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Diagnosis and Treatment of Anaplastic Thyroid Carcinoma

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ABSTRACT

Anaplastic thyroid carcinoma (ATC) is a poorly differentiated thyroid cancer. It cannot uptake iodine or synthesis thyroglobulin. The incidence is low; about 2% - 5% of thyroid cancer. The peak age incidence is 60 - 70 years and it is more common in females (55% - 77% of all patients). In recent years, the incidence has declined; however, it may be higher in areas of endemic goiter. ATC may occur with a coexisting carcinoma and may represent transformation of a well-differentiated thyroid cancer. Patients typically present with a rapidly growing anterior neck mass and aggressive symptoms. The most reliable tool in detecting thyroid malignancies is fine-needle aspiration cytology (FNAC). Sensitivity of FNAC for thyroid malignancy ranged from 61% to 97.7%. Fine-needle aspiration can diagnose ATC by the demonstration of spindled or giant cells, bizarre neoplastic cells that may be multinucleated, or atypical cells with high mitotic activity. A syncytial pattern is the predominant cellular pattern of anaplastic thyroid carcinoma. Other laboratory tests, including tumor markers (cytokeratin, vimentin, and carcinoembryogenic antigen) are helpful in diagnosis and follow-up of the patients. Multimodality therapy (surgery, external beam radiation, and chemotherapy) is the recommended treatment and it seems to have slightly improved outcomes. The prognosis is not as bad in younger patients with smaller tumors. The most common cause of death is lung metastasis. The mean survival time is less than 6 months from the time of diagnosis. The prompt diagnosis and aggressive treatment are essential modality to achieve optimal outcomes.

Keywords: Anaplastic Thyroid Carcinoma; Thyroid; Cancer

1. Introduction

Anaplastic thyroid carcinoma (ATC) is a poorly differentiated thyroid cancer. It cannot uptake iodine or synthesis thyroglobulin. The incidence is low; about 2% - 5% of thyroid cancer. The peak age incidence is 60 - 70 years and it is more common in females (55% - 77% of all patients). In recent years, the incidence has declined; however, it may be higher in areas of endemic goiter. ATC may occur with a coexisting carcinoma and may represent transformation of a well-differentiated thyroid cancer (WDTC). In Mumbai, the incidence decreased from 7.7% to 4.2% between 1969-1973 and 1989-1993 [1]. A study from Italy also showed a decrease from 11% to 5% between 1979 to 1989 [2]. This decline may be caused by the improvement of immunochemistry technique that can exclude lymphomas or undifferentiated medullary thyroid carcinoma from previously diagnosed ATC patients [3-6] and the aggressive surgical resection of WDTC has reduced the risk of anaplastic transformation (dedifferentiation) of WDTC to ATC [7].

Patients typically present with a rapidly growing anterior neck mass and aggressive symptoms such as hoarseness, dysphagia, upper airway obstruction, pulmonary metastases, and superior vena cava obstruction. The most common cause of death is pulmonary metastases and mean survival time is less than 6 months from the time of diagnosis [8]. In this article, we review on diagnosis and treatment of ATC.

2. Diagnosis

The most common presenting symptom of anaplastic thyroid carcinoma (ATC) is a rapidly enlarging fixed, hard neck mass, often with a lateral cervical mass (metastatic lymph node) [9-12]. The mass effect of the tumor usually produces symptoms of hoarseness (77%), dysphagia (56%), vocal cord paralysis (49%), neck pain (29%), weight loss (24%), dyspnea (19%), and stridor [13]. A single nodule may be present in 58% of patients, multiple nodules in 36%, bilateral involvement in 24%, and a diffuse hard, fixed lesion in 75% [13]. Lymph node metastases and extrathyroidal extension in the absence of distant metastases are present in 53% to 64% of patients.

Distant metastases are present in a one quarter to two-thirds of patients. The most common site are the mediastinum and lungs (42%), followed by bone (32%) and brain (9%) [14].

Microscopically, the tumours are composed of anaplastic cells with marked cytologic atypia and high mitotic activity. The morphologic criteria employed to define poorly differentiated thyroid carcinoma in most publications have been trabecular, solid, insular, cribriform and scirrhous growth patterns [15-17]. The pathogenesis of ATC remains undefined. The most widely accepted theory is that ATC develops from pre-existing differentiated thyroid cancer of papillary or follicular type. Because of the infrequency of the tumor, it is rarely possible to study sufficient numbers of patients to obtain a better understanding of the natural history and the factors that may influence treatment and survival. Dedifferentiation manifested by a loss of specific thyroid cell characteristics and functions, including expression of thyroglobulin, thyroid peroxidase, thyroid-stimulating hormone receptor, and sodium/iodide symporter expression is a hallmark of ATC. Consequently, thyroglobulin can not be used as a tumor marker for diagnosis or monitoring. Cytokeratin is a useful epithelial immunohistochemical marker and present in 40% to 100% of tumors [13,18]. Other markers suggesting epithelial origin of the tumor may be epithetlial membrane antigen, and carcinoembryonic antigen [13]. Vimentin is another helpful immunohistochemical marker [8,18].

Fine-needle aspiration cytology (FNAC) is the most reliable tool in detecting thyroid malignancies. FNAC should be performed in any thyroid nodule >1 cm and in those <1 cm if there is any clinical (history of head and neck irradiation, family history of thyroid cancer, suspicious features on palpation, presence of cervical adenopathy) or ultrasonographic suspicion of malignancy [19]. Sensitivity of FNAC for thyroid malignancy ranges from 61% to 97.7% [20-23]. Fine-needle aspiration can diagnose ATC by the demonstration of spindled or giant cells, bizarre neoplastic cells that may be multinucleated, or atypical cells with high mitotic activity. Syncytial pattern (sheets of follicular cells with loss of polarity and lack of distinct cell borders) is the predominant cellular pattern of anaplastic thyroid carcinoma [24].

It has been proposed that fine needle capillary sampling (FNC) was better than FNA by reducing trauma to cells and tissues, resulting in less pain, less haemorrhage and specimens of higher quality [25]. In a meta-analysis, no method was found superior to the other [26]. Complications of FNAC included pain/discomfort, haemorrhage/haematomas, recurrent laryngeal nerve palsy, vasovagal reactions, needle track seeding, nodule volume alterations, and post-aspiration thyrotoxicosis [27]. Needle track seeding was a rare complication. Only one study has reported needle track seeding in anaplastic thyroid carcinoma [28]. Tumor cells released into the surrounding tissues or circulation are probably destroyed by the host immune response or other mechanisms before giving rise to clinically apparent [27].

Ultrasound scans provide information about the location and nature (cystic vs non-cystic) of the tumor. The sensitivity of ultrasound in evaluating thyroid nodules for malignancy ranges from 41.4% to 86.5% [23,29,30]. Ultrasound-guided FNAC should be carried out in tumors located posteriorly or those with more than 50% cystic content, which are poorly evaluated with palpation-guided FNAC [31]. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are necessary in some cases to determine the staging and extent of the disease, and in planning surgery [32]. 18F-fluorodeoxygluconate positron emission tomography (18F-FDG PET) is useful in the early evaluation of treatment response and follow-up [33,34].

Frozen section should be considered unnecessary because it does not affect the intraoperative decision making [35]. The sensitivity of frozen section ranges widely from 32.4% to 93% [23,36-39]. Frozen sections distort and collapse the blood vessels of the thyroid gland, increaseing the difficulty in detecting angioinvasion which is an important feature in differentiating between follicular adenomas and carcinomas [40].

3. Treatment

Multimodality treatment is the recommended treatment although it seems to have only slightly improved outcomes. It consists of surgery, external beam radiation and chemotherapy. Besides tumor resection, tracheostomy may be indicated for advanced disease. Surgery has an important role in ATC, especially when complete removal can be achieved. However, the extent of the resection must be carefully weighed against its morbidity, given the poor prognosis of the disease. Although tracheal resection may be performed in selected cases, resections of the larynx, pharynx, and esophagus are generally discouraged [8,41,42]. Furthermore, some studies found that neither the extent of the operation nor the completeness of the tumor resection affected survival[14]. Because of its aggressive nature, complete surgical resection is recommended whenever possible if excessive morbidity can be avoided [8,43].

Lateral neck dissections should be performed if neck nodes are palpable and resectable. Although postoperative external beam irradiation or adjunctive chemotherapy adds little to the overall prognosis [44], some studies found that it may prevent death from local airway obstruction and at best may slightly prolong survival [8, 13,14,45].

Doxorubicin has become established as a standard chemotherapy [46-52], often in combination with cisplatin [51,53]. Tracheostomy may be the initial management for patients with impending airway obstruction and may be the single treatment for patients who are not candidates for local resection or chemoradiation [8,54]. Prophylactic tracheostomy in the absence of impending risk to the airway is discouraged [11].

Mclver [14] found that the median survival was 3.5 months in patients undergoing surgery versus 2.3 months in patients receiving radiotherapy, but only 3 weeks if palliative care was provided. Smallridge reviewed 35 studies including 1771 patients treated between 1949 and 2007. He found that the median survival of all series was only 5 months and the median 1-year survival was 20% [55]. Several investigators concluded that younger patients [41,56-58] and smaller tumor size carried a better prognosis [3,57,59]. The most common causes of death are lung metastasis (35%), airway obstruction (16%), and tumor-related heamorrhage (14%). The tumor sites mainly responsible for death included concomitant local and distant metastases (40%), local disease (34%), and distant metastases (24%) [54].

4. Conclusion

Anaplastic thyroid cancer (ATC) is a rare malignancy which behaves aggressively. Currently, FNAC is useful for diagnosis and tumor markers (cytokeratin, vimentin, and carcinoembryogenic antigen) help in diagnosis and follow-up of the patients. The treatment of choice is surgery with radiotherapy and chemotherapy. Complete surgical resection is desirable in ATC, but most patients present with inoperable tumor and thus palliative care and other modalities should be considered in these circumstances. Prompt diagnosis and aggressive treatment are the essential if there is to be any hope of curing this disease.

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