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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Multimodality Treatment Improves Locoregional Control, Progression-Free and Overall Survival in Patients with Anaplastic Thyroid Cancer: A Retrospective Cohort Study Comparing Oncological Outcomes and Morbidity between Multimodality Treatment and Limited Treatment

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ABSTRACT

Background. Patients with anaplastic thyroid cancer (ATC) have poor overall survival, and the optimal management approach remains unclear. The aim of this study is to evaluate our experience with multimodality (MMT) versus limited treatment (LT) for ATC.

Patients and Methods. A cohort study of patients with ATC managed in a tertiary referral center was undertaken. The outcomes of MMT were compared with those of LT. The primary outcome measures were locoregional control and progression-free and overall survival. Secondary outcome measures were treatment-related complications and factors associated with improved survival.

Results. In total, 59 patients (35 females) with a median age of 73 years (range 39–99 years) and ATC stage IVA (n = 2), IVB (n = 28), or IVC (n = 29) were included. LT was utilized in 25 patients (42%), and 34 cases had MMT. MMT patients had a longer time of locoregional control (18.5 versus 1.9 months; $p < 0.001$), progression-free survival (3.5 versus 1.2 months; $p < 0.001$), and overall survival (6.9 versus 2.0 months; $p < 0.001$) when compared

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with LT. For patients with stage IVC ATC, locoregional control ($p = 0.03$), progression-free survival ($p < 0.001$), and overall survival ($p < 0.001$) were superior in the MMT cohort compared with LT. MMT had more treatment-related complications than LT ($p < 0.001$). An Eastern Cooperative Oncology Group performance status < 2 (HR 0.30; $p = 0.001$) and MMT (HR 0.35; $p = 0.008$) were associated with improved overall survival.

Conclusion. MMT is likely to improve locoregional control, progression-free survival, and overall survival in selected ATC patients including stage IVC tumors but comes with a greater complication risk.

Anaplastic thyroid cancer (ATC) is a rare and lethal form of thyroid cancer. Median survival is approximately 6 months.[1] Only 20% of patients presenting with this aggressive disease survive the first year following diagnosis.[2] Individualized treatment in ATC is based on factors such as age, comorbidities, performance status, and disease extent at presentation.[3] ATC can be treated with an aggressive multimodality treatment (MMT) regimen that aims to achieve locoregional control and survival benefit. Alternatively, limited treatment (LT) may be provided to reduce local tumor progression. There is no standard definition of MMT or LT in the setting of ATC. Previous centers that reported MMT outcomes utilized surgery and/or systemic treatment combined with high-dose radiotherapy.[4–22] Intensity-modulated radiotherapy is preferred when available, and a cumulative radiotherapy dosage of at least 50 Gray (Gy) in 20 fractions is recommended as definitive treatment.[3] Radiotherapy dosages higher than 60 Gy in 30 fractions may further improve locoregional control and overall survival.[23] LT can be defined as monotherapy (surgery, radiotherapy, or systemic treatment) or dual therapy with combined surgery, low-dose radiotherapy (<50 Gy), or systemic treatment.[4–8,10,12,14,17,18,20,21] There are few studies comparing the outcomes of MMT versus LT in ATC, and the incorporated treatment modalities are heterogeneous.[5,10,14,15,19,21,24] Studies comparing both approaches report that MMT may improve locoregional control and overall survival when compared with LT in ATC cohorts.[5,10,14,15,19,24] However, the overall locoregional control rates vary greatly per treatment regimen, with reported rates of 50–96% for MMT and 9–55% for LT.[5,14] A similar variation is observed for median overall survival, ranging between 5 and 43 months and 2 and 4 months for MMT and LT, respectively.[5,10,14,15,19,21,24] Previous studies reported conflicting data regarding the overall survival benefit of MMT in stage IVC ATC, and the effect on locoregional control in this patient category is unclear.[25] The advantage of MMT in metastatic ATC therefore remains uncertain. It is suggested that MMT increases treatment-related morbidity compared with LT.[5,14,19] However, a structured comparison of combined surgical complications, systemic treatment toxicity, and radiotherapy morbidity between MMT and LT is lacking. This retrospective single-center study compares locoregional control, progression-free survival, overall survival, total complication rates, and factors associated with survival for ATC patients undergoing MMT or LT.

PATIENTS AND METHODS

Patient Population

The protocol for this single-center retrospective cohort study was approved by the Northern Sydney Local Health District Human Research Ethics Committee. A search query on the diagnosis "anaplastic thyroid cancer" was performed in prospectively established databases of the departments of Endocrine Surgery, Anatomical Pathology, and Radiation Oncology to identify patients eligible for inclusion. Patients with a histopathologically confirmed diagnosis of primary ATC and complete follow-up data were included for analysis. All patients underwent histopathological review of tumor tissue at the Royal North Shore Hospital (RNSH). MMT was administered with optimal locoregional control and a potential survival benefit as the main treatment goal. MMT regimens consisted of a combination of two or more treatment modalities incorporating surgery, radiotherapy, and systemic treatment. Radiotherapy with an intended cumulative dosage of $\geq$ 50 Gy was always incorporated in the bimodal MMT regimen and supplemented with surgery or systemic treatment.[3] A subcategory of patients treated with MMT received targeted molecular therapy with novel agents including tyrosine kinase inhibitors or immunotherapy. LT was defined as single therapy (surgery, systemic treatment, or radiotherapy) or bimodal treatment. Bimodal treatment in the LT cohort consisted of a combination of surgery, systemic treatment, or radiotherapy. When radiotherapy was incorporated in a bimodal LT regimen, the intended cumulative radiotherapy dosage was < 50 Gy.

Outcome Parameters

The primary outcome measures were locoregional control and progression-free and overall survival. These data were compared between MMT and LT. Complication rates and factors associated with improved overall survival in ATC were assessed as secondary outcome measures.

Definitions of Inclusion Criteria and Outcome Variables

Patients were included in each of the cohorts on an intention-to-treat basis. Original hematoxylin-and-eosin-stained slides for patients diagnosed from 1985 were available for review. Slides were reviewed by a pathologist with special expertise in endocrine pathology to confirm the diagnosis (JT/AJG). Diagnosis of ATC was based on the criteria outlined in the 4th edition of the WHO classification of tumours of endocrine organs.[26] Patients were restaged according to the 8th edition of the AJCC/TNM cancer staging system. Restaging was based on neck–chest CT or whole-body PET/CT scans with or without ultrasound, MRI, or bone scans. When not available, chest x-rays (M status) or autopsy reports (TNM status) made within 3 months of initial diagnosis were used. Tumor size was defined as maximum diameter as reported in the histopathology reports or radiology reports from ultrasound or CT scans performed at initial diagnosis. The non-age-adjusted Charlson comorbidity index and Eastern Cooperative Oncology Group (ECOG) performance score were used to classify baseline comorbidity and performance status, respectively. Treatment response was defined according to RECIST criteria and subdivided into local (thyroid bed), regional (locoregional lymph nodes), and distant response. When locoregional or whole-body imaging was not available, treatment response was assessed with chest x-ray reports and reported physical examination. Overall survival was defined as time from initial diagnosis to final follow-up or death. Clavien–Dindo and Common Toxicity Criteria for Adverse Events edition 5.0 were used to report all complications (including complications possibly related to disease progression) that occurred during or within 30 days from surgery, radiotherapy completion, or systemic treatment.

Statistics

Descriptive statistics were used to describe patient, tumor, and treatment characteristics. Differences between groups were assessed using Student's *t*-test, Mann–Whitney *U* tests, and χ^2 tests. Kaplan–Meier survival estimates with log-rank tests were performed to assess the effect of treatment on primary and secondary outcome measures. Multivariate analysis using Cox proportional-hazards model was performed to identify factors associated with overall survival outcomes. The variables age ($\geq$ 70 years versus $<$ 70 years), ECOG performance status ($\geq$ 2 versus $<$ 2), lymph node status at diagnosis (c/pN1 versus c/pN0), distant metastasis at diagnosis, tumor size ($\geq$ 60 mm versus $<$ 60 mm), tumor histopathology, margin status (macroscopic involved versus clear), percentage of ATC in the primary tumor ($\geq$ 50% versus $<$ 50%), and therapeutic regimen (MMT versus LT) were included in the multivariate model. Significance was set at $p < 0.05$. Statistical Package for the Social Sciences (SPSS, Version 25, International Business Machines Corp, Armonk, USA) was used for statistical analysis.

RESULTS

Patient and Treatment Characteristics

A total of 59 ATC patients treated between 1987 and 2019 were included in the study population (Fig. 1). The median diameter of the primary tumor at initial diagnosis was 68 mm. A detailed overview of baseline characteristics is provided in Table 1. The majority of patients were female (59%) with a median age of 73 years (range 39–99 years). Twenty-seven patients (46%) had a history of thyroid disease, and 20 (34%) had long-standing multinodular goiter. A rapidly enlarging neck mass was the most common presentation, occurring in 38 cases (64%), while 28 (47%) had hoarseness of voice at presentation. A description of the presentation, work-up, and staging of the entire cohort is outlined in the Supplementary Text and Supplementary Tables I and II. Following diagnosis, patients were treated with MMT (n = 34) or LT (n = 25) according to the multidisciplinary team recommendations given at the time. Median follow-up time was 4.1 months (range 0.1–46.7 months) for the entire study poulation. Median follow-up time for the MMT and LT cohorts was 6.7 and 2.0 months, respectively. Patients treated with MMT were younger (p = 0.01), had a lower ECOG performance score at presentation (p = 0.01), and smaller tumor size (p = 0.001) prior to treatment than patients receiving LT (Table 1). Both groups were equivalent for comorbidities, tumor stage at presentation, and percentage of the primary tumor that comprised ATC.

Treatment details per cohort are provided in Table 2. All patients undergoing MMT received radiotherapy to the thyroid bed, 29 (85%) underwent thyroid surgery, and 32 (94%) received one or more systemic treatments. Out of 35 patients undergoing MMT, 16 were treated with concurrent chemoradiotherapy. Following initial radiotherapy to the primary tumor, 8 (24%) of the MMT patients received additional radiotherapy for local recurrence or distant disease progression, 13 (38%) received multiple systemic therapies, and 7 (21%) received targeted molecular therapy with tyrosine kinase inhibitors (TKIs) and/or immunotherapy. Patients receiving TKIs and/or immunotherapy were diagnosed with stage IVB (n = 1) or IVC ATC (n = 6), and 15 (44%) were treated with additional invasive interventions other than initial thyroid

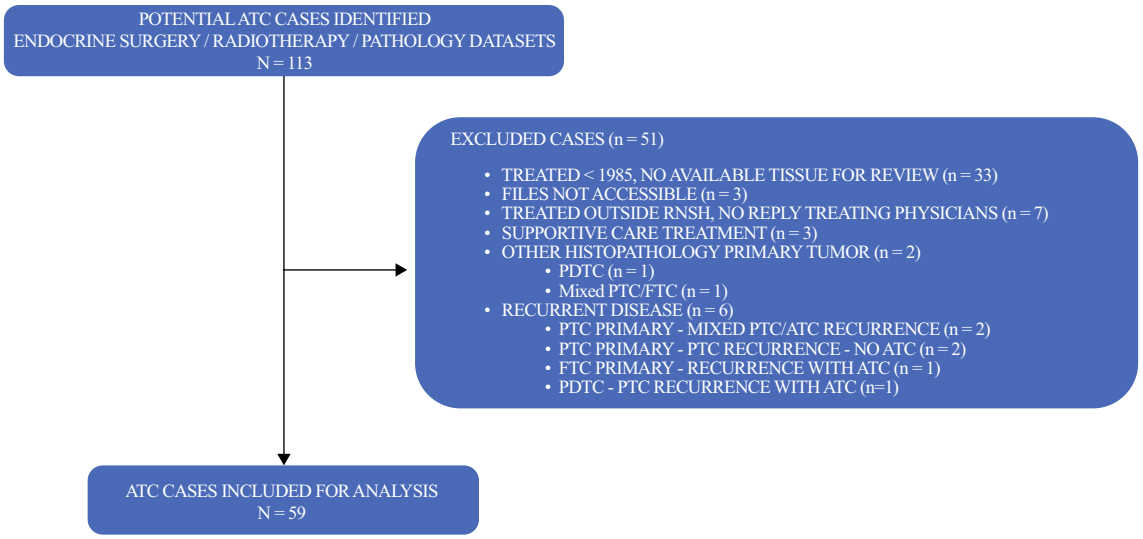

FIG. 1 Overview of study cohort and excluded patients, including reasons for exclusion

surgery. Only two patients in the MMT cohort did not receive systemic treatment because of their age (> 80 years) and the absence of distant metastases at diagnosis. Five patients of the MMT group did not undergo surgical resection because of the development of distant metastases (n = 1), unresectability (n = 1), locoregional progression (n = 2), or complications (n = 1). LT patients were treated with monotherapy (n = 16), radiotherapy followed by chemotherapy (n = 1), radiotherapy with concurrent chemotherapy (n = 2), surgery followed by radiotherapy (n = 4), and surgery followed by chemotherapy (n = 2), as outlined in Supplementary Table III. Seven patients (28%) in the LT cohort received additional invasive interventions following index surgery for primary tumor (Supplementary Table IV), whereas no additional radiotherapy or systemic treatment was administred (Supplementary Table III). No patients in the LT cohort received targeted molecular therapy. Radio- or chemotherapy was ceased in 11 (32%) and 8 (34%) patients undergoing MMT or LT, respectively.

Primary Outcome Measures

MMT improved the median locoregional control when compared with LT (18.5 months versus 1.9 months; $p <$ 0.001). At 1- and 2-year follow-up intervals, no locoregional progression was detected in 51% and 44% of patients in the MMT cohort, respectively (Fig. 2a). Subgroup analysis confirmed that treatment with MMT resulted in a better median locoregional progression-free survival compared with the control cohort for both stage IVB [3.9 (range 0.2–42.0) versus 1.9 (range 0.5–4.6) months; p = 0.007] and stage IVC ATC [5.5 (range 0.7–31) versus 0.9 (range 0.1–4.7) months; p = 0.03]. MMT also improved the progression-free survival when compared with patients who underwent LT [4.9 (range 0.2–46.7) versus 1.9 (range 0.1–4.7) months; $p < 0.001$; Fig. 2b]. In stage IVB tumors, patients treated with MMT had superior progression-free survival [6.5 (range 0.2–42) versus 1.9 (range 0.5–4.6) months; p = 0.005]. Similarly, in stage IVC tumors, progression-free survival was improved in the MMT cohort [4.4 (range 0.7–31.4) versus 1.0 (range 0.07–4.7) months; $p < 0.001$]. Fifty-one ATC patients (86%) had progressive disease (locoregional and/or distant) during follow-up. During follow-up, 10 out of 31 patients diagnosed progressed from stage IVB to stage IVC with novel metastases in lung (n = 6), lung and mediastinum (n = 1), lung, bone, and mediastinum (n = 1), pleura (n = 1), and axilla (n = 1). An overview of the location of novel or progressive distant metastasis in patients diagnosed with stage IVB and IVC is provided in Supplementary Table II.

The median overall survival for the overall cohort was 4.6 months (range 0.1–46.7 months), with a 1-year overall survival of 23% (Fig. 2c). MMT was associated with an increased overall survival compared with the LT cohort [6.9 (range 1.0–46.7) versus 2.0 (range 0.1–8.4) months, $p < 0.001$]. In patients receiving MMT, 1- and 2-year survival were 40% and 25%, respectively, compared with 0% in the LT cohort (Fig. 2d). The stage-specific median overall survival benefit of MMT was confirmed by subgroup analysis of patients with stage IVB [6.9 (range 1.1–42) versus 3.0 (range 0.5–8.4) months; p = 0.003] and IVC ATC [5.6 (0.9–31.4) versus 1.0 (0.1–5.3) months; $p <$ 0.001]. The median overall survival of stage IVC patients receiving MMT with or without TKIs and/or immunotherapy was similar [5.6 (range 3.3–31) versus 4.9 (range 1.0–16.0) months; p = 0.19]. Both MMT with (p = 0.007) and without (p = 0.004) TKI/immunotherapy

TABLE 1 Demographics and histopathology characteristics of included patients

Parameter	Limited treatment (n = 25)	Multimodality treatment (n = 34)	Total (n = 59)	p-Value
General				
Gender, n (%)				0.09
Male	7 (28.0)	17 (50.0)	24 (40.7)	
Female	18 (72.0)	17 (50.0)	35 (59.3)	
Age in years, median (range)	76 (59–99)	71 (39–94)	73 (39–99)	0.01
CCI, median (range)	0 (0–4)	0 (0–3)	0 (0–4)	0.55
ECOG at diagnosis, n (%)				0.01
0	3 (12.0)	18 (52.9)	21 (35.6)	
1	10 (40.0)	7 (20.6)	17 (28.8)	
2	9 (36.0)	7 (20.6)	16 (27.1)	
3	1 (4.0)	2 (5.9)	3 (5.1)	
4	1 (4.0)	0	1 (1.7)	
Missing	1 (4.0)	0	1 (1.7)	
History and presentation				
Thyroid history, n (%)				0.93
Positive	12 (48.0)	15 (44.1)	30 (50.8)	
Negative	13 (52.0)	17 (50.0)	27 (45.8)	
Missing	0	2 (5.9)	2 (3.4)	
Radiation exposure, n (%)				0.83
Yes	1 (4)	1 (2.9)	2 (3.4)	
No	24 (96)	33 (97.1)	57 (96.6)	
Previous thyroid surgery, n (%)				0.45
Yes	1 (4.0)	3 (8.8)	4 (6.8)	
No	24 (96.0)	31 (91.2)	55 (93.2)	
Tumor characteristics, n (%)				
Stage at diagnosis				0.56
IVA	0	2 (5.8)	2 (3.4)	
IVB	12 (48.0)	16 (47.1)	28 (47.5)	
IVC	13 (52.0)	16 (47.1)	29 (49.2)	
Histotype, n (%)				0.07
ATC	18 (72.0)	18 (53.0)	36 (61.0)	
ATC/DTC	4 (16.0)	5 (14.7)	9 (15.2)	
ATC/PDTC	1 (4.0)	4 (11.8)	5 (8.5)	
ATC/DTC/PDTC	2 (8.0)	3 (8.8)	5 (8.5)	
ATC/HCTC	0	3 (8.8)	3 (5.1)	
ATC/SCC/HCTC/PDTC	0	1 (2.9)	1 (1.7)	
ATC percentage primary tumor, n (%)				0.90
< 10%	1 (4.0)	2 (5.9)	3 (5.1)	
10–50%	1 (4.0)	1 (2.9)	2 (3.4)	
> 50%	23 (92.0)	31 (91.2)	54 (91.5)	
Tumor size (mm), median (range)	82 (36–155)	55 (22–110)	68 (22–155)	0.001

ATC anaplastic thyroid cancer, *CCI* non-age-adjusted Charlson Comorbidity Index, *DTC* differentiated thyroid cancer, *PDTC* poorly differentiated thyroid cancer (insular), *HCTC* hurthle cell thyroid cancer, *SCC* squamous cell carcinoma

regimens increased overall survival when compared with the LT cohort [1.0 (range 0.1–5.3) months; Fig. 2e].

Secondary Outcome Measures

The number of complications increased ($p < 0.001$) with treatment intensity, illustrated by the median complication

TABLE 2 Treatment characteristics

Parameter	Limited treatment (n = 25)	Multimodality treatment (n = 34)	Total (n = 59)
Radiotherapy			
2-Gy equivalent dosage, n (%)			
No radiotherapy performed	11 (44.0)	0	11 (18.7)
Low (< 40 Gy)	9 (36.0)	3 (8.8)	12 (20.3)
Moderate (40 to < 50 Gy)	4 (16.0)	4 (11.8)	8 (13.6)
High (50 to < 60 Gy)	0	13 (38.2)	13 (22.0)
Very high (≥ 60 Gy)	0	12 (35.3)	12 (20.3)
Unknown dosage and/or fractions	1 (4.0)	2 (5.9)	3 (5.1)
Surgery			
Index thyroid surgery, n (%)			
Thyroid surgery without LND	9 (36.0)	10 (29.4)	19 (32.2)
Thyroid surgery with LND	5 (20.0)	19 (55.9)	24 (40.7)
No surgery performed	11 (44.0)	5 (14.7)	16 (27.1)
Additional invasive interventions, n (%)			
Yes	4 (16.0)	14 (41.2)	18 (30.5)
No	21 (84.0)	20 (58.8)	41 (69.5)
Resection margin status, n (%)			
R0	1 (4.0)	2 (5.9)	3 (5.1)
R1	2 (8.0)	16 (47.0)	18 (30.5)
R2	11 (44.0)	11 (32.4)	22 (37.3)
Not applicable	11 (44.0)	5 (14.7)	16 (27.1)
Systemic treatment			
Treatment regimen, n (%)			
Single treatment	6 (24.0)	19 (55.9)	25 (42.4)
Multiple treatments	0	13 (38.2)	13 (22.0)
No systemic treatment	19 (76.0)	2 (5.9)	21 (35.6)
Molecular treatment(s), n (%)			
Yes	0	7 (20.6)	7 (11.9)
No	25 (100)	27 (61.8)	52 (88.1)
Radioactive iodine, n (%)			
Yes	1 (4.0)	5 (14.7)	6 (10.2)
No	24 (96.0)	29 (85.3)	53 (89.8)

LND lymph node dissection

number of 5 (range 2–28) compared with 1 (range 0–8) when patients were treated with MMT or LT, respectively. Median complication numbers between surgery, radiotherapy, and index systemic treatment were similar between the MMT and LT cohorts (Table 3). Second- and third-line systemic treatment was only commenced in the MMT cohort and caused a median complication number of 3.5 (range 2–10) per patient. For the overall cohort, radiotherapy with concurrent chemotherapy caused the most complications with a median of 4 (range 3–8) complications per patient. Next, first-line systemic treatment and radiotherapy without concurrent chemotherapy caused a median of 2 (range 1–10) and 2 (range 0–7) complications, respectively (Table 3). The higher complication number in patients treated with MMT was caused by an increased number of grade 1 (p = 0.002), grade 2 (p < 0.001), and grade 3 (p = 0.02) complications. There was no difference in the amount of grade 4 (p = 0.62) or grade 5 (p = 0.39) complications between both cohorts (Table 3). First-line systemic treatment and radiotherapy (with or without concurrent chemotherapy) each caused three out of seven (43%) grade 4 adverse events in the overall cohort. Five out of nine (56%) grade 5 adverse events in the overall cohort were attributed to thyroid surgery. A detailed overview describing complications per grade is provided in Supplementary Table V.

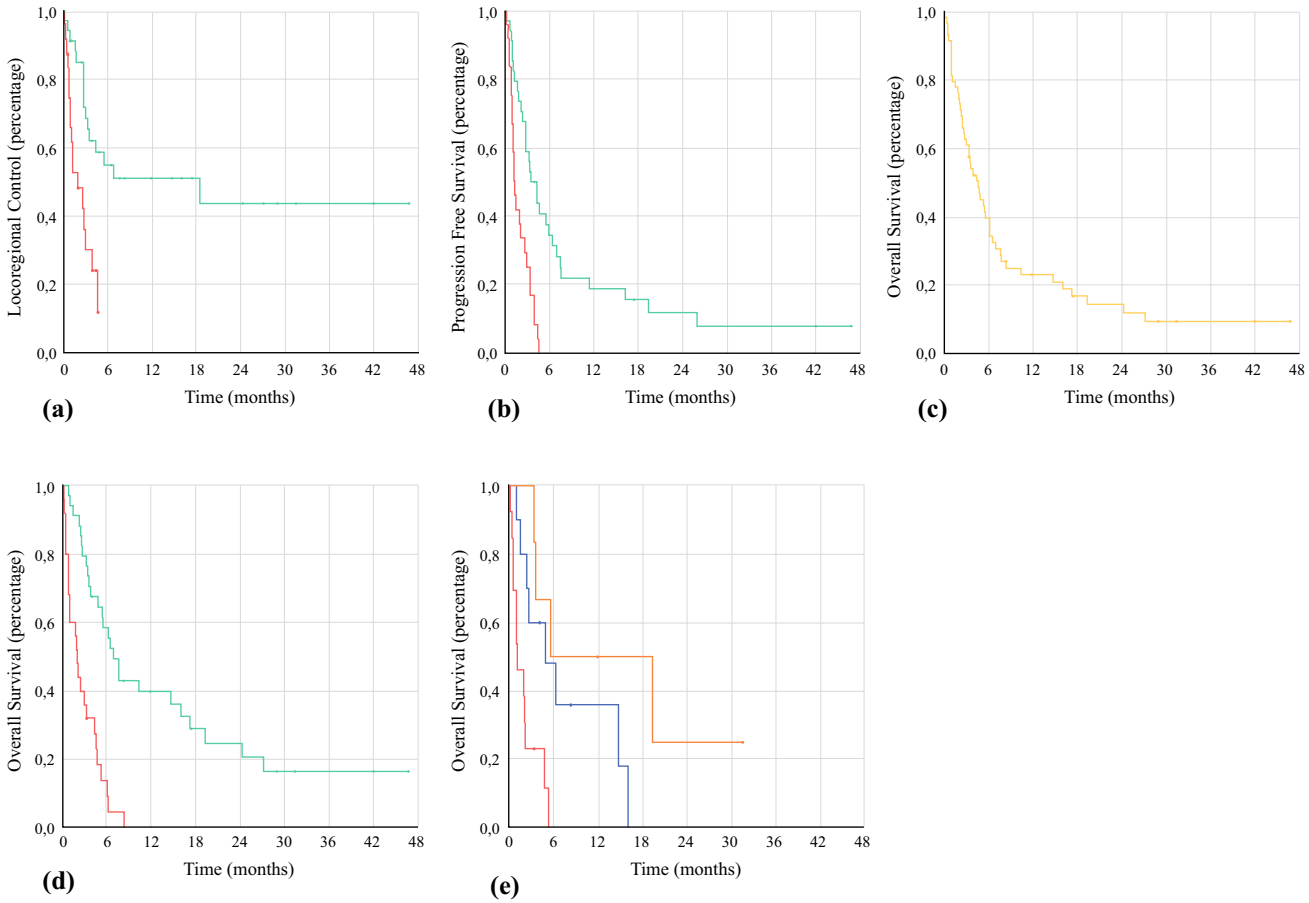

FIG. 2 Benefit of MMT (green line) over LT (red line) on 48-month locoregional control ($p < 0.001$) and progression-free survival ($p < 0.001$), respectively (**a**, **b**); 48-month overall survival from diagnosis for the combined MMT and LT cohorts (**c**); overall survival benefit ($p < 0.001$) of MMT (green line) over LT (red line) (**d**); effect of MMT with (orange line) and without TKI and/or immunotherapy (blue line) versus LT (red line) on overall survival in stage IVC ATC (**e**); MMT with and without TKI and/or immunotherapy have similar effects on overall survival in stage IVC ATC ($p = 0.19$). MMT with ($p = 0.007$) and without ($p = 0.004$) TKI and/or immunotherapy improved OS in stage IVC ATC compared with LT (red). *ATC* anaplastic thyroid cancer, *MMT* multimodality treatment, *TKI* tyrosine kinase inhibitor

Following univariate and multiple regression analysis, an ECOG performance score < 2 [HR 0.30 (95% CI 0.15–0.62); $p = 0.001$] and undergoing MMT [HR 0.35 (95% CI 0.15–0.62); $p = 0.008$] were the only factors associated with improved overall survival in ATC (Table 4).

DISCUSSION

In this retrospective series, we have observed that MMT may improve locoregional control and progression-free and overall survival in selected ATC patients compared with LT. Histopathology and staging of all included patients were centrally re-reviewed and defined according to current guidelines. MMT remained associated with improved overall survival following multivariate analysis. The oncological benefit of MMT is observed in patients with stage IVB and remains present in IVC ATC, but the absolute overall survival gain for both stages is marginal. The benefits provided by MMT should be weighed against the higher number of complications that may affect quality of life during the limited survival gain. In addition to MMT, better performance status at diagnosis may be associated with improved survival in ATC.

Our study shows that MMT may provide an improvement in locoregional control and overall survival when compared with LT. The majority of retrospective studies comparing MMT with LT share our conclusion that the latter is less effective in achieving locoregional control and improving overall survival.[5,8,10,14,15,19,24] The 1-year locoregional control rate of 51% following MMT found in our study is in line with previously reported locoregional control rates ranging between 41% and 96%.[5,11–14,17–19,21] In addition, we found that MMT improves locoregional control in patients with stage IVC ATC. This suggests that MMT may prevent suffocation in a subcategory of patients,

TABLE 3 Treatment Related Complications

Complications	Limited treatment	Multimodality treatment	Total	*p*-Value
Total complications, median (range)	1 (0–8)	5 (2–28)	4 (0–28)	< 0.001
Complications per treatment modality, median (range)				
Surgery				
Thyroid surgery (index surgery)	0.5 (0–6)	0 (0–3)	0 (0–6)	0.36
Palliative surgery (locoregional or distant progression)	0 (0–1)	0.5 (0–2)	0 (0–2)	0.46
Radiotherapy				
Without concurrent chemotherapy	2 (0–4)	3 (1–7)	2 (0–7)	0.19
With concurrent chemotherapy	4 (3–5)	4 (3–8)	4 (3–8)	1.0
Palliative radiotherapy (metastatic sites)	0 (0–0)	0 (0–2)	0 (0–2)	0.89
Systemic treatment				
First-line systemic treatment	3.5 (1–6)	2 (1–10)	2 (1–10)	0.91
Second- and third-line systemic treatment	N/A	3.5 (2–10)	3.5 (2–10)	N/A
Complication grades, *n* (%)				
Grade 1	10 (18.2)	57 (27.5)	67 (25.6)	0.002
Grade 2	19 (34.5)	91 (44.0)	110 (42.0)	< 0.001
Grade 3	19 (34.5)	50 (24.2)	69 (26.3)	0.02
Grade 4	2 (3.6)	5 (2.4)	7 (2.7)	0.62
Grade 5	5 (9.1)	4 (1.9)	9 (3.4)	0.39
Causes of grade 4 and grade 5 complications, *n* (%)				
Grade 4	2 (100)	5 (100)	7 (100)	N/A
Thyroid surgery (index surgery)	1 (50.0)	0	1 (14.3)	N/A
Radiotherapy without concurrent chemotherapy	1 (50.0)	1 (20.0)	2 (28.6)	N/A
Radiotherapy with concurrent chemotherapy	0	1 (20.0)	1 (14.3)	N/A
First-line systemic treatment	0	3 (60.0)	3 (42.8)	N/A
Grade 5	5 (100)	4 (100)	9 (100)	N/A
Thyroid surgery (index surgery)	3 (60.0)	2 (50.0)	5 (55.6)	N/A
Radiotherapy without concurrent chemotherapy	1 (20.0)	0	1 (11.1)	N/A
Radiotherapy with concurrent chemotherapy	0	1 (25.0)	1 (11.1)	N/A
First-line systemic treatment	1 (20.0)	1 (25.0)	2 (22.2)	N/A

N/A not applicable

including stage IVC ATC. Results from our study show that MMT results in a marginal absolute gain in median overall survival compared with LT, with some patients reaching a durable response. Patients receiving MMT had a median overall survival of 7 months, whereas other studies report a median overall survival ranging between 4 and 43 months.[5,8,10–19,24] The low median overall survival gain in our MMT cohort might be attributed to a bias caused by a higher proportion of stage IVC patients selected for MMT or heterogeneity in utilized treatment modalities over the considerable time of this study. Our study further shows that the relative overall survival gain following MMT versus LT in patients with stage IVC ATC is higher when compared with patients with stage IVB ATC. This might be attributed to a treatment response of both locoregional and distant tumor sites. A similar survival benefit of MMT over LT in stage IVC ATC was observed previously in a large cohort study of 2742 ATC patients.[25] Patients treated with surgery, radiotherapy, and chemotherapy (n = 49) had a survival of 4.9 months compared with 1.8 months following surgical resection only (n = 41) or 0.8 months following supportive care (n = 18). Based on our study and current literature, MMT may be provided to achieve locoregional control in ATC, including stage IVC disease. More effective systemic treatment to improve overall survival rates in ATC is urgently needed.

In our study, no difference in overall survival between MMT with and without TKI/immunotherapy in stage IVC ATC was detected. This might be attributed to the small sample size of patients receiving TKI/immunotherapy in our cohort. Other recent studies show encouraging results

TABLE 4 Factors associated with overall survival in anaplastic thyroid cancer

Variable	Overall survival			
	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (≥ 70 years versus < 70 years)	0.73 (0.41–1.30)	0.29	N/A	N/A
Charlson comorbidity index (≥ 2 versus < 2)	0.68 (0.32–1.42)	0.30	N/A	N/A
ECOG performance status (≥ 2 versus < 2)	0.34 (0.19–0.63)	< 0.001	0.30 (0.15–0.62)	0.001
Nodal status (c/pN1 versus c/pN0)	0.62 (0.30–1.30)	0.21	N/A	N/A
Distant status (c/pM1 versus c/pM0)	0.68 (0.39–1.94)	0.18	N/A	N/A
Tumor size (≥ 60 versus < 60 mm)	0.37 (0.19–0.73)	0.004	0.48 (0.22–1.04)	0.06
Margin status (R2 versus R1/R0)	0.62 (0.32–1.20)	0.16	N/A	N/A
Histopathology (ATC versus ATC/DTC)	0.91 (0.47–1.75)	0.78	N/A	N/A
ATC % (≥ 50% ATC versus < 50% ATC)	0.48 (0.15–1.55)	0.22	N/A	N/A
Treatment regimen (LT versus MMT)	0.22 (0.12–0.42)	< 0.001	0.35 (0.16–0.76)	0.008

ATC anaplastic thyroid cancer, *CI* confidence interval, *DTC* differentiated thyroid cancer, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *LT* limited treatment, *MMT* multimodality treatment, *N/A* not applicable

of TKI/immunotherapy treatment in ATC.[27–33] Nevertheless, the exact benefits of these novel therapies in ATC remain to be proven.

The increased overall complication number in patients treated with MMT and equal prevalence of grade 4 and grade 5 complications in both cohorts illustrates the significant risks associated with ATC treatment. MMT was previously associated with increased toxicity compared with LT with higher rates of pharynx, esophagus, and mucous membrane complications.[14] The substantial morbidity risk associated with MMT and LT was further confirmed by multiple other studies.[5,11,13,14,16–19] Complications were mainly reported without the use of standard classifications or selectively for individual treatment modalities. Many studies focus on oncological outcomes, without assessing morbidity.[10,12,15,24,25] In our study, we provide a detailed insight into the complications associated with ATC treatment. Radiotherapy (with and without concurrent chemotherapy) and systemic treatment were responsible for the majority of complications in the LT and MMT cohorts. Patients in the MMT cohort underwent more treatments compared with the LT cohort, subsequently causing more morbidity. The majority of grade 5 complications (56%) occurred within 30 days from index thyroid surgery. The exact reason for this is unclear but might be an argument against complex surgical resections of ATC in frail patients with a poor performance status. A more structured reporting of overall complication numbers in future studies may provide better insight into the actual risks associated with each treatment regimen for the individual patient.

Many previous retrospective case series describing treatment outcomes in ATC did not report the performance score of the included patients.[5,8,10,11,13,15,16,18,19,24] Within the limited studies that did report this parameter, the majority of patients undergoing any treatment for ATC had good performance scores prior to treatment. However, the actual effect of the performance score at diagnosis on oncological outcomes in ATC is unclear. Results from our study indicate that both MMT and a better performance status are associated with improved overall survival in ATC. Consistent reporting of patient performance at diagnosis is needed to confirm our results and help to determine its effect on oncological outcomes. This may help to improve the selection of patients with ATC that may benefit from MMT.

Our study is limited by the retrospective single-center design. The timespan of inclusion in combination with patient tailored treatment causes selection bias and heterogeneity in treatment approaches. Current guidelines suggest to consider age, comorbidities, performance status, and disease extent as part of the selection process towards an optimal treatment approach.[3] It is therefore likely that patients selected for MMT have a better health status than their counterparts undergoing LT. This is reflected by the younger age, better performance status, and smaller tumor size of patients treated with MMT in our study, but opposed by the equal distribution of disease stages between the MMT and LT cohorts. Bias may also have been introduced by a relatively small study population in combination with a high amount of studied variables. Comparing absolute complication numbers between treatment groups limited to 30 days from the final treatment might underestimate the actual complication rate owing to

differences in sample size between cohorts and overseeing possible long-term complications. Finally, no quality-of-life metrics were recorded in the study population. Therefore, it was not possible to determine whether the improved oncological outcomes following MMT weighed against the associated morbidity in terms of quality of life when compared with LT.

Our study and current literature show that the narrow balance between benefits and risks of any treatment in ATC requires that patients are well informed about their options and have realistic expectations. Also, LT should be considered carefully, as survival benefits are minimal, whereas morbidity is substantial and quality of remaining life may be impaired. Patients should be made aware of the option of supportive care, and this should be discussed as an alternative to both MMT and LT. A multidisciplinary approach by a dedicated team based on local clincal protocols may facilitate the process from diagnosis towards a shared decision about the optimal treatment approach.

In conclusion, this study provides further support that MMT may improve locoregional control and progression-free and overall survival in selected patients compared with LT. MMT could improve oncological outcomes in stage IVC ATC, but the overall survival benefit remains modest. The decision of individual patients to undergo any form of treatment for ATC should be weighed against performance status and potential side effects, including major adverse events.

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