Epidemiology, clinical presentation, treatment and prognosis of a regional series of 26 anaplastic thyroid carcinomas (ATC). Comparison with the literature

Résumé

But/Objectif. – L’objectif de cette étude est de décrire rétrospectivement les caractéristiques épidémiologiques, cliniques, les modalités thérapeutiques, les facteurs pronostiques et la survie d’une population de patients atteints d’un carcinome anaplasique de la thyroïde (CAT) répertoriés dans la région Auvergne et de comparer ces données à celles de la littérature. Matériel et méthodes. – L’analyse a été réalisée à partir d’une banque de données informatiques d’un registre régional renseigné par les professionnels de santé prenant en charge les cancers thyroïdiens de la région. Résultats. – Vingt-six CAT parmi les 1500 cancers ont été recensés sur 16 ans. Le sex-ratio H/F était de 1/2.7 et l’âge moyen de 72,1 ans ; des antécédents thyroïdiens étaient présents dans 76,9 % des cas et la taille tumorale moyenne à la découverte était de 7,35 cm, un stade N1 en cours de maladie était constaté dans 6,5 % des cas et M1 dans 34,6 % des cas. Une chirurgie a été réalisée dans 84,6 % des cas, une radiothérapie dans 53,8 % des cas et une chimiothérapie dans 19,2 % des cas. La moyenne de survie était de neuf mois et la médiane de survie de quatre mois. Conclusion. – Nos résultats montrent en analyse univariée que le grand âge, un dépassement capsulaire, un envahissement ganglionnaire, la présence d’un résidu tumoral après chirurgie et l’absence de traitement multimodal en particulier de radiothérapie chez les patients sans résidu tumoral après chirurgie sont des facteurs de mauvais pronostic. Après analyse multivariée, un âge supérieur à 75 ans, suivi de l’invasion capsulaire puis de l’envahissement ganglionnaire et enfin le fait d’être une femme sont des facteurs de mauvais pronostic.

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Mots clés : Cancer anaplasique thyroïdien, Registre, Auvergne

Abstract

Objective. – The aim of this study is to retrospectively describe the epidemiological and clinical features, therapeutic modalities, prognostic factors and survival figures in a population of patients with anaplastic thyroid carcinoma (ATC) observed in Auvergne, France. We compared these data with those in the literature. Material and methods. – The analysis was conducted based on a computer database containing a regional register recorded by health professionals treating ATC. Results. – Of the 1500 cancers observed over 16 years, 26 were identified as ATC. The male/female ratio was 1/2.7 and the average age: 72.1; 76.9% of the cases had thyroid medical history, average tumor size at diagnosis was 7.35 cm with N1 in the course of illness in 61.5% of cases, M1 in 34.6% of cases.

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Surgery was performed in 84.6% of cases, radiotherapy in 53.8% and chemotherapy in 19.2%. The average survival was 9 months, the survival median: 4 months.

Conclusion. – Our results show that, in univariate analysis, age above 75, capsular invasion, lymph nodes metastasis, tumor residue after surgery and lack of multimodal treatment (particularly radiotherapy in patients without tumor residue) are factors of poor prognosis. In a multivariate analysis only age above 75, followed by node invasion, capsular invasion, and finally female gender are factors of poor prognosis.

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Keywords: Anaplastic thyroid carcinoma; Auvergne register

1. Introduction

Anaplastic thyroid carcinoma (ATC) is a rare disease, accounting for less than 2% of all thyroid tumors. Nevertheless, it is one of the most lethal malignant human tumors. ATC usually appears as a rapidly enlarging throat mass, often associated with dysphonia, dyspnea, dysphagia, neck tenderness. The male-female ratio is 1:1.5 with a peak incidence in the sixth and seventh decades of life. In contrast to well-differentiated thyroid cancer, ATC typically follows a rapid and lethal clinical course, with a median survival below 6 months in the majority of the reported studies [1,2,3].

In a high percentage of patients, the condition is usually well-advanced at the time of diagnosis, with extensive local damage and direct spread to adjacent organs, such as the trachea, esophagus, blood vessels and muscles. Furthermore, about 50% of ATC patients have distant metastases, the lungs being the site which is most commonly involved. Most of the patients with anaplastic thyroid cancer do not live longer than 1 year from the day they are diagnosed. Patients usually die from a local and regional progression of the tumor, with airway and esophageal obstruction. The treatment options for ATC include surgery, chemotherapy and radiotherapy. All of these, especially if used alone, most often fail to control local disease. Multimodal therapy, which combines surgery, chemotherapy and radiation therapy, can give better results, preventing death from local invasion and suffocation and improving the survival of some ATC patients.

Anaplastic thyroid cancer often develops within a more differentiated type of thyroid cancer or even within a goiter. We currently have a poor understanding of the basic pathophysiology of anaplastic thyroid cancer. The aggressive nature and rarity of ATC makes it difficult to compare patient outcomes, especially in studies with small cohorts and short follow-up [2,3]. Our retrospective study focuses on a series of 26 ATC cases identified over a period of 16 years in a regional database containing 1500 cases of thyroid cancer. In our study, we have analyzed the characteristics of the population, the prognosis factors and the therapeutic options on survival. The results of the main studies published in the literature have been quoted and discussed in comparison with our results.

2. Materials and subjects

The data analysis was based on the computer database of the regional registry of thyroid cancer cases reported by health professionals treating thyroid cancers (endocrinologists, surgeons, pathologists and nuclear medicine clinicians) who belonged to a thyroid study group (Groupe thyroïde Auvergne [GTA]).

All cases of ATC were identified for the period between January 1990 and January 2006 among a population with the diagnosis of neoplastic thyroid tumor.

The cases defined as ATC were compiled from a file of reported cases maintained by all the hospital and private pathologists of the Auvergne region. This region has three laboratory centers (one private center and two hospital centers: University Hospital Center of Clermont-Ferrand and the Jean Perrin Center). This registry complied with the information and personal freedom regulations controlled by a special commission in France, the Commission nationale de l’informatique et des libertés (CNIL). The patients had to give their consent to be recorded in this registry. Not all the cases of cancer were recorded, but the data collection was nearly exhaustive: estimated rate of data collection was 90% [4,5].

3. Method

Although this was a descriptive and retrospective study, the data were taken from a prospectively registered cohort. The survival for each patient was calculated from the time of diagnosis to the day of death or last follow-up. All causes of death were included. In order to study the impact of clinical signs, tumor characteristics and treatments on survival, the Kaplan-Meier method was used to plot the survival curves which were compared with the Log-Rank test. Potential factors affecting survival in univariate analysis were then compared in a multivariate analysis by applying the Cox model. A standard p-value inferior to 0.05 was considered significant. SEM statistical software was used to perform the statistical analysis.

4. Results

Of the 1500 thyroid cancers identified in the regional database between 1st January 1990 and 1st January 2006, 26 cases were identified as ATC (1.7% of the total number of thyroid cancers). The average age was 72.1 (patient ages ranged from 52.3 to 90.8). The male to female ratio was 1/2.7. Previous personal thyroid history was found in 76.9% of cases; in most cases, it was Goiter (17 patients) and, less frequently, isolated nodules without Goiter (three patients). No patient was known to suffer from a differentiated thyroid cancer before the discovery of ATC. Out of 20 patients with a pre-existing history of thyroid pathology, only three had undergone surgery before the discovery of ATC:
two for a multinodular Goiter and one for a toxic multinodular Goiter. The majority had a normal thyroid function (80.8%), only four patients had hyperthyroidism (15.4%), and one patient had hypothyroidism caused by Hashimoto’s thyroiditis.

Other clinical signs to appear are shown in Table 1. Other signs such as pain, poor general condition, fever or venous compression were fewer. Only one patient, a woman who had surgery for toxic nodular goiter, did not show any sign. The histological analysis revealed a 7 cm papillary cancer with the presence of a 1 cm unexpected anaplastic cell cancer without capsular invasion.

During the course of the disease, a lymph node invasion appeared in six more patients, which brings to 16 (61.5%) the total number of patients with nodal involvement. Five other patients developed distant metastases (34.6% of the population), chiefly located in lungs but also in bones and brain.

The pathology reports of the ATC of our study described spindle cell (53.8%), giant cell (46.2%), and squamoid cell (7.7%) neoplasia, sometimes with different cells within the same tumor. In nine of 26 patients, the pathology examination showed the concomitance of ATC and another type of differentiated tumor (seven papillary carcinomas, one vesicular carcinoma and one sclerosing occult cancer).

Twenty-two patients (84.6%) underwent surgery. Considering all 26 patients, R0 resection was achieved in 12 patients (46.2%) while residual tumor tissue (R1 resection or no surgery) remained in 14. Diagnostic biopsy was the only procedure in four patients (15.4%) because of their poor general condition.

For the 22 patients who had surgical treatment, the surgery breakdown was as follows:

- 16 total or subtotal thyroidectomy including eight R0;
- 4 lobo-isthmectomies or semi-thyroidectomies of which two R0; 157
- 2 tumorectomies without macroscopic post surgery tumor residue (two R0).

A lymph node dissection was done in five cases at the same time. The exploration of the cervical lymph node areas was

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Table 1
Characteristics of the population and tumor extension at diagnosis.
Caractéristiques de la population et extension tumorale au diagnostic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>7/19</td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td>72.1 (52.3–90.8)</td>
</tr>
<tr>
<td>Rapidly growing thyroid tumour (%)</td>
<td>92.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>50%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>46.2%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>42.3%</td>
</tr>
<tr>
<td>Tumor size</td>
<td>7.35 cm (1–19)</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>69.2%</td>
</tr>
<tr>
<td>Muscular and/or tracheal and/ or esophageal and/or vessels invasion</td>
<td>50%</td>
</tr>
<tr>
<td>Nodal metastasis (N1)</td>
<td>38.4%</td>
</tr>
<tr>
<td>Distant metastasis (M1)</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

central, and was either homolateral to the side of the tumor or bilateral. The upper mediastinal lymph node areas were explored in one patient. One patient underwent a second surgery after radiotherapy for a residual muscular tumor which had been missed initially.

The surgery was complicated in six patients. Four lesions of a recurrent nerve resulted in three cases of permanent dysphonia. Three patients had an amputation of an internal jugular vein.

Three patients underwent surgery for their metastases: one for a skin lesion known since the diagnosis, another for a lung metastasis to improve the respiratory condition of the patient, another for a lung metastasis which appeared 1 year after the diagnosis and the initial cervical surgery. No procedures such as tracheotomy to prevent suffocation or feeding gastrostomy in cases of esophageal compression were required.

The protocols of radiotherapy and chemotherapy used from the beginning of the recruitment of the patients until the end of this study were not detailed. Before 2004, the decision to complement the surgery by chemotherapy or radiotherapy was taken on a case-by-case basis after discussion with the surgeon, the cancerologist and/or the radiotherapist.

Fourteen patients (53.8%) underwent radiotherapy. Of these 14 persons, 13 received adjuvant radiotherapy. Only one patient received radiotherapy prior to surgery. This treatment was performed to decompress the upper airways and digestive tract in a patient in poor general condition who could not undergo surgery. Four patients had dual radiotherapy, on the thyroid area and on lung and bone metastatic lesions. The woman with unexpected anaplastic cells with papillary cancer underwent total thyroidectomy (R0) with radiotherapy after surgery, radioiodine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Macroscopic residue after surgery</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Survival (days)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1</td>
<td>+</td>
<td>+</td>
<td>155</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>2</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>130</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>3</td>
<td>R1</td>
<td>+</td>
<td>–</td>
<td>110</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>4</td>
<td>R0</td>
<td>+</td>
<td>+</td>
<td>101</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>5</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>281</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>6</td>
<td>R0</td>
<td>–</td>
<td>–</td>
<td>115</td>
<td>Upper airways compression and metastasis</td>
</tr>
<tr>
<td>7</td>
<td>R1</td>
<td>+</td>
<td>–</td>
<td>250</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>8</td>
<td>R1</td>
<td>+</td>
<td>+</td>
<td>57</td>
<td>Pneumopathy secondary to immunosuppression</td>
</tr>
<tr>
<td>9</td>
<td>R0</td>
<td>+</td>
<td>–</td>
<td>1825</td>
<td>No link to cancer</td>
</tr>
<tr>
<td>10</td>
<td>R0</td>
<td>+</td>
<td>–</td>
<td>356</td>
<td>Heart event</td>
</tr>
<tr>
<td>11</td>
<td>R1</td>
<td>+</td>
<td>–</td>
<td>50</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>12</td>
<td>R0</td>
<td>–</td>
<td>–</td>
<td>114</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>13</td>
<td>R0</td>
<td>+</td>
<td>–</td>
<td>587</td>
<td>Malnutrition and mucositis following radiotherapy</td>
</tr>
<tr>
<td>14</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>365</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>15</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>38</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>16</td>
<td>R0</td>
<td>+</td>
<td>–</td>
<td>810</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>17</td>
<td>R1</td>
<td>+</td>
<td>–</td>
<td>76</td>
<td>Upper airways compression, metastasis and poor general condition</td>
</tr>
<tr>
<td>18</td>
<td>R0</td>
<td>+</td>
<td>+</td>
<td>1886</td>
<td>Metastasis and poor general condition</td>
</tr>
<tr>
<td>19</td>
<td>R0</td>
<td>–</td>
<td>–</td>
<td>188</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>20</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>unknown</td>
<td>TAC without details about cause of death</td>
</tr>
<tr>
<td>21</td>
<td>R0</td>
<td>+</td>
<td>–</td>
<td>309</td>
<td>Poor general condition</td>
</tr>
<tr>
<td>22</td>
<td>R0</td>
<td>–</td>
<td>–</td>
<td>29</td>
<td>Poor general condition</td>
</tr>
<tr>
<td>23</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>24</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>25</td>
<td>R1</td>
<td>–</td>
<td>–</td>
<td>41</td>
<td>Upper airways compression</td>
</tr>
<tr>
<td>26</td>
<td>R0</td>
<td>+</td>
<td>+</td>
<td>441</td>
<td>Upper airways compression, metastasis and poor general condition</td>
</tr>
</tbody>
</table>
ablation dose and supraphysiologic doses of thyroid hormone to suppress serum TSH. Tumor containment was achieved in 42.9% of patients who received radiotherapy, compared to 8.3% of those who did not receive this therapeutic option. Only five out of 26 patients with ATC received an adjuvant chemotherapy treatment (19.2%) after surgery and radiotherapy.

At the end of our study, the number of patients who died, all causes included, was 25 out of 26 people (96.2%). The woman with the small ATC discovered incidentally in a differentiated tumor died more than 5 years following the diagnosis from a cause not related to the thyroid cancer. She was considered as cured of ATC. The cause of death for all patients is shown in Table 2.

Radiotherapy and chemotherapy caused two deaths (7.7%). One death was due to radiotherapy because of post radiation mucositis and malnutrition and another death was caused by chemotherapy which was responsible for immunosuppression and pneumonia. One patient died following surgery because of poor general condition, and one patient died of heart failure unrelated to the ATC or its treatment.

The average survival was approximately 9 months, and the median was approximately 4 months.

When surgery was macroscopically complete (12 cases), the survival average was 18.5 months. Two-thirds of these patients had only radiotherapy and one quarter had a multimodal treatment. Four died following local compression of the upper airways, the others died from distant extension of the disease with or without local signs, poor general condition, a cardiac event or from complications of radiotherapy. One woman went on living for more than 5 years.

In 10 other cases, with a residual tumor after surgery (except biopsy), the average survival was only 4 months. Fifty percent of these cases had radiotherapy and 20% had multimodal treatment. One patient died following chemotherapy complications, while 90% of observed patients died from the local compression of the upper airways.

The five patients who underwent multimodal treatment had an average survival of 17 months (median survival of 5 months). Two of them died from compression of the upper airways, two from a metastatic development of the disease, and one patient died following complications of the chemotherapy.

The statistical impact of patient and tumor characteristics and modalities of treatment on overall survival is summarized in Table 3. In an univariate analysis, age above 75, capsular invasion, lymph nodes metastasis, tumor residue after surgery and lack of multimodal treatment, particularly radiotherapy, in patients without tumor residue were poor prognosis factors (Fig. 1).

The multivariate analysis based on initial patient – (age 75, gender) and tumor-related factors (capsular invasion, spread to adjacent organs and node invasion), without taking into account the therapeutic modalities, allowed significant Cox model classification of the following as poor prognosis factors: age superior to 75, followed by node invasion, capsular invasion, and finally female gender.

By adding the treatment factors (tumor residue after surgery, surgery or radio ± chemotherapy according to the tumor residue) to the above-mentioned prognosis factors and after the elimination of nonsignificant variables (gender, local extension, metastasis) therapeutic modalities prove to be nonsignificant.

### 5. Discussion

The epidemiological data of our retrospective study were generally similar to those observed in larger studies regarding incidence (<2% of all thyroid cancers) [2,3,6–9] and average age of diagnosis [10–15]. The M/F ratio seemed to be much smaller, while the existence of personal thyroid history was higher [10–15] (Figs. 2 and 3).

The limited number of patients, the systematic search for thyroid history in the collection of data from the register and especially the iodine deficiency in the region may explain this difference.

Similarly to our group of patients, the very rapidly enlarging throat mass has been described in many studies [16–21]. For compression signs, the results are shown in Fig. 4. The concept of the rapid clinical course of ATC is widely recognized, with tumor size doubling sometimes within one week [2,3,21,22]. For tumor size, our results were quite similar to those of other retrospective studies: average tumor size 7 to 8 cm, range 3 to 20 cm [13,16,23–26]. The extension to the adjacent anatomic structures at the time of the diagnosis was also very common (more than 60% of cases and up to 98% in some studies) [13,27]. Nodal involvement was present in the same proportion as published by Ain KB (in over 40% of cases) [23]. However, metastases at diagnosis were more frequent (20 to 50%) in the literature [2,3]. We hypothesize that in some patients in poor general condition, search for metastasis was not systematic because of the decision to deliver palliative treatment.
Different cell types within the same tumor have been described by Carcangiu et al. [7]. Since ATC generally arises from dedifferentiation of an initially differentiated thyroid tumor, finding an ATC and a differentiated cancer in the same patient can be expected [9,17–19,28]. The population of differentiated tumor cells might disappear completely when the dedifferentiation process has progressed over a long period of time [7,23,29].

Surgery is the best therapeutic option and must be carried out whenever possible [17,24]. Regarding radiation therapy, several studies have shown, as has our study, that cervical radiation improves local control of the tumor process and that hyperfractionated local and accelerated radiation at cumulative doses above 45 Gy produces a very positive outcome in terms of local control and possibly increased survival [20,30].
ATC is often discovered at a stage of regional extension or metastasis, and many studies have shown that it is useful to use chemotherapy. Due to the very small number of patients who received chemotherapy in our series, it is difficult to identify the benefits in terms of survival and tumor control in comparison with other studies. A multimodal treatment involving surgery first, followed by adjuvant radiotherapy, is beneficial for patients in terms of survival [31,32]. However, the benefit of chemotherapy is controversial [12,13,15,31,33,34].

If surgery cannot be macroscopically complete, the current recommendations, including the consensus conference proposed by the American Association of Clinical Endocrinologists (AACE) and by the American College of Endocrinology (ACE) is the association of neoadjuvant chemotherapy with radiotherapy to reduce tumor mass before surgical resection [30]. It should be noted that none of the patients in our series underwent this procedure.

Reported survival time has varied from 3 to 7 months [6,9,14–17,20,22,25,32,34] (Fig. 5). Several factors have been reported to have a negative impact on survival, including patient- and tumor-related characteristics and therapeutic modalities. In the literature, old age, poor general condition, rapid growth of a pre-existing goitre, tumor size, local tumor extension and distant metastases are factors of poor prognosis because of tumor aggressiveness and difficulties in carrying out a complete surgical resection [12,14,15,17–20,22,33,36]. When a small contingent of anaplastic cells is associated with a differentiated carcinoma, the prognosis is better probably because of a very early stage of diagnosis [8,10,11,18,19,23,28,34]. Regarding treatment, the best prognosis is recorded after complete macroscopic surgical resection in patients free of metastasis [10,12,17,28].

In univariated analysis, our study shows that age above 75 years, capsular invasion and node invasion are factors of poor prognosis, although neither the absence of a differentiated cancer nor the size of the tumor are factors of poor prognosis. Tumor spread to adjacent cervical structures and female gender tend to be factors of poor prognosis, without reaching significance. The fact that in our study there were few metastatic patients at the moment of diagnosis and that they had a better prognosis is an unusual situation. The search for extension was probably not exhaustive in our patients or was carried out partially in patients in a poor general condition for whom the choice of therapies was limited. It is also possible that the horrifying reputation of this type of tumour limited the complementary studies to the simplest clinical and complementary tests, which were not sensitive enough to allow for an accurate detection of metastatic spreads.

In the literature, hyperfractionated local and accelerated radiotherapy has demonstrated its advantage for better local control of the tumor and for reducing the number of local recurrences [35–37]. The possibility to perform a multimodal treatment combining surgery, radiotherapy and/or chemotherapy has led to an improvement in the average survival time in many studies. At the present time, no one protocol of multimodal treatment has shown its superiority [24,31,38–40]. In our study, a multivariate Cox model analysis found only age above 75, followed by node invasion, capsular invasion, and finally female gender as factors of poor prognosis. Treatment factors (tumor residue after surgery, surgery or radio ± chemotherapy according to the tumor residue) proved to be nonsignificant. Tumor residue after surgery was probably not significant because of its relationship to the four clinical parameters.

6. Conclusion

ATC is fortunately rare but remains the most aggressive of all solid tumors in humans. The prognosis of this disease is poor despite therapeutic progress in recent years [41]. The factors of good prognosis are identified, offering a chance for a longer survival time, but without a definitive cure. Thus, a younger patient without a major medical history, with an early diagnosis (no signs of compression), with a cancer limited to the thyroid (no capsular invasion, no local extension, no lymphadenopathy, no metastasis), and with a content of differentiated cells is more likely to survive for a longer time. Such a patient is a good candidate for aggressive multimodal treatment (complete macroscopic surgery followed by radiotherapy and chemotherapy).
References


