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Review

ACR Appropriateness Criteria® thyroid carcinoma

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SUMMARY

The ACR Head and Neck Cancer Appropriateness Criteria Committee reviewed relevant medical literature to provide guidance for those managing patients with thyroid carcinoma. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Thyroid cancer is the most common endocrine malignancy in the United States, most often presenting as a localized palpable nodule. Surgery is the mainstay of treatment for WDTC, with most patients undergoing complete resection of their disease having good outcomes. Following surgery thyroxine supplementation should begin to suppress TSH, which unchecked can stimulate residual disease and/or metastatic progression, Adjuvant treatment with radioactive iodine (RAI) using iodine-131 (^{131}I) is frequently used for diagnostic and therapeutic purposes. 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. Chemotherapy plays a minimal role in the management of WDTC. Novel biologic agents, such as systemic therapy options, are being actively investigated, and patients with metastatic thyroid cancer that is not iodine avid should be encouraged to enroll in clinical trials exploring novel systemic agents.

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 1600 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

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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 $\leqslant$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 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 1355 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 $\leqslant$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