

Anaplastic Thyroid Cancer: a case report of a long term survival patient and review of literature data

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Abstract. – Anaplastic thyroid carcinoma (ATC) is a very rare disease accounting for less than 2% of all thyroid malignancies and associated to a dismal prognosis.

The median survival is between 3 to 9 months with less than 10% of patients alive at 3 years after the time of diagnosis.

This low cure rate is due to the late clinical presentation as a bulky unresectable tumour mass often associated with synchronous lung metastases (20-50%).

A multimodality treatment consisting in a radical surgery followed by radiotherapy and chemotherapy is reported to be associated with better clinical outcomes while young age (< 65 years), tumour size (< 6.5 cm) and absence of distant metastases at time of diagnosis are recognized as strong prognostic factors of survival.

We report the case of a 65 year-old man who was referred to our hospital for an ATC which extended to the external right tracheal wall and muscular layer of esophagus.

The patient underwent radical thyroidectomy with bilateral neck dissection followed by 3 cycles of adjuvant chemotherapy (Cisplatin /Epirubicin) and subsequent radiochemotherapy with Cisplatin as radiosensitizer.

At more than 6 years since diagnosis the patient is still alive without evidence of local recurrence or distant metastases.

Therefore, aggressive multimodality treatment after radical surgery might improve clinical outcomes and perhaps should be tested in prospective clinical trials.

Key Words:

Anaplastic thyroid cancer, Radical Surgery, Radiochemotherapy, Intensity and modulated radiotherapy.

Introduction

Anaplastic thyroid cancer (ATC) is the least common of all thyroid malignancies (less than

2%), with a female/male ratio of 3:1 and a peak incidence occurring during the sixth to seventh decade of life.

This cancer has the worst prognosis among all thyroid malignancies due to a very low curative rate with a median survival between 3 to 9 months, 3 year overall survival rate (OS) of 10% and most patients not alive one year from the time of diagnosis¹.

It usually arises with a gross extensive local disease often surgically unresectable at the time of diagnosis and associated with lung metastases in 20-50% of cases, while 25% will develop during the course of the disease²⁻⁴.

In most cases clinical appearance is characterized by a fastly growing anterior central neck mass invading trachea and esophagus and causing severe dyspnoea, dysphagia, voice change and stridor often associated with lymph node mass (54%) and neck pain (26%).

Approximately 50% of patients develop anaplastic carcinoma from a pre or coexistent differentiated carcinoma after a multistep process of dedifferentiation mainly based on loss of the p53 oncogene suppressor⁵.

Molecular pathogenetic mechanisms of this histological transformation are not well known.

Pathological misclassification (e.g lymphoma or poorly differentiated medullary thyroid carcinoma) may be a confounding factor leading to better clinical results than those reported by the literature.

There is a non uniform consensus about the standard treatment approach of ATC due to the very low incidence, its aggressive nature with a very poor prognosis and the consequent lack of large clinical series.

In these patients local control (LC) disease is a major concern in order to prevent complications such as airways and/or upper gastrointestinal obstruction requiring emergency procedures (tracheotomy or stent positioning).

There is a general consensus to consider ATC a systemic disease since diagnosis due to the very rapid hematogenous dissemination of cancer cells usually resistant to standard chemotherapeutic drugs.

Therefore, a multimodality approach is strongly recommended in the guidelines.

Surgery and/or radiochemotherapy, both as radical or palliative treatments, are considered in most cases combined with full-dose chemotherapy even if clear efficacy of standardized schedule is not recognized.

Case Report

A 63 year old man was referred to our Institution Hospital after a 6 month period of dry cough associated with voice change, stridor and hoarseness and without relief using common medical care.

The family history reported father and mother died respectively for pancreatic and brain cancer.

He was an ex-smoker of about 10 cigarettes until he was 50 years old and had a low alcohol and coffee intake at meals.

Moreover, the patient referred a moderate hypertension controlled with antihypertensive medicines and a previous medical history of polyp vocal cord excision.

On the contrary, no concomitant benign thyroid disease was reported.

At first examination patient appeared physically active and able to carry on all pre-disease performances without restriction.

Hence, according to Eastern Cooperative Oncology Group (ECOG) for Performance Status Score, he was classified as ECOG grade 0.

At physical examination, a well palpable nodule in the right lobe of thyroid gland was detected associated with an approximately 10 mm lymph node located at the IV level of ipsilateral neck; then an US-guided fine needle aspiration (EUS-FNA) was performed on both sites which was highly suggestive for thyroid cancer.

Haematological exams showed an increase of pituitary and a reduction of thyroid gland function, with a FT3 and FT4 value respectively of 1.73 pg/ml and 0.82 ng/ml and a TSH value of 16.17 μ UI/ml, proving a nearly subversion of thyroid gland function (Hypergonadotropic Hypothyroidism).

Thereafter, the patient underwent staging exams.

The ^{131}I Whole Body Scintigraphy confirmed a roundish increased activity of the paramedian cervical region while the subsequent contrast enhanced Computed Tomography (CT) of the head, neck and thorax region showed a inhomogeneous hypodense thyroid gross tumour mass extended to surrounding normal trachea and cervical esophagus without evidence of a clear cleavage plan.

Patient was judged surgically resectable and underwent to a total thyroidectomy extended to the right tracheal wall and external esophagus muscular layer combined with bilateral functional neck dissection (II-V levels) plus VI level.

At first examination, the surgical specimen showed a 3.5 cm gross tumour mass invading the right thyroid lobe with a complete incorporation of recurrent nerve combined with infiltration of the sternum thyroid muscle (radically removed).

Definitive pathologic examination confirmed undifferentiated carcinoma of the right lobe infiltrating isthmus, thyroid surrounding tissues, striated muscle and tracheal wall, associated with endovascular carcinomatosis. Metastases were detected in 3 thyroid and 1 IV right level lymphnodes. Positive resection margins were found on the tracheal wall.

A post-surgical contrast enhanced CT showed the outcome of a complete thyroid excision and neck dissection without evidence of macroscopic residual cancer while ^{131}I Scintigraphy showed no residual hyperactivity.

Thus, according to TNM Staging (7th ed., 2010) and American Joint Committee on Cancer System (AJCC) he was staged as pathological T4a N1b (Stage IVA) and R1 indicating microscopic residual tumour cells.

Levothyroxin and calcium carbonate as replacement therapy after thyroidectomy were given.

Three cycles of adjuvant chemotherapy using a full dose of Cisplatin (80 mg/mq every 21 days) and Epirubicin (75 mg/mq every 21 days) and a subsequently radiochemotherapy treatment using a low dose of Cisplatin (40 mg/mq weekly) were administered.

Radiotherapy was performed at a Linear Accelerator (2100 Varian) using a tridimensional dynamic conformal arc technique (3DCRT). An intensity modulated radiotherapy (IMRT) technique was not used because it hadn't been implemented at our institution yet.

A 50 Gy prescription dose with conventional fractionation was delivered to the bilateral whole neck including surgical bed and upper mediastinum followed by two sequential boost using a

fixed beam technique to the intermediate (IV level of the right side of the neck) and high risk areas (thyroid surgical bed and surrounding trachea) respectively up to 60 Gy and 66 Gy in order to maximally reduce the probability of tumour local recurrence.

During radiochemotherapy the patient experienced a mild acute toxicity reporting a grade 2 mucositis and dysphagia, according to Common Toxicity Criteria Adverts Events Toxicity scale (CTCAE vs 3), that caused a weight loss of 8 kg at the end of treatment.

No percutaneous endoscopic gastrostomy (PEG) or feeding tube placement but only a supplement of parenteral nutrition during the last week and one week after radiation treatment was required.

8 months post- treatment the patient experienced a respiratory failure that required posterior laser cordectomy associated with temporary tracheotomy.

The histological exam pointed out a chorion sclerosis and hyperplasia of submucosal glands likely due to combination of surgery and high dose radiation therapy.

Patient follow up was performed at 1 month after the completion of treatment, at 3 months for the first year and subsequently at 6 month intervals.

Endocrinological evaluation (including thyroid function exams) was required at each visit. Neck ultrasound and contrast enhanced CT of the head, neck and thorax were performed regularly.

At 6 years since diagnosis patient is still alive, without evidence of locoregional recurrence or distant metastases and with a good quality of life (Figure 1).

After last follow up we requested a pathological revision of surgical specimen that confirmed the initial diagnosis of ATC (Figure 2).

Discussion

ATC is a very uncommon malignancy associated with a dismal prognosis.

Despite a decrease in its incidence worldwide it still accounts for 14-50% of mortality from thyroid cancer.

The most common cause of death is the invasion of vital structures in the neck so that achieving of good local control is the primary purpose in the treatment strategy for this cancer.

Although a general consensus on the standard treatment is not recognized, literature guidelines report better outcomes with multimodality treatment consisting of surgery combined both with radiation and chemotherapy than a single modality alone.

Surgery is reported to be the cornerstone of treatment in many series and it seems to be associated with better clinical results whenever is followed rather than preceded by radio or radiochemotherapy (44 months vs 4 months; $p < 0.01$)⁶.

Complete resection of tumor mass with microscopically clear margins (R0) or minimal residual disease (R1) is associated with a better clinical outcomes compared with a palliative debulking surgery.

Haigh et al⁷ reported their case load on 33 patients (26 operated and 7 undergone to chemo and radiotherapy) showing a significantly better overall survival in those undergone to radical than to palliative surgery (43 months vs 3 months; $p = 0,001$) while no difference of survival was shown between palliative resection and only chemo and radiotherapy ($p = 0.63$).

In this serie 2 cases of long surviving patients at 32 and 62 months were reported.

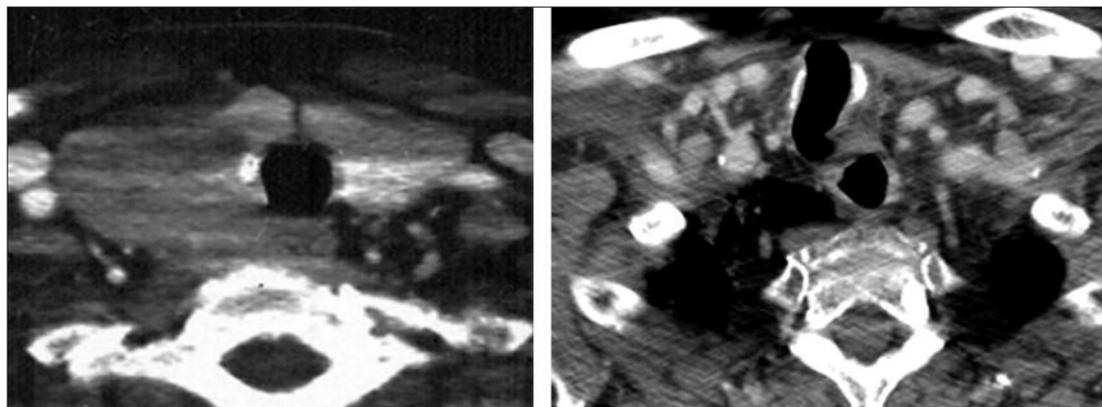


Figure 1. VCT scan at time of diagnosis (before surgery) and at last follow-up.

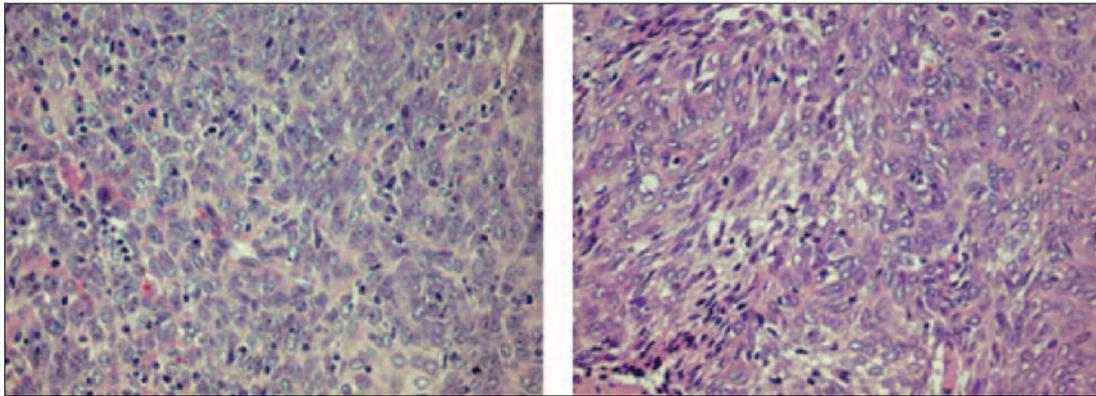


Figure 2. Revision of surgical pathological specimen The picture is taken at magnification 20x and is PAS stained.

One patient underwent to radiation therapy and the other to radiochemotherapy with concomitant doxorubicin after radical surgery.

Multivariate analysis of these data revealed that radical surgery is the only factor associated with prolonged survival.

In Pierie et al⁴ case series on 67 patients⁸ a 1 year overall survival (O.S) of 91% was reported after radical surgery and radiotherapy compared with 35% after palliative surgery plus radiotherapy.

Furthermore similar results were reported by Yau et al case load⁹ on 50 patients showing that the age < 65 years, lesion size < 6 cm and absence of distant metastases were variables significantly associated with prolonged survival as well as radical surgery.

Nevertheless, there is a wide consensus that surgery alone, even if curative, is not adequate in most cases so that a supplementary treatment such as radio or radio and chemotherapy is needed in order to achieve the best LC outcomes.

Despite a large variety in the timing of multimodality treatment, the feeling is that better results should be obtained with an up front surgery followed by a radio or radiochemotherapy¹⁰⁻¹².

De Crevoisier et al¹³ reported results of a multimodality prospective trial on 30 ATC patients.

Of the 24 patients without distant metastases, 17 underwent to initial surgery (9 R0/1 and 8 R2) followed by 2 cycles of cisplatin plus doxorubicin based chemotherapy, then hyperfractionated RT (two daily fractions of 1.25Gy up to a total dose of 40Gy) and finally 4 cycles of the same schedule of chemotherapy according to the protocol.

After a median follow up of 35 months (5-78 months) a complete remission was reported in a total of 8 patients (7/9 R0/1 and 1/8 R2 surgery) confirming that long term survival can be obtained when RT-CT is given after complete surgery.

Moreover, the Authors underlined that death was much more related to distant metastases than only to local progression (68% vs 5% of cases) while in 27% of cases it was related to the failure in both sites.

Swagak-Kragten et al experience¹⁴ on 75 ATC patients treated between 1972 and 2003 clearly confirm above data reporting a probability of high LC (89% complete remission) and OS (>5 years) only in the group of patients who had undergone to initial surgery (R0/R1 resection) followed by chemoradiation.

The Authors reported that 3/30 patients were alive respectively at 119, 110 and 76 months after diagnosis (10%) and considered definitely cured of their disease.

Moreover, total radiation dose (< 40Gy versus > 40Gy) was found to be an important prognostic factor significantly related to OS ($p < 0.001$).

This observation has been further underlined in a recent retrospective review of MSKCC data on 37 ATC patients by Sherman et al¹⁵.

Although few patients underwent to radical surgery, Authors found out radiation dose (< 60Gy versus > 60Gy) to be a significant prognostic variable together with age (< 70 years versus > 70 years), on both LC and OS in the multivariate analysis.

Thus, despite the heterogeneity of most retrospective experiences and absence of prospective randomized studies, conclusions are difficult to draw from the literature.

Surgery should be aimed to radical intent and performed up front in all feasible cases.

An adjuvant treatment consisting of radiochemotherapy is strongly recommended even after R0/R1 surgery while the impact of chemotherapy alone seem to be scarce in the prognosis of the disease.

Furthermore, emerging data are coming up about tumor control probability and higher radiation doses in several latter experiences.

Finally, absence of distant metastases at time of diagnosis, tumor size (less than 6-7 cm) and young age (< 65 years) seem to be significant prognostic factors of LC and OS.

The patient in the present case report had several positive prognostic factors that may explain his long term survival.

Radical surgery followed by aggressive multimodality treatment as well as tumor size less than 6 cm and absence of distant metastases at presentation, probably contributed to the good clinical result.

Moreover, despite the presence of microscopic disease near the tracheal wall, a high radiation dose combined with concomitant cisplatin based chemotherapy, has been delivered to the surgical bed likely yielding to complete sterilization of positive margins.

Finally, the role of chemotherapy and his clinical benefit is still unclear because different schedules in different clinical settings and with variable success rates have been used in most series.

Nevertheless, our patient underwent to an adjuvant full dose of cisplatin plus epirubicin based chemotherapy that might be efficacious in distant micrometastatic disease.

Conclusions

An aggressive multimodality adjuvant treatment may be of clinical benefit in a selected group of patients with ATC. We underline the role of a high radiation dose using advanced techniques (3DCRT or IMRT) to improve LC. Prospective clinical trials are required to define the standard multimodal approach of ATC.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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