

TITLE: Anaplastic Thyroid Carcinoma

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Anaplastic thyroid carcinoma is one of the most aggressive human malignancies, with patient survival usually measured in months. It is a rare malignancy, with a rate of 2 per million per year, and accounts for approximately 1.6% of all thyroid cancers. Anaplastic thyroid carcinoma (ATC) is often associated with well differentiated thyroid cancers, with a reported evidence of dedifferentiation of less than 1%. Those ATC's that are associated with well differentiated thyroid carcinomas are usually found on pathological analysis as a small focus of ATC within a well differentiated thyroid carcinoma. The incidence of ATC is declining. This is attributed to the development of precise immunohistochemical staining that came about in the 1980's, resulting in more accurate diagnosis. Also thought to contribute to the declining incidence of ATC is the iodination of food and food products world wide, as well as the more aggressive treatment of well differentiated thyroid cancers.

The clinical presentation of those ATC's not associated with a well differentiated thyroid carcinomas is usually in the 6-7th decade, and there is a 55-77% female preponderance. Most patients present with a rapidly enlarging neck mass. The mean size at presentation is 8 cm. Most patients present with local compressive symptoms. Greater than 40% of patients present with cervical lymphadenopathy, 30% present with true vocal cord paralysis, 90% present with direct invasion of adjacent structures and 50% present with distant metastasis. Approximately 75% of patients with ATC will develop distant metastasis during the course of their disease. Distant metastasis occurs in the lung (80%), bone (6-15%), brain (5-13%), and in the gastrointestinal tract.

In diagnosing ATC, fine needle aspiration has been found to be about 90% accurate. Grossly, ATC appears as an unencapsulated, tan-white mass with invasion into adjacent soft tissues. ATC does not exhibit radioactive iodine uptake, so this modality is ineffective both diagnostically as well as therapeutically. Computerized tomography is often necessary to evaluate the extent of invasion of ATC.

Microscopically, there are three histologic patterns of ATC. These are spindle cell, giant cell, and squamoid. There is no prognostic difference in the three types of ATC. Previous nomenclature included small cell and insular cell types. The small cell type has been

determined to be lymphoma and the insular type is merely a morphologic description that is not specific for ATC. The molecular pathology of ATC includes the deletion of the NM23 gene. This gene has been characterized as a metastasis suppressor gene. Also, P53 mutants have been found in 14% of all thyroid cancers, and are found more commonly in ATC. These mutants result in a loss of genome stability.

Prognostic factors that have been reported include distant metastasis, acute symptoms, duration of symptoms, and tumor size. Vankatesh reported that patients without distant mets had an eight month survival as opposed to a three month survival of patients with distant mets. Sugitani, in a multivariate analysis of several different factors reported that acute symptoms, tumor size >5cm, distant mets, and leukocytosis each was an independent risk factor. Ojeda reported that longer duration of symptoms, tumor size <10cm, and ATC as an incidental finding within a well differentiated thyroid cancer all resulted in an overall better prognosis.

Treatment options for patients with ATC include surgery, radiation, chemotherapy or a multimodality approach. Surgical treatment of ATC is controversial. The Mayo Clinic reported a 50 year experience that included 134 patients with ATC and concluded that neither the extent of operation nor the completeness of resection had a significant impact on survival. However, Kobayashi reported in a series of 37 patients that removal of macroscopic disease increased survival from 2 months to 6 months. The benefit of radiotherapy in treatment of ATC is also controversial. ATC is relatively radioresistant, so radiation is more a palliative treatment. Radiation has been shown to achieve 68-80% local control, but also has greater treatment morbidity. Levendag reported a series of 51 patients who received radiation. Those who received >30Gy had a median survival of 3.3 months, as opposed to the 0.6 month survival of those receiving less than 30Gy. Junor reported no survival benefit with radiation therapy, despite an 80% initial response in patients. Chemotherapy has been utilized as both a monotherapy as well as in combination. The use of chemotherapy was originally aimed at prevention of distant metastasis. Chemotherapy was unsuccessful at altering the fatal outcome of ATC. Doxorubicin has been the most frequently used agent, but resulted in less than 20% response rate and no evidence of complete response. Ain reported a 53% response rate in a phase II trial using paclitaxel. All patients eventually died of their disease, with a median survival of 24 weeks. Those deemed as responders to paclitaxel had a median survival of 32 weeks, those described as nonresponders had a 7week survival. This study did however stimulate further investigation of using paclitaxel. Combination chemotherapy includes the use of doxorubicin, bleomycin, and cyclophosphamide. This has resulted in very little effect in multiple studies. Yeung reported the use of a combination of paclitaxel and manumycin (a farnesyl:protein transferase inhibitor). This combination resulted in an enhanced cytotoxic effect and increased apoptotic cell death *in vitro* and *in vivo*. This combination inhibits angiogenesis and promotes the apoptotic regulatory pathway. A multimodality approach to treatment of ATC has shown the most promise. Tennevall reported a series of 33 patients treated with hyperfractionated radiotherapy, doxorubicin, followed by surgical debulking. Local control was achieved in 50%, with only 24% of deaths due to local failure. The median survival was only 4.5 months, with only 4 patients surviving longer than 2years. Sugino retrospectively evaluated 40 patients and reported improved 1 year survival with surgical debulking plus radiation (60%) as opposed to radiation only (20%). In this study, "debulking" was defined as a thyroidectomy for well differentiated thyroid cancer with a focus of ATC. MD Anderson reported a series of 121 patients. 12 patients that underwent complete macroscopic resection of their tumor survived longer than 24 months.

Of those twelve, ten received post op chemo and radiation. In a retrospective study by Haigh, 26 patients underwent surgical resection. Eight patients had resection for cure, resulting in no residual or minimal residual disease. The median survival was 43 months. Eighteen patients underwent palliative resection, with a median survival of 3 months. Both groups received post operative chemotherapy, radiation or both. The authors noted a significant selection bias.

Future studies in the treatment of ATC just underway include elucidating a more detailed understanding of dedifferentiation at the molecular level, a better understanding of genes involved in cell regulatory pathways, chromosome mapping (i.e. chromosome 7 and 16), and clinical trials involving the use of gene therapy. Several gene therapy experiments are already underway. Adenovirus-mediated p53 gene therapy has shown to increase chemosensitivity to adriamycin and doxorubicin. Bone morphogenic protein (BMP-7) has been demonstrated to inhibit proliferation of ATC cells by G1 arrest. Bovine seminal ribonuclease induced a high rate of apoptosis in ATC cells. Injection into nude mice with established ATC tumors resulted in a complete regression of the tumor. Other studies include the use of histone deacetylase inhibitors to promote apoptosis and differential cell cycle arrest in ATC cells. Human sodium iodide symporter, when transfected into ATC cells *in vivo* and *in vitro* established the uptake of iodide.

The prognosis for ATC remains dismal. The current treatment of ATC has not changed the prognosis or outcome, regardless of the modality. Future study at the molecular level, as well as treatment at the molecular level remains the only hope to change the outcome of this aggressive malignancy.

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