Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany

Julia Wendler^{1,*}, Matthias Kroiss^{1,*}, Katja Gast², Michael C Kreissl³,
Stephanie Allelein⁴, Urs Lichtenauer^{5,†}, Rainer Blaser⁶, Christine Spitzweg²,
Martin Fassnacht⁷, Matthias Schott⁵, Dagmar Führer⁸ and Vera Tiedje⁸

¹Department of Internal Medicine I, Division of Endocrinology and Diabetes, University of Würzburg, University Hospital Würzburg, Würzburg, Germany, ²Department of Internal Medicine II, University Hospital Munich, Ludwig-Maximilians-Universität München, München, Germany, ³Department of Nuclear Medicine, Central Hospital Augsburg, Augsburg, Germany, ⁴Division for Specific Endocrinology, University Hospital Düsseldorf, Düsseldorf, Germany, ⁵Department of Internal Medicine IV, University Hospital Munich, Ludwig-Maximilians-Universität München, München, Germany, ⁶Technical University Munich, Klinikum rechts der Isar, Institute for Medical Statistics and Epidemiology, München, Germany, ⁷University of Würzburg, Comprehensive Cancer Center, Würzburg, Germany, and ⁸Department of Endocrinology and Metabolism, University Hospital Essen, University Duisburg-Essen, Essen, Germany

* (J Wendler and M Kroiss contributed equally to this work)

† (U Lichtenauer is now at Helios Kliniken Schwerin, Wismarsche Straße, Schwerin, Germany)

Correspondence
should be addressed
to M Kroiss or V Tiedje

Email

Kroiss_M@ukw.de or
vera.tiedje@uk-essen.de

Abstract

Context: Anaplastic thyroid carcinoma (ATC) is an orphan disease and confers a dismal prognosis. Standard treatment is not established.

Objective: The aim of this study is to describe clinical characteristics, current treatment regimens and outcome of ATC and to identify clinical prognostic markers and treatment factors associated with improved prognosis.

Design: Retrospective cohort study at five German tertiary care centers.

Patients and methods: Totally 100 ATC patients diagnosed between 2000 and 2015 were included in the analysis. Disease-specific overall survival (OS) was compared with the Kaplan–Meier method and log-rank test; Cox proportional hazard model was used to identify risk factors.

Results: The 6-month, 1-year and 5-year disease-specific OS rates were 37, 28 and 5%, respectively. Stage-dependent OS at 6 months was 78, 54 and 18% for stage IVA, B and C, respectively. 29% patients survived >1 year. Multivariate analysis of OS identified age ≥ 70 years, incomplete local resection status and the presence of distant metastasis as significant risk factors associated with shorter survival. Radical surgery (hazard ratio [HR] 2.20, 95% confidence interval (CI) 1.19–4.09, $P=0.012$), external beam radiation therapy (EBRT) ≥ 40 Gy (HR = 0.34, 0.15–0.76, $P=0.008$) and any kind of chemotherapy (CTX) (HR = 11.64, 2.42–60.39, $P=0.003$) were associated with longer survival in multivariate analyses adjusted for age and tumor stage. A multimodal treatment regimen was significantly associated with a survival benefit (HR = 1.04, 1.01–1.08, $P<0.0001$) only in IVC patients.

Conclusion: Disease-specific OS is still poor in ATC. Treatment factors associated with improved OS provide a rationale to devise treatment pathways for routine care. Collaborative research structures should be aimed to advance treatment of ATC.

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Introduction

Anaplastic thyroid carcinoma (ATC) is an orphan disease with an annual incidence of 1–2 per million.

Even though ATC accounts for less than 2% of all thyroid cancers, it is the cause of more than half of all thyroid

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cancer-associated deaths (1, 2, 3). Unlike differentiated thyroid cancer (DTC), ATC confers a disease-specific mortality of nearly 100% (4).

Whereas in DTC, combination of surgery, adjuvant radioactive iodine ablation and TSH-suppressive therapy enable high rates of cure even in cases of extrathyroidal tumor manifestation, in ATC extensive disease precludes complete resection in many cases. In addition, lack of sodium iodine symporter (NIS) expression renders radioiodine treatment ineffective (4).

The clinical diagnosis of ATC is usually made upon a rapidly growing neck mass and symptoms caused by extension beyond the thyroid gland and invasion into neighboring organs such as trachea, esophagus and recurrent laryngeal nerve (5).

Multimodal therapy is usually advocated to prevent locoregional complications such as dyspnea, dysphagia and hemorrhage (6). However, most treatment options have low degrees of evidence and case series from single institutions are hampered by long study periods conferring significant bias. Prospective clinical trials are still scarce (7) and only one phase III clinical trial has been published but was prematurely discontinued due to slow recruitment (8).

Whereas in radioiodine refractory DTC tyrosine kinase inhibitors are established (9, 10), data are lacking in ATC and reported results of phase II clinical trials performed with sorafenib and pazopanib show limited efficacy (11, 12). Single case studies have exploited the presence of genetic driver alterations in ATC tumors to apply molecular targeted therapies (13, 14, 15). Even with current treatments, median survival of ATC remains less than 6 months (16, 17) and there is an unmet need of improved treatment options.

Here, we set out to systematically collect 100 cases of ATC from five German tertiary referral centers in order to describe the clinical presentation and current treatment of ATC, to develop clinical prognostic markers and to identify treatments associated with more favorable prognosis.

Patients and methods

Setting

Data were retrieved from patients diagnosed with ATC between 2000 and 2015 in the following tertiary referral centers: Central Hospital Augsburg, University Hospital Düsseldorf, University Hospital Essen, University Hospital Munich and University Hospital Würzburg. The study

protocol was approved by the ethics committee of the University of Würzburg (ID 96/13) and subsequently of all participating centers.

Data acquisition

Data on initial symptoms, diagnostic procedures, surgical interventions, histopathological findings and treatment modalities of ATC cases diagnosed between 2000 and 2015 at six German centers were retrieved by trained personnel at all sites through chart review using specifically designed report forms. The inclusion criteria were age ≥ 18 years and evidence of ATC at histopathologic examination of the primary tumor (or lymph node or distant metastases in seven cases). Pathological reports were available in all but five cases. In those, histopathologic diagnosis was retrieved from other chart documents. The study endpoints were disease-related death or time interval from diagnosis to last follow-up alive. Disease stage was according to UICC (18).

Statistical analysis

Overall survival (OS) after ATC diagnosis was analyzed using Kaplan–Meier method and groups were compared using the log-rank test. For data with non-nominal distribution we used the Mann–Whitney *U*-test. Assessment of risk factors was performed by using the Cox proportional hazard regression model (forward and backward step-up regression). *P* values < 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Version 23.

Results

Clinical characteristics

Clinical characteristics of the 100 patients are provided in Table 1. Median follow-up was 5.7 months (range 0.03–162). Median age at initial diagnosis was 70.5 years (range 38–92). Seventy deaths due to ATC were observed and five patients died due to other causes. Median OS of the 70 disease-specific deaths was 172 days (range 1–3962). The 6-month, 1-year, 3-year and 5-year cause-specific survival (CSS) rates regardless of tumor stage were 35, 26, 18 and 8%, respectively. A total of 29 patients (16 males) achieved disease control exceeding 1 year after initial diagnosis. Mean age of these patients was 62.0 years (range 38–81).

Table 1 Patient characteristics in ATC patients.

Characteristic	No. of patients
Number of patients	100
Sex	
Female	52
Male	48
Age at diagnosis (years)	
Median (range)	70.5 (38–92)
Tumor stage at initial diagnosis*	
IVA	9
IVB	32
IVC	54
Not reported	5
Diameter of largest single tumor node (mm)	
Median (range)	60 (12–160)
Lymph node metastases at initial diagnosis	55
Distant metastases at initial diagnosis	54
Aerodigestive infiltration	31
Esophagus	6
Trachea	18
Both	7
Differentiated tumor part	17
PTC	12
FTC	5
Symptoms at initial diagnosis	
Local swelling/palpable nodule [‡]	66
Hoarseness	28
Dysphagia	33
Dyspnea	20
Others [§]	22
Unavailable	27

*UICC 7th edition 2009; [‡]Lymph node or thyroid gland nodule; [§]Weight loss, stridor, hypernatremia, symptoms of distant metastases.

Symptoms at presentation and tumor stage

Symptoms at primary diagnosis of ATC are shown in Table 1. In almost one-third of patients, information about initial symptoms were not available. Two-thirds of patients were diagnosed due to cervical mass either of the thyroid gland or related to cervical lymph node swelling. Other common complaints were dysphagia (33%), hoarseness (28%) and dyspnea (20%) caused by compression or invasion of adjacent organs such as trachea, esophagus or recurrent laryngeal nerve. Previous thyroid disease included surgery for goiter in six, presence of benign thyroid nodules in three diseases and Hashimoto's thyroiditis in one patient before ATC diagnosis.

Disease was restricted to the thyroid gland (stage IVA) at diagnosis in only 9% of cases. Almost 32% had extrathyroidal infiltration (stage IVB), 55% had cervical lymph node metastases and 54% distant metastases (stage IVC). In 12% metastatic disease was confirmed by biopsy and in 88% metastatic spread was diagnosed by

imaging studies only. Location of distant metastases were lung ($n=51$), mediastinum ($n=14$) and bone ($n=15\%$). Rare cases showed metastatic spread in liver ($n=5$), brain ($n=4$), pleura ($n=3$) and abdominal lymph nodes ($n=1$).

Treatment administered

Complete thyroidectomy either as primary procedure or completion surgery of previous subtotal or hemithyroidectomy was performed in 51% (Table 2). Complete local resection was achieved in only 14%.

Surgery of metachronous cervical lymph node metastases was performed in three patients, of pulmonary

Table 2 Therapeutic characteristics in ATC patients.

Therapeutic regimen	No.
Primary surgery	83
Thyroidectomy	43
Hemithyroidectomy	19
Two-stage thyroidectomy	8
Completion of previous	6
Thyroid surgery	
Tumor reduction	3
Explorative surgery	4
No surgery	17
Resection status	
Local R0	14
Local R1	27
Local R2	52
Local Rx	6
External beam radiation	81
Adjuvant	32
Local palliative	49
Distant metastases*	11
Palliative treatment	
Dose (Gy)	
Median (range)	57.6 (13.5–80)
Chemotherapy [‡]	56
Doxorubicin weekly	25
Paclitaxel weekly	9
Paclitaxel + pemetrexed	8
Doxorubicin + cisplatin	8
Carboplatin + paclitaxel	14
Tyrosine kinase inhibitors	10
Other	10
Multimodal approaches	
Surgery, CTX [§] and EBRT [§]	49
Surgery and EBRT	19
Only surgery	11
Only radiation	9
Radiation + CTX	4
Surgery + CTX	4
Chemotherapy only	0
Best supportive care	4

*All patients who received EBRT of metastases also received EBRT to the neck; [‡]More than one regimen in 18 patients; [§]CTX, chemotherapy; EBRT, external beam radiation therapy.

metastases in two cases and pleurectomy was performed for treatment of pleural metastases in a single case.

Almost 56% of all ATC patients received chemotherapy (CTX, Table 2). Common cytotoxic drugs were doxorubicin, paclitaxel, pemetrexed and platinum-containing regimens. About 10% of patients underwent targeted therapies with pazopanib ($n=4$), sorafenib ($n=4$), erlotinib ($n=1$) and vemurafenib ($n=1$, administered in a case with evidence of BRAF V600E mutation). Almost 18 patients received more than one chemotherapeutic regimen after progression of disease.

About 81% of ATC patients received external beam radiation therapy (EBRT; 32% as adjuvant, 49% as palliative treatment). Median overall dose was 57.6 Gy (range 13.5–80 Gy). Eleven of the forty-nine patients with palliative external beam radiation therapy (EBRT) had EBRT of metastases (bone, $n=6$; brain, $n=3$; mediastinum, $n=2$) in addition to local EBRT. Two patients received a second series of EBRT to the neck due to local recurrence.

Only 49% of patients received a multimodal therapeutic approach defined as surgery, and sequential or simultaneous external beam radiation and chemotherapy.

About 17% of patients underwent tracheotomy and 11% percutaneous endoscopic gastrostomy during the course of the disease for palliation of local tumor complications or side effects of local EBRT.

Tumor stage-dependent OS

The UICC stage-dependent survival is shown in Fig. 1. Stage-dependent median OS was 26, 11 and 3 months for stage IVA, IVB and IVC, respectively ($P<0.0001$ by log-rank). The 6-month and 1-year CSS were 78 and 66% (IVA), 54 and 39% (IVB), and 18 and 13% (IVC) ($P<0.0001$ by log-rank).

Pre-therapeutic factors of prognosis

Patient- and tumor-related factors were assessed for prognostic relevance with OS and 6-month and 1-year survival rates as endpoints (Table 3). Univariate analysis using Cox proportional hazard modeling revealed the following factors to be significantly associated with improved outcome: age <70 years, absence of metastases (lymph node and distant), absence of aerodigestive infiltration and complete local tumor resection. After multivariable adjustment statistical significance was retained for age <70 years, presence of distant metastases and complete local tumor resection.

Treatment-related factors of prognosis

After multivariable adjustment for age and tumor stage, radical surgery (HR=2.201, 1.186–4.086, $P=0.012$), EBRT (HR=0.339, 0.152–0.759, $P=0.008$), any kind of CTX (HR=11.636, 2.242–60.394, $P=0.003$), and – most importantly – a multimodal therapeutic regimen of combined surgery, EBRT and chemotherapy (HR=0.050, 0.009–0.276) were significantly associated with improved OS (Fig. 2A).

To explore the impact of different chemotherapies on survival, we focused on those patients who received surgery, EBRT and chemotherapy and found treatment with combined paclitaxel and pemetrexed to be associated with statistically significant likelihood of longer OS compared with other chemotherapeutic regimens ($P<0.001$, Mann–Whitney U -test, Table 4).

Stage-dependent treatment outcome

In order to gain insight into the impact of treatment in a stage-specific manner, we analyzed treatment-related disease-specific OS separately for each stage (Table 5). The low number of patients precluded this type of analysis in stage IVA.

Figure 1

Kaplan–Meier analyses of overall survival by tumor stage: IVA ($n=7$), IVB ($n=29$), IVC ($n=47$). Log-rank test $P<0.0001$.

Univariate analysis demonstrated a significantly longer survival for EBRT ≥ 40 Gy compared with < 40 Gy in stage IVB patients ($P=0.017$) and any kind of CTX versus no CTX and EBRT ≥ 40 Gy vs < 40 Gy in stage IVC patients ($P<0.0001$ and $P=0.004$). Combination of treatment modalities such as surgery, EBRT and CTX was associated with more favorable outcome in IVC patients ($P=0.012$).

After multivariate adjustment for age, in IVB patients external beam radiation ≥ 40 Gy (HR=0.109, 0.019–0.631, $P=0.013$) and in IVC patients CTX (HR=0.231, 0.083–0.641, $P=0.005$) remained associated with significantly longer OS.

In stages IVA and IVB, all patients received additional treatment beyond surgery.

Combination of surgery with either CTX or EBRT versus surgery combined with CTX and EBRT showed no statistically significant association with OS in stage IVA OS (HR=1.589, 0.159–15.930) and stage IVB (HR=0.772, 0.267–2.234). At variance, a multimodal therapeutic regimen combining radical surgery with sequential or simultaneous CTX and EBRT showed a survival benefit in IVC patients (HR=0.1, 0.03–0.31, $P<0.0001$). Surgery combined with either CTX or EBRT alone had no statistically significant benefit compared with surgery alone in stage IVC (HR=0.490, 0.02–1.44) (Fig. 2B).

Table 3 Prognostic factors in ATC patients. Bold values indicate statistical significance $P<0.05$.

Prognostic factors	Univariate analyses				Multivariate analyses		
	Median survival (days)	6-month survival rate (%)	1-year survival rate (%)	P (log rank)	HR	95% CI	P (cox regression)
Pretreatment factors							
Sex							
Male ($n=48$)	207	37	27	0.132			
Female ($n=52$)	251	32	25				
Age at initial diagnosis (years)							
< 70 ($n=46$)	340	60	33	<0.0001	1.048	1.015–1.082	0.004
≥ 70 ($n=54$)	140	69	29				
T status							
4a ($n=11$)	458	56	44	0.064			
4b ($n=79$)	192	27	21				
N status							
N0 ($n=24$)	537	65	49	0.001	1.601	0.759–4.068	0.217
N1 ($n=55$)	178	24	17				
M status							
M0 ($n=40$)	519	61	48	<0.0001	2.718	1.384–5.342	0.004
M1 ($n=55$)	148	17	12				
Aerodigestive infiltration							
No ($n=67$)	304	42	33	0.005	1.915	0.901–4.068	0.091
Yes ($n=31$)	140	23	15				
Complete local resection							
Yes ($n=14$)	1098	71	71	0.001	5.539	1.858–16.514	0.002
No ($n=79$)	180	30	20				
DTC tumor part							
No ($n=78$)	197	32	28	0.179			
Yes ($n=17$)	395	55	24				
Treatment factors*							
Thyroid surgery							
Radical ($n=51$)	264	33	28	0.376	2.201	1.186–4.086	0.012
Other or none ($n=49$)	169	37	25				
External beam radiation							
≥ 40 Gy ($n=61$)	366	50	38	<0.0001	0.339	0.152–0.759	0.008
< 40 Gy ($n=14$)	124	9	0				
Chemotherapy							
No ($n=44$)	131	21	17	0.003	11.636	2.424–60.394	0.003
Yes ($n=56$)	338	45	33				

*Corrected for age and tumor stage at initial diagnosis.

Figure 2

(A) Kaplan–Meier curve: therapy-dependent survival. Log-rank test ($P < 0.0001$); (B) box plots: survival analyses by tumor stage according to treatment.

Discussion

Despite an increasing number of publications over the past ten years, the available evidence is still limited to estimate prognosis and to provide evidence for optimal treatment of ATC. Sugitani *et al.* collected the largest ATC cohort yet published including 677 patients (19). The second largest study by Kebebew *et al.* (2) reported on 516 ATC patients of the U.S. National Cancer Institute's Surveillance, Epidemiology and End Results diagnosed between 1973 and 2000.

Table 4 Survival-dependent administered chemotherapeutic regimen.

Chemotherapeutic drug*	Survival (days)	P (Mann–Whitney U-test)
Doxorubicin weekly		
Yes (n=20)	316.5	0.784
No (n=29)	380	
Paclitaxel weekly		
Yes (n=9)	239	0.869
No (n=40)	345.5	
Paclitaxel and pemetrexed		0.001
Yes (n=9)	651	
No (n=40)	252	
Paclitaxel and carboplatin		0.610
Yes (n=13)	438	
No (n=36)	316.5	
Doxorubicin+ cisplatin		0.165
Yes (n=7)	235	
No (n=42)	383.5	
TKI		0.113
Yes (n=9)	519	
No (n=40)	238.5	

Bold values indicate statistical significance $P < 0.05$.

*Analyses only contain the 49 patients who received multimodal treatment including surgery, external beam radiation and chemotherapy; TKI, tyrosine kinase inhibitor.

In the present study, we included data of 100 patients with ATC diagnosed between 2000 and 2015 at five German tertiary referral centers. In comparison with the studies mentioned above, our case collection has the advantage that source data of ATC were retrieved from the case records using specifically designed report forms and trained personnel. In addition, our study is likely to more closely mirror contemporary treatment practice given the more recent time frame of the study. However, our study suffers from its retrospective nature and referral bias since only tertiary care centers were included.

In this cohort, OS and 1-year survival rates were similar to data reported earlier. Median OS and 1-year survival rates were 26 months and 66% in stage IVA, 11 months and 39% in IVB and 3 months and 13% in IVC. In comparison with the cohorts of Sugitani or Ito *et al.*, this cohort contains a larger proportion of IVC patients (Sugitani *et al.*: IVA 13%, IVB 44%, IVC 12%; Ito *et al.*: IVA 0%, IVB 62.5%, IVC 37.5%; this cohort IVC 54%) The reason for this difference may be related to referral bias given that only tertiary care centers participated in this study.

By applying multivariate analysis, we found age ≥ 70 years, presence of distant metastases and incomplete local tumor resection to be independent risk factors of unfavorable outcome.

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Table 5 Stage-dependent treatment and multimodality of therapy in ATC patients.

Treatment	Univariate analyses				Cox proportional hazards model		
	Median survival (days)	6-month survival rate (%)	1-year survival rate (%)	Log rank P	HR	95% CI	P value
Stage IVA							
Surgery							
Radical (n=6)	526	67	48	0.356			
Other or none (n=3)	1098	100	100				
External beam radiation							
≥40 Gy (n=8)	1098	71	54	0.093			
<40 Gy (n=0)	–	–	–				
Chemotherapy							
No (n=3)	1098	67	67	0.601			
Yes (n=6)	1098	80	57				
Stage IVB							
Surgery							
Radical (n=16)	529	57	49	0.349			
Other or none (n=16)	478	62	43				
External beam radiation							
≥40 Gy (n=24)	604	26	20	0.017	0.109	0.019–0.631	0.013
<40 Gy (n=2)	183	0	0				
Chemotherapy							
No (n=13)	381	51	38	0.571			
Yes (n=19)	548	63	50				
Stage IVC							
Surgery							
Radical (n=27)	155	9	9	0.661			
Other or none (n=27)	137	22	10				
External beam radiation							
≥40 Gy (n=27)	257	71	56	0.004	0.549	0.211–1.432	0.220
<40 Gy (n=12)	117	50	0				
Chemotherapy							
No (n=26)	100	0	0	<0.0001	0.231	0.083–0.641	0.005
Yes (n=28)	258	28	18				

Bold values indicate statistical significance $P < 0.05$.

This is in accordance with the data by Sugitani *et al.* (19) who found age ≥ 70 years, presence of acute symptoms and leukocytosis at initial diagnosis, T4b tumor, diameter of tumor size > 5 cm and distant metastasis to be independent predictors of poor OS, which is in line with previous results (20). The study from the National Cancer Institute (2) concluded that age < 60 years, intrathyroidal tumor mass and surgery combined with radiotherapy are independent favorable prognostic factors of disease-specific mortality that is similar to smaller cohorts (21, 22).

Given that the therapeutic management of ATC has not been firmly established, we queried our data for treatments associated with improved prognosis.

Surprisingly, complete thyroidectomy was not significantly correlated with longer OS in univariate analyses. As previous studies (2, 19) strongly suggested a beneficial effect, we adjusted for tumor stage and age and confirmed a significant association of complete

surgery with improved outcome. Of note, microscopically complete local resection was achieved in only 17.6% of patients in our cohort. This is at variance to other cohorts where complete local resection rates of 30% (23) and 31% (9 out of 29) were reported (24). However, it has been stated earlier (25) that the significance of complete thyroidectomy remains a matter of controversy due to the majority of unresectable tumors at initial diagnosis and the important morbidity related to aggressive local resection (26).

It is a remarkable characteristic of our study, that unlike in the studies by Ito *et al.* (25) and Sugitani *et al.* (19), 80% of patients received chemotherapy and/or external beam radiation in addition to surgery with no single patient receiving surgery only in stage IVA and IVB patients. About 49% of all patients received a multimodal treatment combining three modalities. At variance, in previous studies a multimodal approach was applied in 16% in stage IVA (19), 15% (19) and 24% (25), respectively,

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in stage IVB and 0% (25) (not reported by Sugitani *et al.*) in stage IVC.

This may relate to referral bias but also might reflect the fact that in the centers contributing to this study and within the pre-defined timescale, aggressive surgical treatment has partly ceded place to other treatment modalities. Along these lines, data from the entire cohort suggest a treatment benefit from external beam radiation and chemotherapy after adjustment for stage and age.

Considering only patients who received multimodal treatment, not all chemotherapy regimens showed association with improved survival to the same extent. Doxorubicin plus cisplatin was significantly associated with a less favorable prognosis, potentially due to the significant hematologic toxicity. At variance, combined paclitaxel and pemetrexed showed statistically significant association with improved OS in comparison with other regimens. These data have to be interpreted with caution, because only 51 patients received chemotherapy in a multimodal approach with only 8 (paclitaxel + pemetrexed) to 18 (doxorubicin) patients receiving the same regimen.

In a stage-dependent perspective, the low number of patients in stage IVA did not permit statistically significant associations with treatment to be found. In IVB patients we observed a trend toward longer OS with multimodal treatment, which, however, missed statistical significance. This is similar to the data published by Sugitani *et al.* (19) and Higashiyama *et al.* (27); hence, providing a rationale to administer high-dose EBRT and chemotherapies in these cases.

More clearly, in patients with stage IVC, treatment with combined radical surgery, EBRT and CTX was associated with significantly longer OS. However, median OS in the multimodal treatment group was still poor with a median of 330 vs 68 days. It must be stated, that this result may in part be attributable to selection bias. It is conceivable that only patients in good general health received multimodal therapy including radical surgery, external beam radiation and chemotherapy. In the group of patients initially diagnosed at age ≤ 60 years, 76.9% received multimodal treatment compared with 16.7% in patients aged ≥ 80 years of patients. Of note, the retrospective nature of our study precludes conclusions regarding quality of life in all groups, which, however, is of paramount importance in this dismal disease. Further, tumors in this study have not been characterized at the molecular level and hence we cannot offer molecular markers of treatment response.

This multicenter analysis illustrates the heterogeneous treatment approaches applied in ATC patients in

Germany, due to lack of established therapies and the rare and aggressive nature of the disease. To unify and subsequently improve ATC patient treatment in Germany, a therapy protocol was developed by representatives involved in ATC care (endocrine surgery, pathology, endocrinology, radiotherapy and medical oncology). This protocol involves surgery in selected cases, followed by combined EBRT and chemotherapy and mutational screening of known oncogenes with subsequent targeted therapy (28). Importantly, we suggest that all patients should have access to specialized palliative care early in the course of the disease.

In conclusion, this study confirms previous reports implicating age, which may be regarded as a surrogate marker of general performance, and tumor stage as the key factors. For stage IVB and IVC at least, a comprehensive and aggressive multimodal approach including high-dose EBRT and chemotherapy is the current treatment of choice. Whereas none of the retrospective studies published so far was able to recommend for or against a particular combination of cytotoxic chemotherapy, we found a highly significant association of paclitaxel plus pemetrexed with improved outcome, although numbers are small. Owing to the limitations of retrospective analyses, there is a strong argument in favor of a prospective international clinical trial to determine the most favorable chemotherapeutic regimen.

However, given the overall poor outcome of current treatment, it is recommended to include patients into early clinical trials or administer targeted therapies on a compassionate use basis whenever a plausible molecular target can be identified (14, 15, 29).

In the absence of a molecular targeted clinical trial, development of consensus treatment pathways such as the one described above constitute a way to characterize predictors of treatment response and to improve current treatment concepts.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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