Anaplastic thyroid carcinoma

Author: Prof Martin Jean Schlumberger[1]
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Scientific editor: Prof Sebastiano Filetti

[1]Service de médecine nucléaire. Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94805 Villejuif. France. schlumbg@igr.fr

Abstract
Anaplastic carcinoma of the thyroid (ATC) is an aggressive form of cancer of the thyroid gland; it represents less than 2% of all thyroid cancers, knowing that the annual incidence of thyroid cancers varies considerably in different registries, ranging from 1.2-3.8 per 100,000 individuals. Clinically, most patients have a dominant fixed mass of 5 cm or more in diameter, multiple other nodules in both thyroid lobes, and enlarged lymph nodes. Invasion of adjacent organs (trachea, esophagus, vessels and muscles) is frequently observed. Twenty to 50% of patients have distant metastases, chiefly in lungs but also in bones, liver and brain. Over a third of the patients with ATC have a long-standing goiter. Compressive symptoms including hoarseness, dyspnea, cough and dysphagia are frequent, and a third of the patients have neck pain. Diagnosis of ATC should be established by surgical biopsy. Prolonged stimulation by TSH may be responsible for the changes of a thyroid tumor to anaplastic one; it may account for the higher incidence of ATC in areas of endemic goiter. Mutations of tumor antigen *p53* are frequently found in anaplastic but not in differentiated thyroid carcinomas, suggesting that *p53* mutations play a crucial role in progression from differentiated to undifferentiated carcinoma. ATC progresses rapidly and treatment should be initiated as soon as possible. Only combined multimodality therapy can impact favorably on the local control rate and thus avoid death from suffocation, so combination of Chemotherapy, Radiotherapy and Surgery is required.

Keywords
Aggressive thyroid cancer, nodules in thyroid, goiter, multimodality therapy

Disease name and synonyms
Anaplastic thyroid cancer
Anaplastic carcinoma of the thyroid

Définition
Anaplastic carcinoma of the thyroid (ATC) is an aggressive form of cancer of the thyroid gland, it is one of the most rapidly growing and invasive types of thyroid malignancies and probably the most destructive cancers encountered in humans. Thyroid function tests are usually normal. .Anaplastic cells do not express thyroid specific genes: they do not produce thyroglobulin, are unable to transport iodine and thyrotropin (TSH) receptors are not found on their plasma cell membrane.

Etiology and pathogenesis
The most common clinical sequence is the long-standing existence of a thyroid tumor, in which an anaplastic change occurs. The frequency of transformation is rare because undifferentiated cancers represent such a small percentage of thyroid carcinomas. Prolonged stimulation by TSH may be responsible for the changes and may account for the higher incidence of ATC in areas of endemic goiter.
Mutations of tumor antigen *p53* are frequently found in anaplastic but not in differentiated thyroid carcinomas, suggesting that p53 mutations play a crucial role in progression from differentiated to undifferentiated carcinoma. Furthermore, the high frequency of *p53* mutations in anaplastic carcinoma may to some extent explain their insensitivity to the majority of chemotherapeutic agents available.

Clinical description
Over a third of the patients with ATC have a long-standing goiter. The most common mode of presentation is a rapidly enlarging neck mass. Compressive symptoms including hoarseness, dyspnea, cough and dysphagia are frequent, and a third of the patients have neck pain. At initial examination, most patients have a dominant fixed mass of 5 cm or more in diameter, multiple other nodules in both thyroid lobes, and enlarged lymph nodes. Invasion of adjacent organs (trachea, esophagus, vessels and muscles) is frequently observed. Twenty to 50 % of patients have distant metastases, chiefly in lungs but also in bones, liver and brain.

Diagnostic methods
Anaplastic carcinomas are solid masses that are hypofunctioning on thyroid scintigraphy. Serum thyroglobulin concentrations are frequently elevated, because of the pre-existing thyroid abnormalities but serum calcitonin and carcinoembryonic antigen concentrations are normal. In rare cases, fever and leukocytosis occur and have been attributed to tumor production of granulocyte-macrophage colony stimulating factor (GM-CSF).
Fine-needle biopsy is an effective diagnostic modality but the diagnosis of anaplastic carcinoma should be established by surgical biopsy or at surgery. The extent of the tumor can be determined by ultrasonography, computed tomography, and endoscopy and by searching for distant metastases in lungs, bones, liver and brain.

Pathology
The tumor is typically composed of varying proportions of spindle, polygonal and giant cells, often harboring squamous cells and sarcomatoid foci. Keratin is the most useful epithelial marker and is present in 40 % to 100 % of the tumors. Many anaplastic carcinomas have a well-differentiated component. Conversely, differentiated carcinomas with small-undifferentiated foci should be considered as anaplastic. Thyroglobulin staining is negative in anaplastic carcinoma cells.
Immunohistochemical studies indicate that most tumors previously classified as small-cell undifferentiated carcinomas were in fact primary malignant lymphomas (positive for leukocyte common antigen) or less often medullary carcinomas (positive for calcitonin and carcinoembryonic antigen), poorly-differentiated follicular carcinomas or a thyroid metastasis from another primary tumor. Some tumors do not react with any antibody; they are considered as anaplastic carcinomas and carry the same prognosis.
In the 2002 TNM staging system (*TNM* stands for *T*umor, *N*odes, *M*etastases, a 1992 cancer staging classification of the American Joint Committee on Cancer and the International Union Against Cancer that has been updated), all anaplastic carcinomas are stage IV. The TNM system distinguishes 3 stages IV:
stage IVA, where tumor is limited to the thyroid and considered surgically resectable;
stage IVB wheretumor extending beyond the thyroid , is considered surgically unresectable, and
Stage IVC, where tumor is present with distant metastases.

Prevalence
In recent years, a trend has been noted towards a reduction in the incidence of anaplastic carcinomas in industrialized countries. They represent less than 2% of all thyroid cancers. The annual incidence of thyroid cancers varies considerably in different registries, ranging from 1.2-2.6 per 100,000 individuals in men and from 2.0-3.8 per 100,000 in women. The incidence of ATC is higher in areas of endemic goiter.
Most patients affected are elderly. The peak incidence is in the sixth-seventh decades of life and the male/female ratio is 1:1.5.

Treatment
Anaplastic carcinomas progress rapidly and treatment should be initiated as soon as possible.
Survival is not improved when monomodality treatment is applied: Used as unique treatment, neither surgery nor radiotherapy or chemotherapy are efficient. In most patients, death is caused by local tumor invasion. The median survival is 2 to 6 months, and few patients have survived beyond 12 months.
More radical surgery was no more effective than less radical surgery, and radiotherapy failed to induce any tumor regression. The most effective single cytotoxic agent against anaplastic carcinomas is doxorubicin, and a few responses have been reported with combined doxorubicin-cisplatin regimens. The adjunction of bleomycin

does not enhance the effectiveness of this combination. Recently, paclitaxel provided a 53% response rate including one complete response in 19 tested patients.
Only combined multimodality therapy can impact favorably on the local control rate and thus avoid death from suffocation. Three types of therapeutic trials have been carried out, all of which include surgical resection of tumor masses in the neck, systemic chemotherapy and radiation therapy to the neck and upper mediastinum.

Combination Chemotherapy-Radiotherapy-Surgery
Hyperfractionation, using a small dose per fraction may decrease toxicity, since it spares normal tissues more than tumor cells.
A combined regimen consists of a weekly dose of doxorubicin (20mg or 10mg/m^2) associated with hyperfractionated radiotherapy and surgery, which is performed either before or after this combination. No unexpected toxicity occurred. Complete tumor response in the neck was frequently obtained and patients who survived beyond a year had radical surgery and minimal residual disease at the time of irradiation.
A combination of hyperfractionated radiotherapy and aggressive chemotherapy (bleomycin, 5 mg daily, cyclophosphamide, 200 mg daily and 5-fluorouracil, 500 mg every second day or doxorubicin, 60 mg/m^2 and cisplatin, 90 mg/m^2 every 4 weeks) produced similar results.

Hyperfractionated and Accelerated Radiotherapy
Acceleration of radiotherapy allows the delivery of an efficient radiation dose in a limited period of time; this may have an increased efficiency by decreasing cell repopulation in rapidly growing tumors with short doubling times. This is the case for anaplastic carcinomas.
In a more recent Swedish trial, a combination of doxorubicin (20 mg / week) and radiotherapy (1.6 Gy (160 rads) twice daily up to a preoperative total dose of 46 Gy in 3 weeks) was used in 22 patients. Local control was obtained in 17 patients and none had a local tumor remnant or local recurrence when surgery was feasible. Death, attributable to local failure, occurred in 5 patients.
A French trial, combining surgery, doxorubicin (60 mg/m^2) and cisplatin (120 mg/m^2) every 4 weeks, with hyperfractionated and accelerated radiotherapy (1.25 Gy (125 rads) twice daily for 5 days per week, up to a total dose of 40 Gy (4000 rads) between the second and third course was used in 32 patients. Toxicity was similar to that observed with the previous protocol. With a median follow-up of 32 months, 9 of the 26 patients with no distant metastases at presentation were alive in complete remission, The 7 remaining patients had initially a macroscopically radical surgery.

Conclusion
All combined multimodality therapy protocols provide similar rates of local control and long-term survival. Benefits are observed mostly in patients who had macroscopically complete tumor resection and in whom the anaplastic cancer component represented a small fraction of the thyroid tumor mass and had a limited neck extent. Comparison of results obtained in successive Swedish trials suggests that accelerated radiotherapy increases the rate of local tumor control; however, presentation changed with time, and in recent years, patients are treated at an earlier stage of the disease. Acute toxicity is high and is the main factor limiting therapy in these elderly patients who are often in a poor general condition. If surgery cannot be performed initially, it may become feasible after combination of chemo- and external radiation therapy; surgery should be macroscopically complete.
In these series, no response was observed in distant metastases. This underscores how essential it is to treat these patients as soon as possible, before distant metastases emerge. The treatment modalities mentioned here might be useful, even in patients with metastatic disease, because they can avoid death by suffocation caused by local tumor growth. Novel strategies are still needed to improve the prognosis of one of the most aggressive human cancers.

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