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Prognostic Factors and Survival Score for Patients With Anaplastic Thyroid Carcinoma: A Retrospective Study from a Regional Registry

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Abstract. *Background/Aim: Anaplastic thyroid carcinoma (ATC) is the least common but most lethal of thyroid cancer, despite various therapeutic options, with limited efficacy. In order to help therapeutic decision-making, the purpose of this study was to develop a new prognostic score providing survival estimates in patients with ATC. Patients and Methods: Based on a multivariate analysis of 149 retrospectively analyzed patients diagnosed with ATC from 1968 to 2017 at a referral center, a propensity score was developed. A model was generated providing survival probability at 6 months and median overall survival estimates. Results: The median survival was 96 days. The overall survival rate was 35% at 6 months, 20% at 1 year and 13% at 2 years. Stepwise Cox regression revealed that the most appropriate death prediction model included metastatic spread, tumor size and age class as explanatory variables. This model made it possible to define three categories of patients with different survival profiles. Conclusion: Distant metastasis, age and primary tumor size are strong independent factors that affect prognosis in patients with ATC. Using these significant pretreatment factors, we developed a score to predict survival in these patients with poor prognosis.*

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Although anaplastic thyroid carcinoma (ATC) is rare, it is one of the most aggressive malignancies. This type of carcinoma accounts for 1.7% of all thyroid malignancies and one-half of all thyroid cancer deaths (1, 2). The median survival for patients with ATC is 3-6 months, and it has a 1-year survival rate of 20% (3-6). Indeed, ATC most commonly presents in elderly patients with poor performance status, making it difficult to tolerate an active therapeutic approach (7), although some patients survive for a relatively long time after aggressive treatment (8, 9). In such frail patients, aggressive treatment may worsen the quality of life and occasionally even shorten survival; therefore, the selection of patients who will benefit from such aggressive multimodal therapy seems important. Optimal ATC treatment is questionable due to lack of randomized trials; most studies validate the benefit of surgery. Although some reports questioned the benefit of radiotherapy (10), improved survival has been shown with post-operative radiotherapy (11) and radiation dose escalation was also associated with longer survival rates in selected patients with metastatic disease (12). Combined chemoradiotherapy was favored over radiation alone (13, 14). However, several series reported no benefit for chemotherapy (6, 15). Retrospective studies identified some prognostic factors such as age, gender, presence of acute symptoms, tumor size, multicentricity, metastatic spread, white blood cell level, blood platelet level and serum albumin level, influenced survival of patients with ATC (13, 16, 17). Here, we reviewed data from 149 patients with ATC in an attempt to identify subsets of patients that either would benefit best from a more aggressive treatment strategy or for whom palliative care would be most appropriate.

Patients and Methods

Patients. We reviewed the medical records of 149 patients with ATC treated at the Institut Godinot (Reims, France) between 1962 and 2017. Data come from a regional registry of a single institution as ATC requires specific care that only the Institut Godinot can offer in the Champagne Ardennes region (North-East of France). We included all patients for whom ATC diagnosis had been confirmed in pathology. Other histologies such as malignant lymphoma, medullary carcinoma, or poorly differentiated insular carcinoma were excluded. For each patient, the following variables were collected: Gender, age, metastatic spread, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), nodal involvement, tumor size, clinical symptoms (dysphagia, hoarseness and dyspnea), hematological markers before treatment (white blood cell count, lymphocyte count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR) and platelet count), latest patient status and treatment received (surgery, radiotherapy, and chemotherapy). Authors indicate the procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration.

Statistical analysis. All available data on the registry were used to maximize the power and generalizability of the results. Patient characteristics are reported as frequencies and proportions, and mean and standard deviation. Kaplan–Meier curves were used to visualize the cumulative probability of survival. Comparison between groups was performed only for variables with less than 25% missing data, using the likelihood ratio test. Continuous variables for which the hypothesis of log-linearity was not acceptable were dichotomized using a relevant clinical threshold or median and were included in this form in the multivariate model. A multivariate Cox proportional hazards model was used to examine overall survival after adjustments for clinical and demographic factors. A complete case analysis was undertaken. Each of the variables was entered into a stepwise regression (forward and backward) designed to minimize the Akaike Information Criteria. This allowed selection of a model taking into account n prognostic variables (X_i to X_n) with ci categories. The patients were then divided into $c_1*c_2*\ldots*c_n$ categories according to the prognostic variables they presented. Finally, the categories were grouped together to propose a means of classifying patients in a simple way. Significance was determined at $p<0.05$ for all statistical tests.

Results

Baseline patient and tumor characteristics are shown in Table I. Of the 149 patients, 93 (63%) were women. The median age of patients was 72.9 years (range=20-91 years) and 25% had an ECOG-PS score of 2 or more. Clinical data were unknown in 44 cases. Of the 105 remaining patients, 44% had hoarseness, 46% had dysphagia and 36% dyspnea. Seventy-four patients had at least one of these three physical symptoms (71%). At the time of diagnosis, 51 had metastatic spread (35%). Data on nodal involvement were missing in 49 cases. Of the 100 remaining patients, 73 had lymph nodal involvement (73%). Tumor median size was 70 millimeters (range from 20 to 200 millimeters). Concerning hematological markers, 48% (n=71) was missing. The median counts for white blood cells, neutrophils, lymphocytes and platelets were 10.2, 7.9, 1.3 and 253×10^6/l, respectively. The median NLR was 5.7 (mean=7.8). Regarding management, 125 (86%) underwent surgery, 98 (70%) received radiotherapy (median=46 Gy, range=8-74 Gy), 55 (37%) received chemotherapy. Complete surgery (including immediate or deferred total thyroidectomy) and partial surgery (including lobectomy, partial lobectomy, isthmectomy, lobo-isthmectomy and subtotal thyroidectomy) was performed for 65 (48%) and 43 (32%) patients, respectively. Among patients who received radiotherapy, 32 (33%) were treated with a palliative dose (8-30 Gy) to relieve local symptoms and 66 (67%) were treated with a curative dose (46-74 Gy), 34 with post-operative radiotherapy and 32 with definitive radiotherapy. The median survival was 96 days as shown in Figure 1. One hundred and thirty-one patients died of their disease; 12 patients died of other causes. The overall survival rate was 35% at 6 months, 20% at 1 year and 13% at 2 years. Most of the patients (86%) died within 17 months; 17% died within the first month, 35% lived for 1-6 months and 47% of the patients lived longer than 6 months after the initial consultation.

Univariate analysis of prognostic variables was carried out based on the length of survival of the 149 patients, and the results are shown in Table II. Patients with metastatic spread at presentation, nodal involvement, tumor size greater than 75 mm, age greater than 75 years, ECOG-PS score of 1 or more or the presence of at least one clinical sign had a significantly shorter survival time. Dysphagia alone, dyspnea alone and hoarseness alone were not statistically significant. Multivariate analysis (Table III) revealed that metastatic spread ($p=0.026$), advanced age ($p=0.013$) and larger tumor size ($p=0.026$) were the most important and independent factors for predicting death from ATC.

Stepwise regression selected a model taking into account three binary prognostic variables: The metastatic stage, the age class, and the size class of the lesion (with a cut-off of 75 mm). The patients were divided into eight categories according to the prognostic variables they presented. Then patients with one or two pejorative prognostic factors were grouped together resulting in three categories of patients: Those with no pejorative prognostic factor, who had a survival probability at 6 months of 0.84 [95% confidence interval (CI)=0.69-1.00; median survival=3,769 days]; patients with one or two pejorative prognostic factors, with a survival probability at 6 months of 0.32 (95% CI=0.22-0.46) (median survival=109 days, hazard ratio=5.17 2.66-10.02); and those with three pejorative prognostic factors, who had a survival probability at 6 months of 0.11 (95% CI=0.018-0.71) [median survival=48 days, hazard ratio=11.94 (4.66-30.60)]. The Kaplan–Meier survival curves of the three groups are shown in Figure 2.

Table I. *Patient and tumor characteristics of the 149 patients with anaplastic thyroid carcinoma.*

Characteristic (eligible for analysis)	Value
Age, years	
Median (range)	72.9 (20-91)
<75 Years	85 (57)
>75 Years	64 (43)
Gender, n (%)	
Male	56 (38)
Female	93 (62)
ECOG-PS score, n (%)	
0	35 (36)
1	37 (39)
≥2	24 (25)
Clinical signs, n (%)	
None	31 (30)
At least one	74 (70)
Dyspnea	36 (34)
Dysphagia	46 (46)
Hoarseness	49 (44)
Tumor size, mm	
Median (range)	70 (20-200)
<75 mm	64 (53)
>75 mm	57 (47)
Nodes involvement, n (%)	
Yes	73 (73)
No	27 (27)
Distant metastasis, n (%)	
Yes	51 (35)
No	94 (65)
Hematological markers, n (%)*	
White blood cell count	10.4×10^6/l
Neutrophil count	8.2×10^6/l
Lymphocyte count	1.4×10^6/l
Neutrophil-lymphocyte ratio	7.8
Platelet count	270.8×10^6/l

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status. *Mean values.

Table II. *Univariate analysis for overall survival.*

Factor	HR (95% CI)	*p*-Value
ECOG-PS ≥1	2.7 (1.6-4.5)	**<0.001**
Nodal involvement	2.7 (1.5-5)	**<0.001**
Metastatic spread	2.2 (1.5-3.2)	**<0.001**
Age >75 years	2.1 (1.5-3)	**<0.001**
Tumor size >75 mm	2.1 (1.4-3.3)	**<0.001**
At least one local clinical sign	1.7 (1.1-2.8)	**0.025**
Dysphagia	1.5 (0.94-2.3)	0.093
Hoarseness	1.2 (0.79-1.9)	0.35
Dyspnea	1.1 (0.69-1.7)	0.69

CI: Confidence intervaI; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; HR: hazard ratio. Statistically significant *p*-values are shown in bold.

Table III. *Multivariate Cox proportional hazard models for overall survival.*

Factor	HR (95% CI)	*p*-Value
At least one local clinical sign	3.0 (1.1-8.7)	**0.038**
Age >75 years	2.2 (1.2-4.0)	**0.013**
Tumor size >75 mm	2.1 (1.1-3.9)	**0.026**
Metastatic spread	2.0 (1.1-3.7)	**0.026**
ECOG-PS score >1	1.9 (0.8-4.7)	0.16

CI: Confidence intervaI; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; HR: hazard ratio. Statistically significant *p*-values are shown in bold.

Discussion

Anaplastic thyroid carcinoma is a rare (1-2%), extremely aggressive malignancy that has a very poor prognosis. In our study, the median survival time was 96 days and 128 (86%) of the 149 patients died within 17 months of being diagnosed with ATC. However, 18 (12%) patients survived for more than 4 years. A long remission therefore seems achievable in a limited number of patients with certain favorable factors at the time of diagnosis. These results are in line with the literature (1, 3, 4, 6, 18, 19). This study focused on pretreatment prognostic factors in order to provide assistance to the initial consultation of patients with ATC. An increasing number of studies are investigating molecular prognostic factors that can potentially be identified at the time of diagnosis (20-26). Thus, high expression of enhancer of zeste homolog 2; β-catenin; MCL1 apoptosis regulator, BCL2 apoptosis regulator family member; and programmed cell death protein 1 seem to be associated with a worse prognosis (20, 22, 24, 25). On the contrary, positivity for paired box gene 8 correlated with statistically significantly better OS (21). Epidermal growth factor receptor is overexpressed in ATC and *in vivo* results showed that gefitinib had significant antitumor activity against ATC in a subcutaneous nude mouse tumor model (26). However, gefitinib did not demonstrate efficacy in patients with advanced thyroid cancer (27). Furthermore, between 20% and 50% of ATCs harbor activating B-Raf kinase (*BRAF*) V600 mutations with unknown prognostic significance (23, 28). For patients with *BRAF* V600E-mutated ATC, combined inhibition of BRAF and mitogen-activated extracellular-signal-regulated kinase (dabrafenib plus trametinib) appears to be a promising new targeted therapy, demonstrating a high overall response rate, prolonged duration of response, and prolonged survival with manageable toxicity (29). However, the routine use of such targeted treatments or molecular markers does not seem feasible in the near future.

We identified several studies in the past two decades that focused on non-molecular pretreatment prognostic factors in patients with ATC (11, 13, 30-41). Only one provided a prognostic index based on data from 44 patients (40). The

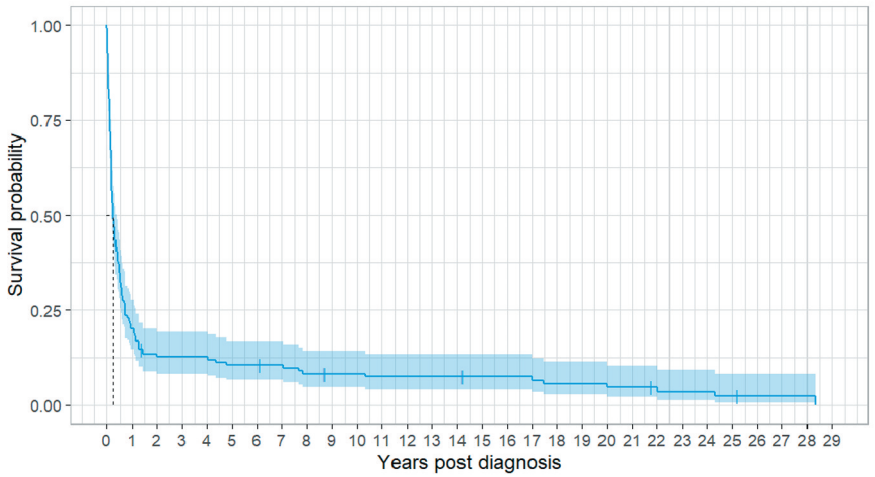

Figure 1. *Overall survival of patients with anaplastic thyroid cancer (n=149).*

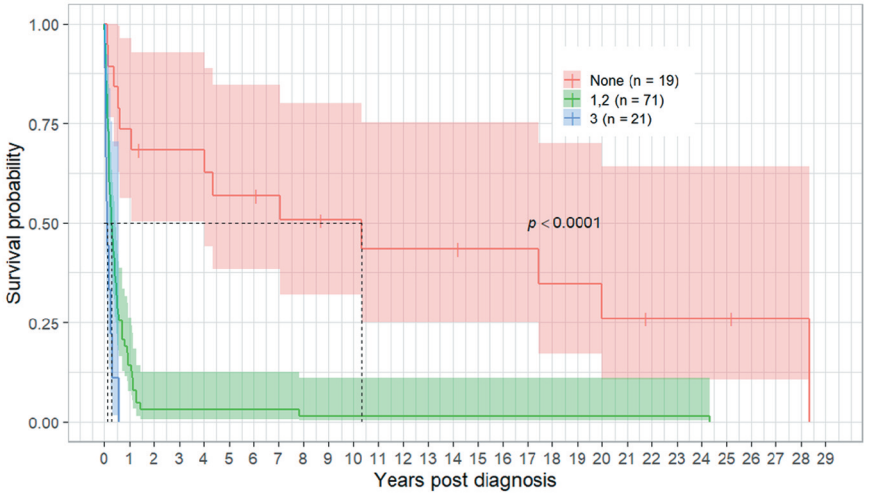

Figure 2. *Kaplan–Meier survival curves for patients with anaplastic thyroid cancer stratified by number of pejorative prognostic factors.*

following factors were significantly associated with survival in patients suffering from ATC: Metastatic disease (shown in nine of these studies), tumor size (also in nine), age (in seven), white blood cells count (in five), presence of acute symptoms (in three), extrathyroidal invasion (in two), lymph node involvement (in two). The following variables were associated with survival in only one of these studies: Blood platelet level, swollen thyroid gland, serum albumin level, ECOG-PS score, duration of symptoms, and gender.

Concerning hematological markers, we also looked at the NLR. A high NLR is associated with an adverse OS in many solid tumor types (42, 43). Most studies used a cutoff ranging from 2 to 6 (44-51). In our study, the median NLR was 5.2 (mean=7.8). This high median NLR is consistent with the fact that patients with ATC have a poor prognosis. NLR failed to be included in the score due to missing values (48%). To our knowledge, only one study analyzed the prognostic value of NLR in patients with ATC treated with lenvatinib, showing that overall survival was longer in patients with lower NLR (<8) than higher NLR (≥8) (52). Another study did show that NLR can discriminate ATC from poorly or well-differentiated cancer with a cutoff value of 3.8 (53).

While this study had the benefit of including many patients from a regional registry, it suffers from a lack of data. This is mainly due to the long period of patient inclusion (from 1962 to 2017); most of the missing data

came from patients treated prior to 2000. Indeed, biological data, ECOG-PS score, nodal status and clinical signs failed to be collected in 48%, 36%, 33% and 30% of patients, respectively. Thus, although significantly associated with OS in multivariate analysis, clinical signs and lymph nodal invasion were not included in the scoring system.

The final score took into account only the following three factors, making it easy to use in a practical way: Distant metastasis, advanced age and tumor size. Using this score, a new patient with ATC can therefore be classified into one of three groups, allowing physicians to guide management. If a patient experiences all three pejorative factors (survival probability at 6 months=11%), management should be directed towards palliative care. On the contrary, if a patient has none of these factors (survival probability at 6 months = 84%), the treatment should be as exhaustive as possible. Finally, in the delicate situation where a patient presents one or two of these factors (survival probability at 6 months = 32%), a balance between aggressive treatment and preservation of quality of life should be found (54). External validation of the score is still recommended before using in clinical practice.

Conclusion

Most patients with ATC, particularly those with poor pretreatment prognostic factors, derive only a small benefit from even aggressive treatment. However, multimodal treatment might significantly improve the OS of highly selected patients with favorable prognostic factors. In this study, we found that age, metastatic spread and primary tumor size are strong independent factors that affect prognosis in patients with ATC. Using these pretreatment factors, a score was developed to predict survival in order to provide an easy-to-use tool for clinical practice before starting treatment for a patient with ATC. External validation in an additional dataset is needed.

Conflicts of Interest

The Authors declare that they have no competing financial interests.

Authors' Contributions

CMC, SSV, SB wrote the article. CMC, LM, ADT collected data. MP, MB performed the medical statistical analysis. All Authors read and approved the final article.

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