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Radiation to the Primary Tumor in Metastatic Anaplastic Thyroid Cancer

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Abstract. *Background/Aim: Metastatic anaplastic thyroid cancer is associated with a dismal prognosis. We evaluated outcome and prognostic factors in patients receiving radiation to the primary tumor in metastatic anaplastic thyroid cancer (ATC). Patients and Methods: All consecutive patients with metastatic ATC (n=20) undergoing irradiation between 2009 and 2019 for anaplastic thyroid cancer were investigated. Results: Median survival time and median progression-free survival were 2 (range=1-22) and 2 (1-20) months. In univariate analyses, surgery, concurrent or sequential chemotherapy and higher radiation dose escalation (>39 Gy) were correlated with longer overall survival (p=0.005, p=0.018 and p=0.038), respectively. Karnofsky performance status >70% showed a trend of longer survival time (p=0.062). Limited metastatic disease, surgery and concurrent/sequential chemotherapy are correlated with longer progression-free survival times (p=0.043, p=0.024 and p=0.039), respectively. Conclusion: Radiation to the primary tumor in metastatic anaplastic thyroid cancer is safe and offers durable local control. Treatment intensification including concurrent or sequential chemotherapy and radiation dose escalation were associated with longer survival rates and should be considered in selected patients with metastatic disease.*

Anaplastic thyroid cancer (ATC) is an orphan disease with a dismal prognosis (1-6). Median survival times range between 3 and 16 months depending on Union for International Cancer Control tumor–node–metastasis (UICC TNM) stage (7-9). National and international guidelines recommend that ATC patients with stage IVA/B should be considered for radical surgery if negative pathological margins (R0/R1) can be achieved and should be avoided if there is a high chance of gross residual disease (R2) (2-5).

However, the majority of ATC patients are considered to be inoperable due to locally advanced disease and comorbidities. So far, no standard treatment regimen has been successfully established in stage IVC (4, 5).

Local radiotherapy (RT) should always be considered as part of the initial multimodal therapy approach to improve overall survival (OS) (6, 9-11) and provide local and symptom control in order to maintain quality of life. However, it is a matter of debate if local RT is still recommended in metastatic disease where aggressive systemic therapy has to be weighed against benefits from local control and limited systemic approaches.

The aim of the present study was to evaluate outcome and prognostic factors in patients receiving radiation to primary tumor of metastatic anaplastic thyroid cancer.

Patients and Methods

Study population. The medical charts of 20 consecutive patients with metastatic anaplastic thyroid cancer treated with irradiation to primary tumor between 2009 and 2019 were reviewed. Patient and treatment characteristics are summarized in Table I. The Institutional Research Ethical Review Board approved the study (approval number: 19-885).

Diagnostics and treatment. ATC was histologically confirmed in all patients and diagnosed as stage IVC according to the revised 8th edition of the UICC TNM classification (7). A lobectomy was performed in two (10%) patients and three (15%) patients had received a total thyroidectomy. Chemotherapy was administered in 9 (45%) patients, of which 5 (25%) patients received concurrent chemotherapy with carboplatin AUC 2 with Paclitaxel 50 mg/m^2 weekly, which has been the standard at our Institution in the recent years, and 3 patients (15%) received concurrent chemotherapy with

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doxorubicin (10 or 20 mg/m2) weekly. Sequential chemotherapy (doxorubicin/cisplatin) was administered in one (5%) patient before radiation. Three-dimensional conformal radiotherapy (3D-CRT) technique was administered in 13 (65%) patients and 7 (35%) patients received intensity modulated radiation therapy (IMRT). The median radiation dose in equivalent dose in 2 Gy fractions (EQD2) was 42 (range=5-70) Gy. Seven potential patient- and treatment-related features, namely age, gender, Karnofsky performance status (KPS), number of involved metastatic sites, surgery, concurrent and sequential chemotherapy and radiation dose escalation were analysed for their impact on OS and progression-free survival (PFS). Treatment-related side-effects were evaluated using Common Terminology Criteria for Adverse events (CTCAE) version 4.

Statistical analysis. Statistical analyses were performed using SPSS statistics 25 (IBM, New York City, NY, SA). The log-rank test was used to compare subgroups. All significant variables in univariate analysis were included in a multivariate analysis (Cox regression). OS was defined as the time between diagnosis and death. PFS was defined as the time between diagnosis and the development of local relapse, distant metastases or death from all causes.

For all statistical analyses, a p-value <0.05 was considered statistically significant.

Results

Median survival time was 2 (range=1-22) months. Survival at 1, 3 and 12 months of the entire cohort was 65, 30 and 5%, respectively. No local progression was observed in the first 12 months after radiotherapy. Progression-free survival was 2 (range=1-20) months. In univariate analyses, surgery (p=0.005), sequential or concurrent chemotherapy (p=0.018) and radiation dose escalation (>39 Gy, p=0.038) resulted in improved OS (Table II), respectively. Karnofsky performance status >70% showed a trend for longer survival time (p=0.062). On multivariate analysis, no factor achieved significance for OS. Limited metastatic sites (1 *vs*. 2-4 sites, p=0.043), surgery (p=0.024) and chemotherapy (p=0.039) are associated with improved PFS (Table III). On multivariate analysis for PFS no factor achieved significance.

Acute toxicity (grade 3) of dysphagia, dyspnea, dermatitis, mucositis and dysphonia were found in 20%, 30%, 5%, 5% and 10% of patients, respectively. CTCAE grade 4/5 was not observed.

Table I. *Patient- and treatment-related characteristics*.

	N	%
Age, years		
<73	10	50
≥73	10	50
Gender		
Female	11	55
Male	9	45
Karnofsky performance status, %		
≤70	14	70
>70	6	30
T stage		
3	1	5
4	19	95
N category		
0	5	25
1	15	75
Number of metastatic sites		
1	11	55
2-4	9	45
Metastatic sites		
Pulmonary	19	95
Distant lymph node	8	40
Bone	3	15
Brain	1	5
Liver	1	5
Surgery		
No	15	75
Yes	5	25
Chemotherapy		
No	11	55
Yes	9	45
Radiation dose, Gy		
≤39	8	40
>39	12	60

T: Tumor, N: nodal, Gy: Gray.

Discussion

The treatment of patients with metastatic ATC should be planned in a multidisciplinary expert team also considering prognostic factors, which allow estimating the patient's prognosis (1, 10, 12). Systemic treatment remains the main treatment of metastatic ATC, but usually results in low response rates and significant toxicities. Treatment with paclitaxel or doxorubicin or combined treatment approaches (*e.g.* carboplatin/paclitaxel, docetaxel/doxorubicin) are recommended (5).

Tumor-related complications such as airway or esophageal obstruction, hemorrhage and vocal cord paralysis can be lethal and should be taken into account for shared-decision making (2-5). Therefore, prognostic factors that indicate the effect of radiotherapy on local control and survival are important to identify high-risk patients who do not achieve a satisfying outcome and may benefit from treatment intensification such as radiation dose escalation or concurrent chemotherapy.

Several studies investigated potential prognostic factors in ATC such as age, presence of acute symptoms, leukocytosis, large local tumors, resection status and distant metastasis (1, 13, 14). Data about prognostic factors in stage IVC are still limited (8, 13, 15).

The present study aimed to evaluate outcome and prognostic factors in patients with metastatic anaplastic thyroid cancer that received radiation to the primary tumor. As a result, cervical irradiation appears to be effective and offers durable local

Table II. *Uni- and multivariate analyses of overall survival.*

	At 1 month,%	At 3 months, %	At 12 months, %	*p*-Value (univariate analyses)	*p*-Value (multivariate analyses)
Age, years					
<73	60	30	10		
≥73	70	30	0	0.47	
Gender					
Female	64	27	9		
Male	67	33	0	0.802	
Karnofsky performance status, %					
≤70	57	21	0		
>70	83	50	17	0.062	
Metastatic sites					
1	73	36	9		
2-4	56	22	0	0.322	
Surgery					
No	53	13	0		
Yes	100	80	20	0.005	0.051
Chemotherapy					
No	44	11	0		
Yes	82	46	9	0.018	0.988
Radiation dose, Gy					
≤39	38	13	0		
>39	83	42	8	0.038	0.415

Gy: Gray.

Table III. *Uni- and multivariate analyses of progression-free survival.*

	At 1 Month, %	At 3 months, %	At 12 months, %	*p*-Value (univariate analyses)	*p*-Value (multivariate analyses)
Age, years					
<73	50	20	10	0.926	
≥73	70	30	0		
Gender					
Female	64	18	9		
Male	56	22	0	0.896	
Karnofsky performance status, %					
≤70	50	14	0		
>70	83	33	17	0.192	
N stage					
0	60	40	20		
1	60	13	0	0.263	
Metastatic sites					
1	64	36	9		
2-4	56	0	0	0.043	0.336
Surgery					
No	47	7	0		
Yes	100	60	20	0.024	0.23
Chemotherapy					
No	44	0	0		
Yes	73	36	9	0.039	0.598
Radiation dose, Gy					
≤39	38	0	0		
>39	75	33	8	0.075	

Gy: Gray.

control of the disease. In our analysis surgery, chemotherapy (carboplatin/paclitaxel or doxorubicin) and radiation dose escalation (>39 Gy) were correlated with longer OS. This is consistent with the findings by Wendler *et al*. who reported a significant association of multimodal treatment approaches with a survival benefit in ATC stage IVC patients (1) as well as the study of Sugitani *et al*. with 223 ATC patients in stage IVC which found that radical surgery (p=0.0002), dose escalated radiotherapy (≥40 Gy) (p<0.0001) and chemotherapy (p<0.0001) were correlated with longer survival rates (13).

A National Cancer Data Base (NCDB) study of 606 patients with ATC stage IVC found a dose-survival correlation in patients receiving 60 to 75 Gy compared to 45 to 59.9 Gy (15). These data go along with the findings of our present study.

Despite local and symptom control, pattern of failure in ATC tends to be metastatic progression, which is consistent with our study (16). We found that a limited number of metastatic sites ('oligometastatic disease') appears to be a prognostic factor for PFS (see Table III) and that these patients may benefit from more aggressive treatment approaches which offer reliable local control and longer OS.

Treatment-related side-effects were manageable according to our study. However, treatment intensification should be discussed in multidisciplinary teams including surgeons, radiation oncologists, endocrinologists, medical oncologists, and palliative care teams.

Due to a substantial increase of druggable tumor-specific molecular aberrations in the past decade, molecular profiling has become an integral part of diagnosis and therapy in oncology, gaining more and more importance in the treatment of ATC. The most frequently investigated single agents or agents in combined treatment approaches are multikinase inhibitors (*e.g.* lenvatinib, sorafenib), PI3K/mTOR inhibitors (*e.g.* everolismus), vascular-targeting agents (*e.g.* fosbretabulin), BRAF-inhibitors (*e.g.* dabrafenib) and checkpoint inhibitors (*e.g.* pembrolizumab, spartalizumab) (17-23).

The combination of BRAF-inhibitor dabrafenib and MEK-inhibitor trametinib achieved approval by the Food and Drug Administration (FDA) in 2018 based on the promising results of a phase II study comprising BRAFV600E-mutated ATC (21). The overall response rate in the ATC-subgroup was 61%, of which 57% experienced a partial and 4% a complete response. In addition, several checkpoint inhibitors such as pembrolizumab, spartalizumab and durvalumab alone or in combination with conventional treatment regimens (RT, ChT) have been investigated (22-24).

Recently, the combination of lenvatinib with pembrolizumab has achieved excellent results in metastatic ATC (25). However, larger trials investigating this combined treatment approach are ongoing and highly anticipated (26).

Several limitations must be considered in interpreting the results of our study such as the retrospective design and, therefore, a risk of including hidden selection biases. In addition, the patient cohort is relatively small with a long recruitment period. However, ATC is an orphan disease and stage IVC is associated with a dismal prognosis. We found that local irradiation offers durable local control in metastatic ATC patients and identified several prognostic factors in this setting. As a result, we are convinced that our study may help physicians to tailor personalized treatment approaches.

In summary, treatment-related side-effects appear to be manageable and therapy intensification including concurrent or sequential chemotherapy and radiation dose escalation were correlated with longer survival rates.

Conclusion

Radiation to the primary tumor in metastatic anaplastic thyroid cancer is safe and offers durable local control. Treatment intensification including concurrent or sequential chemotherapy and radiation dose escalation were correlated with longer survival rates and should be considered in selected patients with metastatic disease.

Conflicts of Interest

There are no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and Design: L.K., T.A., D.O.; Administrative support: C.B., C.S., L.K.; Provision of study materials or patients: L.K., C.S., C.B., J.R.; Collection and assembly of data: L.K., T.A., D.O.; Data analysis and interpretation: L.K., T.A., D.O.; Manuscript writing: All authors; Final approval of manuscript: All Authors.

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