) [70]. In another series of 51 patients with elevated postoperative calcitonin, 24 were treated with EBRT; local control was 71% versus 41% favoring EBRT, although this was not statistically significant [71]. Additionally, a series of 34 patients with stage IVa-c disease treated with EBRT (median 60 Gy) showed a local control rate of 87%, confirming the role for adjuvant EBRT in locally extensive disease [73]. The recommended dose for EBRT is 56 Gy to cervical lymph nodes, 66 Gy to areas concerning microscopic residual disease, and >70 Gy for gross disease. Patients are followed with regular serum calcitonin and carcinoembryonic antigen measurements to detect recurrence. In the recurrent setting, EBRT should be considered after the surgical resection of a locoregional recurrence or for palliation of a symptomatic distant metastasis. Therefore, when locoregional control is important, consideration should be given for EBRT use.

Metastatic MTC is difficult to treat. Chemotherapy provides minimal benefit. Recently, the FDA approved vandetanib for the treatment of symptomatic or progressive MTC in patients with unresectable, locally advanced, or metastatic disease. Vandetanib is the first drug approved for this indication. Approval was based on the results of a double-blind trial, in which patients were randomized 2:1 to vandetanib (300 mg/d orally) versus a placebo. The primary objective was to demonstrate improvement in PFS with vandetanib compared with the placebo. Other endpoints included evaluation of the overall survival and objective response rates. The PFS analysis showed a marked improvement for patients randomized to vandetanib (hazard ratio = 0.35; 95% confidence interval, 0.24–0.53; P<.0001). The objective response rate for the vandetanib arm was 44% compared with 1% for the placebo arm [74]. Cabozantinib, a potent dual inhibitor of the mesenchymal-epithelial transition (MET) and VEGF pathways designed to block MET-driven tumor escape, has also shown promise in a recently reported, randomized, placebo-controlled study in patients with progressive metastatic MTC [75]. (See Variant 4.)

Anaplastic Thyroid Cancer

Patients with ATC have a uniformly poor prognosis. ATC is a locally aggressive disease process frequently involving the regional lymph nodes, perithyroidal fat, neck musculature, larynx, trachea, esophagus, and vasculature of the neck and mediastinum. Given the rapidly growing and infiltrative nature of ATC, aggressive local therapy is often recommended, although there is no randomized evidence to support this approach. Distant metastases are present in ≤50% of newly diagnosed cases, most commonly to the lungs. In addition to locoregional treatment, end-of-life issues and palliative care should be addressed early in the disease process. Diagnostic studies should include CT of the neck and chest to evaluate for local extent and distant metastases to the lungs. Fine needle aspiration or surgical biopsy should be done to confirm the diagnosis. Given the rarity of this tumor, data are limited, with no randomized controlled trials to support treatment recommendations. Patient age (<60 years) and an intrathyroidal tumor have been shown to be favorable prognostic factors [76].

Surgery is only indicated if imaging shows the disease is localized to the thyroid, although this is uncommon given the locally aggressive nature of ATC. However, some studies have shown long-term survival after the surgical resection of intrathyroidal tumors [76-81]. A thyroid lobectomy with adequate margins is appropriate for resectable disease, as more aggressive surgery, including total thyroidectomy, is associated with increased complications and no improvement in survival [82]. Unlike WDTC, thyroglobulin levels are not used to monitor for recurrence or metastasis in ATC, making total thyroidectomy unnecessary for follow-up purposes. The

addition of radiation to surgery has been shown in a Surveillance, Epidemiology, and End Results analysis to improve survival in patients with disease extending into adjacent tissue but not in those with disease confined to the thyroid or those with distant metastases [83]. Multiple retrospective series have shown a benefit to adjuvant radiation after surgery [76,77,84,85].

Adjuvant combined modality therapy, including radiation and chemotherapy, has been shown to improve outcomes for ATC patients. One study used surgery (when feasible) followed by IMRT and 4 cycles of docetaxel and doxorubicin [86] to treat 10 patients with regionally localized disease. Two patients were hospitalized for treatment-related complications. The median survival for the group was 60 months, which compares favorably with historical outcomes. Another group reviewed 33 patients with ATC and found that ATC treated with a complete resection followed by adjuvant chemoradiation had a median survival of 5 months [79].

The optimal sequencing of therapeutic modalities for ATC patients is not known and is usually decided on a case-by-case basis. One study evaluated the timing of sequential therapy. Seventy-nine patients with ATC were divided into surgery up front (n=26) versus chemotherapy and/or radiotherapy (n=53). The latter group included 12 patients who underwent surgery after induction therapy [87]. No difference in survival was found between the groups, although the primary concurrent chemoradiation group was older, had larger tumors not confined to the thyroid, and had a higher rate of regional metastases. The best outcome was seen in patients who received primary concurrent chemoradiation followed by surgery (the 1-year survival rate was 50%). Another study reported a complete response rate of 25% and a median survival rate of 11 months in patients treated with a combination of total thyroidectomy, chemotherapy, and radiation [88].

Management of ATC that is unresectable at diagnosis is controversial. Radiotherapy alone in conventional fractionation does not prolong survival. One study showed an 80% initial response rate, but most patients developed a local recurrence [89]. Neoadjuvant hyperfractionated radiotherapy combined with radiosensitizing chemotherapy followed by surgery (if feasible) was reported to have an overall survival rate of approximately 12 months, with distant metastasis then becoming the predominant mode of failure [78]. Chemoradiation with standard fractionation in the definitive setting has been reported to provide promising survival outcomes [90].

Altered radiation fractionation has been explored as another method to improve outcomes in ATC. Early reports of hyperfractionated EBRT showed some tumor responses, but there was limited interest due to a significant risk of radiation myelopathy [91,92]. However, improved planning and treatment delivery techniques have renewed interest in altered fractionation for ATC. Comparisons of standard radiation fractionation regimens to hyperfractionated radiation without chemotherapy have failed to show significant benefits in survival [93,94], although 1 study did show a nonsignificant (P=.3) trend toward improved survival with hyperfractionated radiotherapy [94].

Promising outcomes have also been reported for altered radiation fractionation combined with chemotherapy and surgery (if feasible) for locally advanced ATC, although there are no randomized prospective studies evaluating this treatment modality. One recent series reported on 10 patients treated with IMRT (7 of 10 had altered fractionation, with a median dose of 64.25 Gy) and concurrent and adjuvant chemotherapy [86]. One- and 2-year overall survival rates were promising at 70% and 60%, respectively. One group prospectively reported 30 patients (24 had undergone resection) treated sequentially with 2 cycles of doxorubicin and cisplatin, radiotherapy in 1.25-Gy fractions twice daily to a dose of 40 Gy (field extended from mastoid to carina) with a boost to 50–55 Gy, and then 4 cycles of doxorubicin and cisplatin [81]. A total of 19 patients had a complete response to therapy, although there was a high rate of hematologic and pharyngoesophageal toxicity. Outcomes were promising, with a 3-year overall survival rate of 27%. Six of 7 long-term survivors underwent a macroscopic complete resection. On multivariable analysis, tracheal extension and macroscopic complete resection were significant predictors of survival. Another group reported on 22 patients treated with hyperfractionated radiotherapy (1.6 Gy twice daily) to a total dose of 46 Gy, with concurrent weekly doxorubicin followed by surgery 2–3 weeks after completing radiation and then additional weekly doxorubicin, if tolerated [78]. Seventeen of the 22 patients proceeded to operation and none developed a local recurrence, although the median overall survival for this group was only 2 months. This raises the question of possible treatment-related morbidity and mortality. Another series reported on 19 patients treated with concurrent doxorubicin and a radiotherapy dose of 57.6 Gy (1.6 Gy fractions twice daily, 3 days per week) [95]. A complete response was observed in 84% of patients with local control of 68% at 2 years. The median survival rate was 1 year, with most patients dying of metastatic disease.

There is limited evidence for a radiation dose response in ATC. One study reported a survival benefit in patients who received >50 Gy [96], and another showed an improvement in PFS if the radiation dose was >40 Gy [94].

Treatment fields should include the thyroid or thyroid bed and adjacent lymph node echelons in the neck and mediastinum. There are no data to support treating the entire neck and mediastinum. Dose fractionation schemes are variable, but 60 Gy in 1.5 Gy fractions twice daily is an appropriate and accepted fractionation scheme. For patients with poor performance status or metastatic disease, a palliative regimen of 20 Gy in 4-Gy fractions or 30 Gy in 3-Gy fractions should be considered to slow local progression. Some groups treat with 20 Gy in 4-Gy fractions, with a second course of 20 Gy 4 weeks later in patients who show a response to treatment.

As with other thyroid cancer variants, IMRT is being actively explored as a method to reduce toxicity and improve the therapeutic ratio. One retrospective study compared toxicity in patients treated with either IMRT or 3-D conformal EBRT [96]. No difference in toxicity was reported, which was attributed to the wide field coverage used for IMRT.

Overall, for locally advanced ATC, aggressive combined modality therapy (surgery if localized to the thyroid, chemotherapy, and radiation) has been attempted with mixed results. However, given the locally aggressive nature of ATC, aggressive local therapy is recommended to prevent or delay death by local progression. (See Variant 5 and Variant 6.)

Metastatic Thyroid Cancer

Management of metastatic thyroid cancer depends on the histologic variant. Patients with metastatic WDTC may still benefit from local control, given the ability of RAI to eradicate distant disease. Patients with tumors that do not uptake iodine have a worse prognosis. When managing patients with extracervical metastases from thyroid cancer, the goals should be to improve survival, palliate symptoms, prevent morbidity, and limit treatment-related toxicity [97]. If the tumor remains iodine-avid, RAI should be attempted with a dose of 150 mCi–200 mCi [31]. Patients with pulmonary metastases should receive a dose of 150 mCi to reduce the risk of pulmonary toxicity. One series of 444 patients, 295 of whom had iodine-avid metastatic disease, showed a 43% rate of resolution of iodine-avid metastases [98]. The 10-year survival rate was 92% for the group with resolution of RAI avidity compared with 19% in disease that did not completely resolve.

EBRT should be used to palliate local symptoms that are not amenable to RAI or require rapid relief. Lesion positron emission tomography (PET) avidity is inversely correlated with iodine avidity; therefore, PET-avid lesions should be treated with EBRT, as they do not respond to ^{131}I therapy [99]. Dose regimens of 8 Gy in a single fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions are all appropriate.

Novel biologic agents, such as systemic therapy options, are being actively investigated. The tyrosine kinase inhibitor axitinib has shown a 30% overall response rate in incurable thyroid cancer of any histology [65], and thalidomide has shown activity in rapidly progressive metastatic thyroid cancer [100]. Patients with metastatic thyroid cancer that is not iodine avid should be encouraged to enroll in clinical trials that further explore novel systemic agents. (See Variant 7 and Variant 8.)

Summary

- For WDTC, surgery and often adjuvant RAI are common components of therapy.
- The role of radiotherapy is less well defined and is often decided on a case-by-case basis.
- Systemic therapeutic options, particularly with targeted therapies, are being actively investigated.
- ATCs usually require a multimodality approach, typically with concurrent chemotherapy and radiation.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA*. 2006;295(18):2164-2167.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009;59(4):225-249.

3. Schneider AB, Sarne DH. Long-term risks for thyroid cancer and other neoplasms after exposure to radiation. *Nat Clin Pract Endocrinol Metab.* 2005;1(2):82-91.
4. Pal T, Vogl FD, Chappuis PO, et al. Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study. *J Clin Endocrinol Metab.* 2001;86(11):5307-5312.
5. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med.* 2012;366(18):1663-1673.
6. NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma. Version 3.2012. 2012.
7. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid cancer leaping the central lymph node compartment. *Arch Surg.* 2004;139(1):43-45.
8. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res.* 2003;63(7):1454-1457.
9. 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.
10. Ito T, Seyama T, Mizuno T, et al. Unique association of p53 mutations with undifferentiated but not with differentiated carcinomas of the thyroid gland. *Cancer Res.* 1992;52(5):1369-1371.
11. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg.* 2007;246(3):375-381; discussion 381-374.
12. Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery.* 1998;124(6):958-964; discussion 964-956.
13. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med.* 1994;97(5):418-428.
14. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab.* 1990;71(2):414-424.
15. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer.* 1985;56(3):531-538.
16. Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I Scans With SPECT/CT in Postoperative Thyroid Cancer Patients: What Is the Impact on Staging? *J Clin Endocrinol Metab.* 2013;98(3):1163-1171.
17. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery.* 1987;102(6):1088-1095.
18. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery.* 1988;104(6):947-953.
19. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery.* 1993;114(6):1050-1057; discussion 1057-1058.
20. Pasieka JL, Zedenius J, Auer G, et al. Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. *Surgery.* 1992;112(6):1154-1159; discussion 1159-1160.
21. Alevizaki C, Molfetas M, Samartzis A, et al. Iodine 131 treatment for differentiated thyroid carcinoma in patients with end stage renal failure: dosimetric, radiation safety, and practical considerations. *Hormones (Athens).* 2006;5(4):276-287.
22. Grigsby PW, Siegel BA, Baker S, Eichling JO. Radiation exposure from outpatient radioactive iodine (131I) therapy for thyroid carcinoma. *JAMA.* 2000;283(17):2272-2274.
23. Wong JB, Kaplan MM, Meyer KB, Pauker SG. Ablative radioactive iodine therapy for apparently localized thyroid carcinoma. A decision analytic perspective. *Endocrinol Metab Clin North Am.* 1990;19(3):741-760.
24. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2004;89(8):3668-3676.

25. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg.* 2002;26(8):879-885.
26. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am.* 2008;37(2):457-480, x.
27. Sacks W, Fung CH, Chang JT, Waxman A, Braunstein GD. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. *Thyroid.* 2010;20(11):1235-1245.
28. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid.* 2006;16(12):1229-1242.
29. Maxon HR, 3rd, Englaro EE, Thomas SR, et al. Radioiodine-131 therapy for well-differentiated thyroid cancer--a quantitative radiation dosimetric approach: outcome and validation in 85 patients. *J Nucl Med.* 1992;33(6):1132-1136.
30. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med.* 2012;366(18):1674-1685.
31. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19(11):1167-1214.
32. Hackshaw A, Harmer C, Mallick U, Haq M, Franklyn JA. 131I activity for remnant ablation in patients with differentiated thyroid cancer: A systematic review. *J Clin Endocrinol Metab.* 2007;92(1):28-38.
33. Tuttle RM, Leboeuf R, Martorella AJ. Papillary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am.* 2007;36(3):753-778, vii.
34. Molinaro E, Leboeuf R, Shue B, et al. Mild decreases in white blood cell and platelet counts are present one year after radioactive iodine remnant ablation. *Thyroid.* 2009;19(10):1035-1041.
35. Sarkar SD, Beierwaltes WH, Gill SP, Cowley BJ. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. *J Nucl Med.* 1976;17(6):460-464.
36. Fard-Esfahani A, Hadifar M, Fallahi B, et al. Radioiodine treatment complications to the mother and child in patients with differentiated thyroid carcinoma. *Hell J Nucl Med.* 2009;12(1):37-40.
37. Almeida JP, Kowalski LP. Pilocarpine used to treat xerostomia in patients submitted to radioactive iodine therapy: a pilot study. *Braz J Otorhinolaryngol.* 2010;76(5):659-662.
38. Bohuslavizki KH, Klutmann S, Jenicke L, et al. Salivary gland protection by S-2-(3-aminopropylamino)-ethylphosphorothioic acid (amifostine) in high-dose radioiodine treatment: results obtained in a rabbit animal model and in a double-blind multi-arm trial. *Cancer Biother Radiopharm.* 1999;14(5):337-347.
39. Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer.* 2011;117(19):4439-4446.
40. Park HS, Roman SA, Sosa JA. Treatment patterns of aging Americans with differentiated thyroid cancer. *Cancer.* 2010;116(1):20-30.
41. Brierley JD, Tsang RW. External beam radiation therapy for thyroid cancer. *Endocrinol Metab Clin North Am.* 2008;37(2):497-509, xi.
42. Biermann M, Pixberg M, Riemann B, et al. Clinical outcomes of adjuvant external-beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS-trial. *Nuklearmedizin.* 2009;48(3):89-98; quiz N15.
43. Farahati J, Reiners C, Stuschke M, et al. Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). *Cancer.* 1996;77(1):172-180.
44. Chow SM, Law SC, Mendenhall WM, et al. Papillary thyroid carcinoma: prognostic factors and the role of radioiodine and external radiotherapy. *Int J Radiat Oncol Biol Phys.* 2002;52(3):784-795.
45. Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. *J Clin Endocrinol Metab.* 1992;75(3):714-720.
46. Lin JD, Tsang NM, Huang MJ, Weng HF. Results of external beam radiotherapy in patients with well differentiated thyroid carcinoma. *Jpn J Clin Oncol.* 1997;27(4):244-247.
47. Rosa Pelizzo M, Toniato A, Boschin IM, et al. Locally advanced differentiated thyroid carcinoma: a 35-year mono-institutional experience in 280 patients. *Nucl Med Commun.* 2005;26(11):965-968.

48. Staunton MD. Thyroid cancer: a multivariate analysis on influence of treatment on long-term survival. *Eur J Surg Oncol.* 1994;20(6):613-621.
49. Lenio PT. External irradiation in treatment of papillary carcinoma of the thyroid. *Am J Surg.* 1976;131(3):281-283.
50. Simpson WJ, Carruthers JS. The role of external radiation in the management of papillary and follicular thyroid cancer. *Am J Surg.* 1978;136(4):457-460.
51. Kim TH, Chung KW, Lee YJ, et al. The effect of external beam radiotherapy volume on locoregional control in patients with locoregionally advanced or recurrent nonanaplastic thyroid cancer. *Radiat Oncol.* 2010;5:69.
52. Rosenbluth BD, Serrano V, Happersett L, et al. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1419-1426.
53. Urbano TG, Clark CH, Hansen VN, et al. Intensity Modulated Radiotherapy (IMRT) in locally advanced thyroid cancer: acute toxicity results of a phase I study. *Radiother Oncol.* 2007;85(1):58-63.
54. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1083-1091.
55. Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D. External radiotherapy in thyroid cancers. *Cancer.* 1985;55(9 Suppl):2062-2071.
56. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys.* 2009;73(3):795-801.
57. O'Connell ME, A'Hern RP, Harmer CL. Results of external beam radiotherapy in differentiated thyroid carcinoma: a retrospective study from the Royal Marsden Hospital. *Eur J Cancer.* 1994;30A(6):733-739.
58. Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *Int J Radiat Oncol Biol Phys.* 1988;14(6):1063-1075.
59. Gottlieb JA, Hill CS, Jr. Chemotherapy of thyroid cancer with adriamycin. Experience with 30 patients. *N Engl J Med.* 1974;290(4):193-197.
60. Mathur A, Moses W, Rahbari R, et al. Higher rate of BRAF mutation in papillary thyroid cancer over time: a single-institution study. *Cancer.* 2011;117(19):4390-4395.
61. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol.* 2009;27(10):1675-1684.
62. Ahmed M, Barbachano Y, Riddell A, et al. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population. *Eur J Endocrinol.* 2011;165(2):315-322.
63. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol.* 2008;26(29):4714-4719.
64. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol.* 2010;11(10):962-972.
65. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol.* 2008;26(29):4708-4713.
66. Schreinemakers JM, Vriens MR, Munoz-Perez N, et al. Fluorodeoxyglucose-positron emission tomography scan-positive recurrent papillary thyroid cancer and the prognosis and implications for surgical management. *World J Surg Oncol.* 2012;10:192.
67. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med.* 2013;368(7):623-632.
68. Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab.* 1996;81(10):3740-3745.
69. Eng C, Mulligan LM, Smith DP, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf).* 1995;43(1):123-127.
70. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. *Thyroid.* 1996;6(4):305-310.

71. Fersht N, Vini L, A'Hern R, Harmer C. The role of radiotherapy in the management of elevated calcitonin after surgery for medullary thyroid cancer. *Thyroid.* 2001;11(12):1161-1168.
72. Nguyen TD, Chassard JL, Lagarde P, et al. Results of postoperative radiation therapy in medullary carcinoma of the thyroid: a retrospective study by the French Federation of Cancer Institutes--the Radiotherapy Cooperative Group. *Radiother Oncol.* 1992;23(1):1-5.
73. Schwartz DL, Rana V, Shaw S, et al. Postoperative radiotherapy for advanced medullary thyroid cancer--local disease control in the modern era. *Head Neck.* 2008;30(7):883-888.
74. Wells SA, Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol.* 2012;30(2):134-141.
75. Schoffski P, Elisei R, Muller S, et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. *ASCO Meeting Abstracts.* 2012;30(15_suppl):5508.
76. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer.* 2005;103(7):1330-1335.
77. Tan RK, Finley RK, 3rd, Driscoll D, Bakamjian V, Hicks WL, Jr., Shedd DP. Anaplastic carcinoma of the thyroid: a 24-year experience. *Head Neck.* 1995;17(1):41-47; discussion 47-48.
78. Tennvall J, Lundell G, Wahlberg P, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *Br J Cancer.* 2002;86(12):1848-1853.
79. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer.* 2001;91(12):2335-2342.
80. Heron DE, Karimpour S, Grigsby PW. Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups. *Am J Clin Oncol.* 2002;25(5):442-446.
81. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys.* 2004;60(4):1137-1143.
82. 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.
83. Chen J, Tward JD, Shrieve DC, Hitchcock YJ. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983-2002. *Am J Clin Oncol.* 2008;31(5):460-464.
84. Pierie JP, Muzikansky A, Gaz RD, Faquin WC, Ott MJ. The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. *Ann Surg Oncol.* 2002;9(1):57-64.
85. 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.
86. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid.* 2011;21(1):25-30.
87. Besic N, Auersperg M, Us-Krasovec M, Golouh R, Frkovic-Grazio S, Vodnik A. Effect of primary treatment on survival in anaplastic thyroid carcinoma. *Eur J Surg Oncol.* 2001;27(3):260-264.
88. Busnardo B, Daniele O, Pelizzo MR, et al. A multimodality therapeutic approach in anaplastic thyroid carcinoma: study on 39 patients. *J Endocrinol Invest.* 2000;23(11):755-761.
89. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. *Eur J Surg Oncol.* 1992;18(2):83-88.
90. Troch M, Koperek O, Scheuba C, et al. High efficacy of concomitant treatment of undifferentiated (anaplastic) thyroid cancer with radiation and docetaxel. *J Clin Endocrinol Metab.* 2010;95(9):E54-57.
91. Wong CS, Van Dyk J, Simpson WJ. Myelopathy following hyperfractionated accelerated radiotherapy for anaplastic thyroid carcinoma. *Radiother Oncol.* 1991;20(1):3-9.
92. Simpson WJ. Anaplastic thyroid carcinoma: a new approach. *Can J Surg.* 1980;23(1):25-27.
93. Mitchell G, Huddart R, Harmer C. Phase II evaluation of high dose accelerated radiotherapy for anaplastic thyroid carcinoma. *Radiother Oncol.* 1999;50(1):33-38.
94. Wang Y, Tsang R, Asa S, Dickson B, Arenovich T, Brierley J. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer.* 2006;107(8):1786-1792.

95. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. *Cancer.* 1987;60(10):2372-2375.
96. Bhatia A, Rao A, Ang KK, et al. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck.* 2010;32(7):829-836.
97. Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. *J Clin Endocrinol Metab.* 2010;95(3):987-993.
98. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899.
99. Wang W, Larson SM, Tuttle RM, et al. Resistance of [18f]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine. *Thyroid.* 2001;11(12):1169-1175.
100. Ain KB, Lee C, Williams KD. Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas. *Thyroid.* 2007;17(7):663-670.

Clinical Condition: **Thyroid Carcinoma**

Variant 1: **T1a N0 M0 papillary thyroid cancer: 40-year-old woman.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	8	
Total thyroidectomy	8	
Thyroglobulin suppression with levothyroxine	9	
Postoperative Adjuvant Radioactive Iodine (RRA or RAI)		
30 mCi with thyrotropin stimulation	3	
100 mCi with thyrotropin stimulation	1	
30 mCi with thyroid hormone withdrawal	2	
100 mCi with thyroid hormone withdrawal	1	
Postoperative external beam radiotherapy	1	
Postoperative chemotherapy	1	
Adjuvant concurrent chemoradiotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **T1b N0 M0 papillary thyroid carcinoma: 60-year-old man.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	3	
Total thyroidectomy	9	
Thyroglobulin suppression with levothyroxine	9	
Postoperative Adjuvant Radioactive Iodine (RRA or RAI)		
30 mCi with thyrotropin stimulation	5	Depends on final pathology and post-treatment evaluation.
100 mCi with thyrotropin stimulation	7	Many patients will not require this high of a dose.
30 mCi with thyroid hormone withdrawal	4	Associated with worse side effects than thyrotropin stimulation.
100 mCi with thyroid hormone withdrawal	6	Depends on final pathology and post-treatment evaluation. Many patients may not require this high of a dose. Associated with worse side effects than thyrotropin stimulation.
Postoperative external beam radiotherapy	1	
Postoperative chemotherapy	1	
Adjuvant concurrent chemoradiotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Thyroid Carcinoma**

Variant 3: **T4a N1a M0 papillary thyroid carcinoma: 65-year-old man.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	1	
Total thyroidectomy	9	
Thyroglobulin suppression with levothyroxine	9	
Postoperative Adjuvant Radioactive Iodine (RRA or RAI)		
30 mCi with thyrotropin stimulation	1	
100 mCi with thyrotropin stimulation	8	
30 mCi with thyroid hormone withdrawal	1	
100 mCi with thyroid hormone withdrawal	7	
Postoperative External Beam Radiotherapy		
3D-CRT	5	
IMRT	8	
Treat thyroid bed first echelon LN's only	5	
Treat thyroid bed and entire elective neck	8	
Postoperative chemotherapy	1	
Adjuvant concurrent chemoradiotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 4: **T4a N0 M0 medullary thyroid carcinoma: 28-year-old woman.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	1	
Total thyroidectomy with neck dissection	8	
Thyroglobulin suppression with levothyroxine	1	
Postoperative Adjuvant Radioactive Iodine (RRA or RAI)		
30 mCi (after total thyroidectomy)	1	
100 mCi (after subtotal thyroidectomy)	1	
200 mCi (after subtotal thyroidectomy)	1	
Postoperative adjuvant external beam radiotherapy	5	
Postoperative External Beam Radiotherapy Technique		
3D-CRT	5	
IMRT	8	
Postoperative chemotherapy	1	
Adjuvant concurrent chemoradiotherapy	1	
Genetic testing for family members	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Thyroid Carcinoma**

Variant 5: **T4a N0 M0 anaplastic thyroid carcinoma: 64-year-old man with excellent performance status.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	1	
Total thyroidectomy	7	
Lateral lymph node dissection	3	Assuming total thyroidectomy has been done.
Thyroglobulin suppression with levothyroxine	1	
Postoperative adjuvant radioactive iodine (RRA or RAI)	1	
External Beam Radiotherapy		
Postoperative concurrent chemoradiotherapy (if surgery indicated)	8	
Definitive chemoradiotherapy (if no surgery performed)	8	
Postoperative External Beam Radiotherapy Technique/Fractionation		
3D-CRT	6	
IMRT	8	
Altered fractionation	5	
Postoperative External Beam Radiotherapy Volume		
Treat thyroid/postoperative bed only	3	
Treat thyroid/postoperative bed and elective neck	8	
Palliative chemotherapy alone	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Thyroid Carcinoma**

Variant 6: **T4b N1b M0 anaplastic thyroid carcinoma: 58-year-old woman with excellent performance status.**

Treatment	Rating	Comments
Total lobectomy (hemithyroidectomy)	3	
Total thyroidectomy	1	
Lymph node dissection	2	
Thyroglobulin suppression with levothyroxine	1	
Postoperative radioactive iodine (RRA or RAI)	1	
External Beam Radiotherapy		
Definitive concurrent chemoradiotherapy	9	
External Beam Radiotherapy Technique/Fractionation		
3D-CRT	5	
IMRT	7	
Altered fractionation	5	
External Beam Radiotherapy Volume		
Treat thyroid/postoperative bed only	1	
Treat thyroid/postoperative bed and elective neck	8	
Palliative chemotherapy alone	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 7: **T4a N1 M1 papillary thyroid carcinoma: 63-year-old man with excellent performance status and lung micronodules.**

Treatment	Rating	Comments
Total thyroidectomy	8	
Postoperative radioactive iodine	8	
Postoperative external beam radiotherapy	5	
RAI		
150 mCi	7	
200 mCi	6	
Adjuvant concurrent chemoradiation	2	
Cytotoxic chemotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Thyroid Carcinoma**

Variant 8: **T3 N0 M1 papillary thyroid carcinoma: 40-year-old woman with excellent performance status and painful bony metastases; tumor is not iodine-avid.**

Treatment	Rating	Comments
Palliative external beam radiotherapy	8	
Tyrosine kinase inhibitors (TKI) therapy	7	
Total thyroidectomy	5	
Cytotoxic chemotherapy	5	
Postoperative radioactive iodine	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		