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Original Article

Outcomes of Multimodal Therapy in a Large Series of Patients With Anaplastic Thyroid Cancer

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BACKGROUND: The role of radiotherapy (RT) in the treatment of patients with anaplastic thyroid cancer (ATC) for local tumor control is critical because mortality often is secondary to complications of tumor volume rather than metastatic disease. Herein, the authors report the long-term outcomes of RT for patients with ATC. **METHODS:** A total of 104 patients with histologically confirmed ATC were identified who presented to the study institution between 1984 and 2017 and who received curative-intent or postoperative RT. Locoregional progression-free survival (LPFS), overall survival (OS), and distant metastasis–free survival were assessed. **RESULTS:** The median age of the patients was 63.5 years. The median follow-up was 5.9 months (interquartile range, 2.7-17.0 months) for the entire cohort and 10.6 months (interquartile range, 5.3-40.0 months) for surviving patients. Thirty-one patients (29.8%) had metastatic disease prior to the initiation of RT. Concurrent chemoradiation was administered in 99 patients (95.2%) and 53 patients (51.0%) received trimodal therapy. Systemic therapy included doxorubicin (73.7%), paclitaxel with or without pazopanib (24.3%), and other systemic agents (2.0%). The 1-year OS and LPFS rates were 34.4% and 74.4%, respectively. On multivariate analysis, RT ≥60 Gy was associated with improved LPFS (hazard ratio [HR], 0.135; $P = .001$) and improved OS (HR, 0.487; $P = .004$), and trimodal therapy was associated with improved LPFS (HR, 0.060; $P = .017$). The most commonly observed acute grade 3 adverse events included dermatitis (20%) and mucositis (13%), with no grade 4 subacute or late adverse events noted (adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0]). **CONCLUSIONS:** RT appears to demonstrate a dose-dependent, persistent LPFS and OS benefit in patients with locally advanced ATC with an acceptable toxicity profile. Aggressive RT should be strongly considered for the treatment of patients with ATC as part of a trimodal treatment approach. ***Cancer* 2019;0:1-9**.

KEYWORDS: anaplastic thyroid cancer, chemoradiation, chemotherapy, external beam radiotherapy, multimodality, radiation, trimodality, undifferentiated thyroid cancer.

INTRODUCTION

Anaplastic thyroid cancer (ATC) is an aggressive form of thyroid cancer that is associated with poor prognosis. Although ATC accounts for <2% of all thyroid malignancies, it comprises >50% of thyroid-related mortalities.[1-3] Many studies have reported a median overall survival (OS) of ≤6 months with 1-year survival rates of approximately 20%.[3-5]

The morbidity of ATC often is due to locoregional disease rather than distant metastasis because of the numerous critical structures located near the thyroid such as the esophagus and trachea. Invasion into these structures can result in asphyxiation from upper airway compression.[6] Therefore, improving locoregional progression-free survival (LPFS) is vital to enhancing OS among these patients. Given its poor prognosis, patients with ATC typically are treated with a combination of surgery, systemic therapy, and radiotherapy (RT).[7,8] Although doxorubicin has been considered the standard chemotherapeutic agent for patients with advanced ATC,[9,10] various other systemic agents currently are under investigation as combination or single-agent systemic therapy in conjunction with RT and/or surgery.[11-17]

The high incidence of metastatic disease also contributes to the poor prognosis of patients with ATC, with nearly one-half of all patients with ATC presenting with evidence of metastatic disease at the time of initial diagnosis.[6] The most common metastatic sites include the lung, bone, and brain.[18]

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Intensity-modulated RT (IMRT) is the current standard RT modality and has been shown to improve tumor coverage while simultaneously decreasing the dose to surrounding normal tissues.[19-21] Surgical intervention alone in patients with ATC often has limited benefit due to tumor invasion of nearby critical structures in the neck and poorly defined tumor borders.[7] Despite these obstacles, surgical intervention has been shown to improve OS and LPFS in combination with chemotherapy and RT in select patient populations.[8,18] The addition of surgical resection to systemic therapy and RT was found to be associated with an improved OS of 22.1 months versus 6.5 months in a recent retrospective study.[18]

The objective of the current, large, retrospective study was to determine whether aggressive RT in combination with surgery and systemic therapy results in improved outcomes in patients with a definitive diagnosis of ATC.

MATERIALS AND METHODS

Study Design and Patients

The current retrospective study was independently reviewed and approved by the institutional review board of the study institution. A total of 104 consecutive patients with pathologically confirmed ATC who were diagnosed at the study center from 1984 through 2017 were identified; patients with poorly differentiated thyroid carcinoma were excluded. Inclusion criteria required ATC with accurate pathological confirmation and receipt of curative-intent or postoperative RT. Patients were excluded from the current study if they received palliative RT.

Patient data including demographics, disease characteristics, baseline prognostic factors, treatment, and response were extracted from the electronic medical records. Tumor size was assessed using radiographic measurements when possible; otherwise clinical assessments or measurements of a pathological specimen obtained during surgery were used, respectively. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[22]

Treatment

Surgery

Surgical interventions included either partial or total thyroidectomy with or without bilateral neck dissection based on the surgeon's discretion. Resection was defined as R1 if the tumor was within 1 mm of the resected margins as per pathology reports and R2 was defined as the presence of macroscopic residual disease. Patients were not included in the surgical group if the surgery was not completed or was aborted based on physician judgement.

Radiotherapy

All patients underwent immobilization with a thermoplastic head-neck or, more recently, head-neck-shoulder mask, to ensure daily reproducibility of the RT fields. Prior to 2002, all patients (30 patients) received RT twice a day 3 times a week, to a total dose up to 57.60 grays (Gy) (fraction size of 1.6 Gy). Since then, all patients, with the exception of 3 patients (71 patients), received RT once a day 5 times a week, to a total dose up to 70.00 Gy (fraction size, 1.8-2.2 Gy).

Systemic therapy

Patients were treated with varying types of systemic agents including doxorubicin, cisplatin, paclitaxel, docetaxel, and pazopanib. Doxorubicin doses included 10 to 20 mg/m^2, pazopanib at a dose of 400 mg as an oral suspension daily for 2 weeks, and paclitaxel at a dose of 80 mg/m^2 intravenously weekly for 2 weeks.

Outcome Definitions

Follow-up was calculated from the initiation of RT until the last recorded physician visit. LPFS was measured from the initiation of RT until progression of locoregional disease based on increasing size of the primary tumor and/or regional lymph nodes noted on imaging (or clinical examination if imaging was not available) and the date of last follow-up in the absence of locoregional disease progression. Distant metastasis (DM) was defined as any disease outside of the cervical neck and upper mediastinum. OS was assessed from the date of surgery or initiation of RT, whichever occurred first, until death or date of last follow-up. Patients without evidence of metastatic disease at the time of diagnosis were followed to determine the DM-free survival (DMFS), scored using either radiographic evidence or histological evidence of disease progression.

Statistical Methods

We assessed OS, LPFS, and DMFS using the Kaplan-Meier method and performed survival analysis using Cox proportional hazard models. Univariate and multivariate analyses were performed. Any category with a P value $<.05$ on univariate analysis was included in the multivariate analysis. Comparisons between groups were performed using the chi-square test or Fisher exact test, whereas medians were compared using the Mann-Whitney U test.

Data were analyzed using SAS statistical software (version 9.4) and IBM SPSS Statistics 25 software.

Gene Mutation Testing

The mutational status of select patients was obtained at the discretion of the treating physician. All patients with ATC whose tumors were sequenced using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) at Memorial Sloan Kettering Cancer Center were analyzed for established or suspected oncogenic alterations in *TP53*, *TERT*, *BRAF*, and *PTEN*.[23-25]

RESULTS

Patient and Tumor Characteristics

Table 1 details the characteristics of patients and tumors. The median age of the patients was 63.5 years (range, 28-87 years) and 55 of the 104 patients (52.9%) were female. The majority had stage IVB disease (the 8th edition of the American Joint Committee on Cancer system) at the time of diagnosis (73.1%), followed by stage IVC disease (22.1%). Only 5 patients (4.8%) presented with stage IVA disease. Approximately 94% of the patients had extrathyroidal extension, and 69 patients (66.3%) had lymph node involvement. Approximately 38% of the patients had coexistent differentiated thyroid carcinoma. The median tumor size was 6.5 cm (range, 2.0-17.8 cm; information was available for 93.3% of patients). Thirteen patients (12.5%) required tracheostomy. There was no statistically significant difference in the percentage of patients needing tracheostomy noted between the surgically treated group of patients and the nonsurgical group (12.7% vs 12.2%; $P = .941$). Twenty-three patients (22.1%) had evidence of metastatic disease at the time of diagnosis and these patients all were diagnosed after 2002. A total of 31 patients (29.8%) developed metastasis prior to the initiation of RT.

TABLE 1. Patient and Treatment Characteristics (N = 104)

Baseline Characteristics	No. (%)
Median age (range), y	63.5 (28-87)
Sex	
Male	49 (47.1)
Female	55 (52.9)
Stage (8th AJCC staging system)	
IVA	5 (4.8)
IVB	76 (73.1)
IVC	23 (22.1)
Median tumor size (range), cm	6.5 (2.0-17.8)
Coexistent differentiated thyroid carcinoma	
Yes	39 (37.5)
No	65 (62.5)
Tracheostomy	
Yes	13 (12.5)
No	91 (87.5)
Extrathyroidal extension	
Yes	98 (94.2)
No	5 (4.8)
Unknown	1 (1.0)
Macroscopic tumor mass before RT	
Yes	71 (68.3)
No	33 (31.7)
Distant metastases	
At the time of diagnosis	23 (22.1)
Before RT	31 (29.8)
After treatment courses	49 (47.1)
Surgery	
None	49 (47.1)
R2	17 (16.3)
R1	22 (21.2)
R0	13 (12.5)
Unknown	3 (2.9)
RT	
Median dose (range), cGy	6600 (600-7025)
Median no. of fractions (range)	33 (3-40)
Concurrent chemotherapy	
Yes	99 (95.2)
No	5 (4.8)
Concurrent chemotherapy regimens	
Doxorubicin-based regimen	73 (73.7)
Paclitaxel-based regimen	24 (24.3)
Others	2 (2.0)
Trimodal therapy	
Yes	53 (51.0)
No	51 (49.0)

Abbreviations: AJCC, American Joint Committee on Cancer; cGy, centigray; RT, radiotherapy.

Treatment Characteristics

A total of 99 patients (95.2%) received concurrent chemotherapy with RT, and 53 (51.0%) received trimodal therapy with surgical resection followed by concurrent chemoradiation. Of the 55 patients receiving surgical intervention, 13 (12.5%) underwent R0 resection, 22 (21.2%) underwent R1 resection, and 17 (16.3%) underwent R2 resection. Seventy-one patients (68.3%) had a macroscopic tumor mass prior to RT. Among these patients, 17 underwent an R2 resection and 4 patients had R0 or R1 resections but rapidly developed a thyroid mass again prior to the initiation of RT. Of the 99 patients who received systemic therapy, 73 patients (73.7%) received doxorubicin, 24 patients (24.2%) received paclitaxel with or without pazopanib in a clinical trial setting, and 2 patients (2.0%) received other systemic agents. The median dose of EBRT was 66.00 Gy (range, 6.00-70.25 Gy) with a median of 33 fractions (range, 3-40 fractions) (Table 1). Seventy-four patients (71.2%) received IMRT, and the remainder received 3-dimensional conformal RT. RT was given either twice daily (31.7%) or daily (68.3%). Of the patients who received an EBRT dose of <60.00 Gy (46 patients), 26 patients (56.5%) received >50.00 Gy based on the old protocol prior to 2002, and 20 patients could not complete the intended full dose due to progression of disease or deteriorating condition.

All 5 patients with stage IVA disease were treated with trimodal therapy. Of the 76 patients with stage IVB disease, 42 (55.3%) received trimodal therapy, 32 (42.1%) received concurrent chemoradiation, and 2 (2.6%) were treated with RT alone due to age and medical comorbidities. Of the 23 patients with stage IVC disease, 6 patients (26.1%) underwent trimodal treatment, 14 patients (60.9%) received concurrent chemoradiation, and 3 patients (13.0%) were treated with RT alone. Specifically, of those patients with stage IVC disease who underwent surgical resection (6 patients), approximately 83% were diagnosed after 2010 and all 6 patients were treated after 2005. Tumor size ranged from 6.0 cm to 8.0 cm, and 5 patients (83.3%) postoperatively were diagnosed with ATC with a coexisting differentiated component. The median OS of these 6 patients was 4.1 months versus 2.8 months for the remaining patients with stage IVC disease.

Locoregional Progression-Free Survival

The 1-year LPFS rate was 74.4% (Fig. 1A). Twenty-two patients (21.2%) failed locally and 14 patients (13.5%) were alive at the time of last follow-up. There was a statistically significant difference noted with regard to the 1-year LPFS rate between patients according to receipt of trimodal treatment (54.1% vs 85.9%; $P = .003$) (Fig. 1B) and RT dose <60 Gy versus ≥60 Gy (55.3% vs 87.2%; $P < .001$) (Fig. 1C), which also was observed with a cutoff value of 50 Gy (62.9% vs 78.2%; $P < .001$).

On univariate analysis, surgery ($P = .008$), trimodal treatment ($P = .003$), absence of a macroscopic tumor mass prior to RT ($P = .006$), coexistent differentiated thyroid carcinoma ($P = .041$), and an RT dose ≥60 Gy ($P < .001$) were found to be associated with a decreased risk of local disease progression. However, on multivariate analysis, only trimodal treatment ($P = .017$) and an RT dose ≥60 Gy ($P = .001$) were found to be associated with a decreased risk of local disease progression (Table 2).

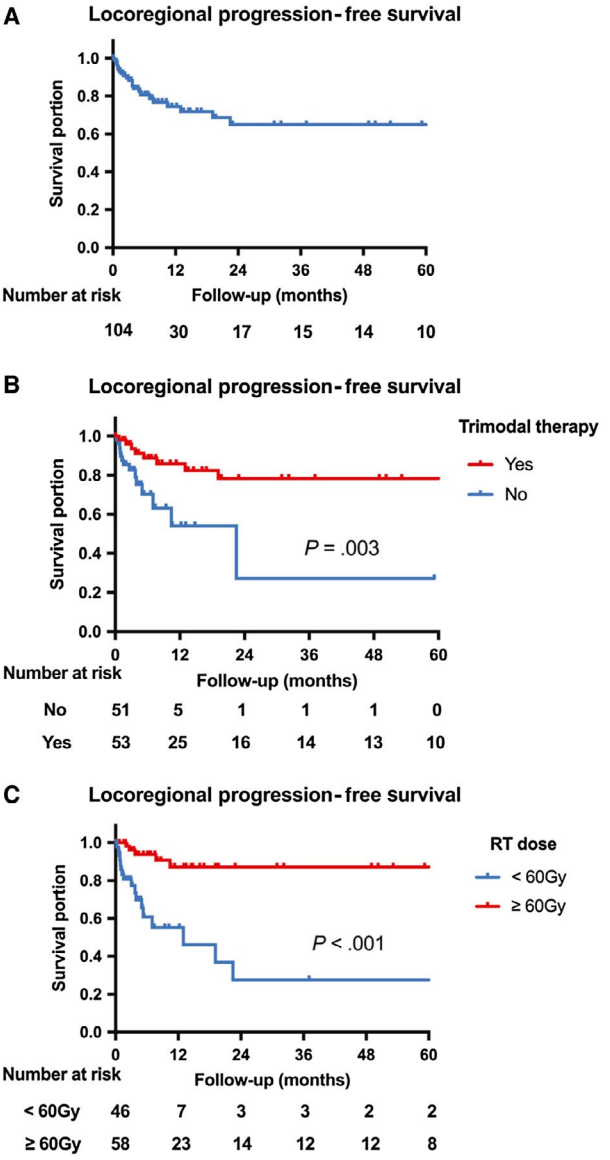

Figure 1. Locoregional progression-free survival (LPFS). (A) LPFS in all patients. (B) Comparative LPFS in patients by receipt of trimodal treatment, and (C) comparative LPFS in patients by receipt of radiotherapy (RT) dose of 60 grays (Gy).

Overall Survival

For the entire cohort, the median OS was 7.0 months (95% CI, 4.5-9.5 months) with a survival rate of 34.4% at 1 year (Fig. 2A). The median follow-up was 5.9 months (interquartile range, 2.7-17.0 months) for the entire cohort and 10.6 months (interquartile range, 5.3-40.0 months) in surviving patients. Ninety patients (86.5%) had died at the time of last follow-up; of these patients, 15 (16.7%) had both local and distant disease, 60 (66.7%) had distant metastasis alone at the time of death, and 7 patients (7.8%) died with local tumor progression alone. There were statistically significant differences noted with regard to the 1-year OS rate according to trimodal treatment (12.8% vs 54.7%; $P < .001$) (Fig. 2B), presence of distant metastases prior to RT (44.9% vs 9.7%; $P < .001$) (Fig. 2C), and RT dose of <60 versus ≥60 Gy (17.4% vs 47.9%; $P < .001$) (Fig. 2D), which also supported a cutoff value of 50 Gy (5.0% vs 41.3%; $P < .001$). The median OS for patients receiving ≥60 Gy of RT was 10.6 months compared with 3.6 months among patients receiving <60 Gy.

TABLE 2. Univariate and Multivariate Analysis of LPFS and OS

Characteristics	UVA P^a	MVA P^a	MVA HR (95% CI)
LPFS			
Trimodal therapy			
No			1
Yes	**.003**	**.017**	0.060 (0.006-0.611)
Surgery			
No			1
Yes	**.008**	.067	11.103 (0.848-145.376)
RT dose, Gy			
<60			1
≥60	**<.001**	**.001**	0.135 (0.042-0.430)
Macroscopic tumor mass before RT			
No			1
Yes	**.006**	.192	2.430 (0.640-9.219)
Coexistent differentiated thyroid carcinoma			
No			1
Yes	**.041**	.765	1.225 (0.323-4.649)
Age (70 y as cutoff)	NS		
Sex	NS		
Extrathyroidal extension	NS		
Stage of disease	NS		
Tumor size (6.5 cm as cutoff)	NS		
Concurrent chemotherapy	NS		
Concurrent chemotherapy regimens	NS		
Tracheostomy	NS		
Distant metastases before RT	NS		
OS			
Age, y			
<70			1
≥70	**<.001**	.281	1.370 (0.773-2.427)
Extrathyroidal extension			
No			1
Yes	**.003**	.200	4.491 (0.452-44.611)
Trimodal therapy			
No			1
Yes	**<.001**	.649	1.628 (0.200-13.277)
Stage of disease (8th AJCC staging system)			
IVA			1
IVB			
IVC	**<.001**	.438	1.522 (0.527-4.393)
Surgery			
No			1
Yes	**<.001**	.269	0.278 (0.029-2.687)
Macroscopic tumor mass before RT			
No			1
Yes	**<.001**	.688	0.868 (0.436-1.729)
Concurrent chemotherapy			
No			1
Yes	**.026**	.382	0.567 (0.159-2.022)
RT dose, Gy			
<60			1
≥60	**<.001**	**.004**	0.487 (0.300-0.791)
Distant metastases before RT			
No			1
Yes	**<.001**	**.009**	3.430 (1.360-8.652)
Coexistent differentiated thyroid carcinoma			
No			1
Yes	**<.001**	.307	0.713 (0.372-1.365)
Sex	NS		
Tumor size (6.5 cm as cutoff)	NS		
Concurrent chemotherapy regimens	NS		
Tracheostomy	NS		

Abbreviations: AJCC, American Joint Committee on Cancer; Gy, grays; HR, hazard ratio; LPFS, locoregional progression-free survival; MVA, multivariate analysis; NS, nonsignificant; OS, overall survival; RT, radiotherapy; UVA, univariate analysis.
[a]Bold type indicates statistical significance.

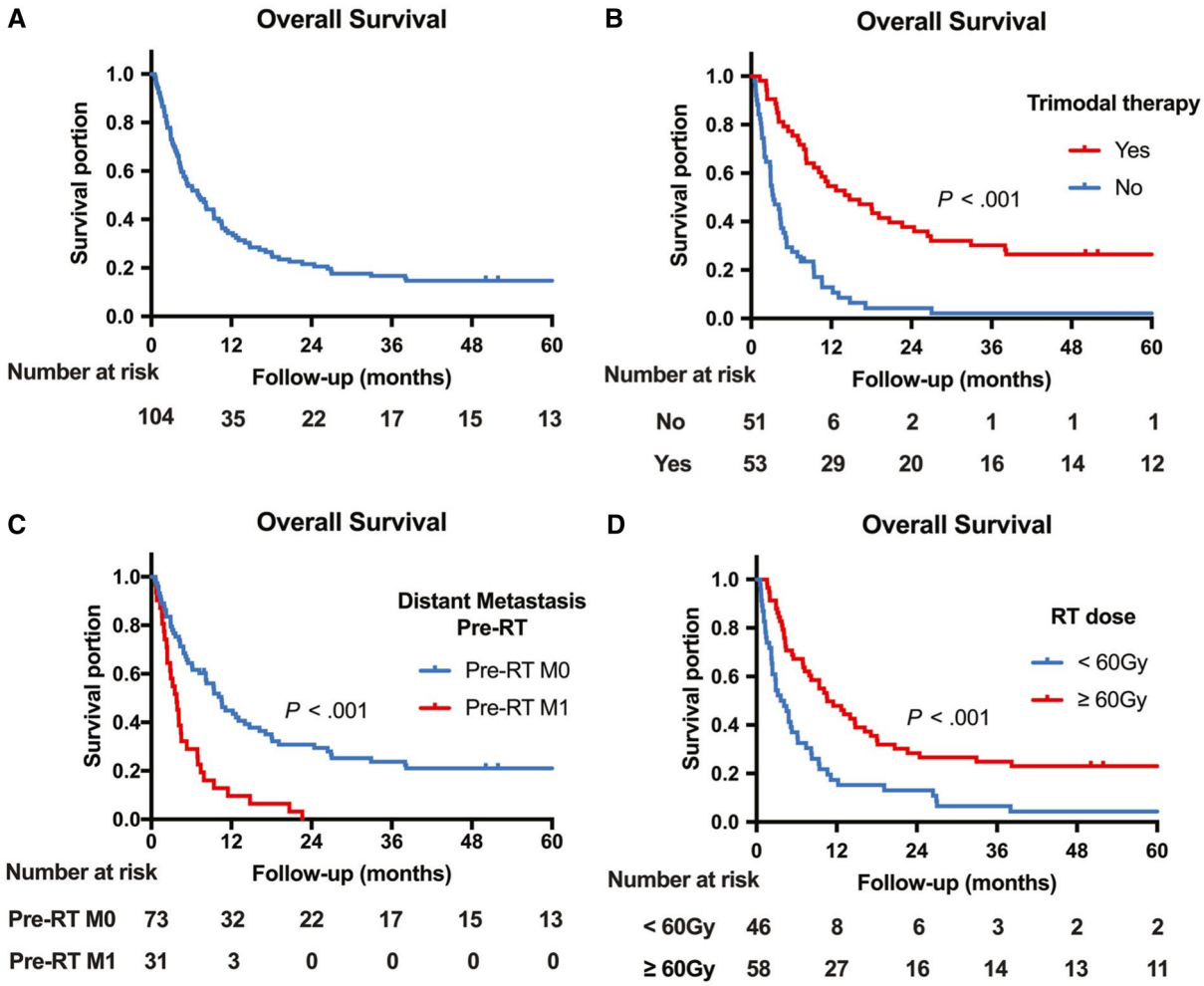

Figure 2. Overall survival (OS). (A) OS in all patients. (B) Comparative OS in patients by receipt of trimodal treatment. (C) Comparative OS in patients by the presence of distant metastasis prior to radiotherapy (pre-RT) and (D) comparative OS in patients by receipt of RT dose of 60 grays (Gy).

On univariate analysis, improved OS was associated with age <70 years ($P < .001$); absence of extrathyroidal extension ($P = .003$); receipt of surgery ($P < .001$), concurrent chemotherapy ($P = .026$), or trimodal treatment ($P < .001$); early-stage disease ($P < .001$); absence of macroscopic tumor mass before RT ($P < .001$); coexistent differentiated thyroid carcinoma ($P < .001$); absence of metastases before RT ($P < .001$); and an RT dose ≥60 Gy ($P < .001$), but only absence of metastases before RT ($P = .009$) and an RT dose ≥60 Gy ($P = .004$) remained statistically significant on multivariate analysis (Table 2).

Distant Metastasis–Free Survival

Of the 81 patients without DM at the time of diagnosis, 56 patients (69.1%) subsequently developed metastases at a median of 5.9 months (95% CI, 4.5-7.3 months), with a 1-year DM rate of 30.5% (Fig. 3). Of the 6 patients with a DMFS >60 months, 2 patients had pure ATC and the remaining 4 patients had coexistent differentiated thyroid cancer. There were 2 patients with stage IVA disease and 4 patients with stage IVB disease. The median tumor size was 6.0 cm (range, 3.0 cm-8.0 cm), and only 1 patient was found to have lymph node involvement. All 6 patients received trimodal therapy and were without evidence of disease at the time of last follow-up.

Toxicities

The most commonly observed acute grade 3 adverse events include dermatitis (20%), mucositis (13%), dysphagia (8%), and fatigue (7%). There were 3 cases of subacute grade 3 fatigue, 4 cases of late grade 3 fatigue, and

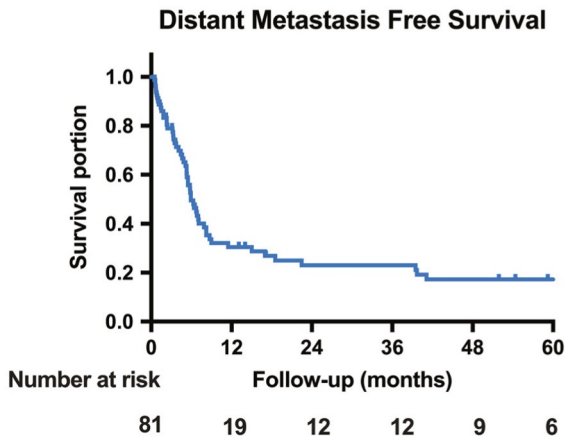

Figure 3. Distant metastasis–free survival. Distant metastasis–free survival in patients without evidence of metastatic disease at the time of diagnosis (81 patients).

1 case of grade 3 mucositis. There were no grade 4 subacute or late AEs noted (Table 3).

Mutational Status

A total of 32 patients (31%) underwent mutation testing at the discretion of the treating physician, with 24 patients (75%) testing positive for at least 1 of the following genes: *TP53* (50% of sequenced patients), *TERT* (47% of sequenced patients), *BRAF* (38% of sequenced patients), and *PTEN* (19% of sequenced patients). After receiving prior multimodal therapy, 6 patients with *BRAF* mutations received systemic therapy consisting of vemurafenib and/or the combination of dabrafenib and trametinib based on molecular profiling. One patient was given everolimus based on *PTEN* mutational status. The median OS of this small population was 20.7 months (95% CI, 14.2-27.2 months) compared with 7.0 months (95% CI, 4.5-9.5 months) for all patients.

DISCUSSION

The management of patients with ATC remains difficult due to its aggressive histology, high rates of locoregional invasion, and the presence of distant metastasis.[18,26] Both the National Comprehensive Cancer Network guidelines and the American Thyroid Association recommend multimodal therapy with upfront surgery when possible.[1,27] Herein, we have reported on improved outcomes in patients with ATC who were undergoing trimodal therapy consisting of surgical resection of the tumor, chemotherapy, and aggressive RT (dose ≥60 Gy).

A critical review by Sherman et al of doxorubicin and RT in the treatment of patients with ATC concluded that a median RT dose of 57.6 Gy and weekly doxorubicin at a dose of 10 mg/m^2 were associated with a 1-year LPFS rate of 45% and a 1-year OS rate of 28%.[7] These authors reported 2-year local tumor control rates of 68% and 49%, respectively, and 1-year survival rates of 50% and 30%, respectively.

In the current study, we conducted a large-scale institutional analysis of all patients with ATC who were diagnosed over a 33-year period, which expanded upon earlier literature.[7,28,29] It is important to note that only patients with accurate pathological confirmation of ATC were included. Although ATC often is studied alongside poorly differentiated thyroid carcinoma, the latter is associated with better outcomes than ATC.

Previous studies have indicated that surgical resection is associated with improved outcomes in patients with ATC.[8,18,30-32] Studies have demonstrated similar improvements in outcome with the use of more aggressive chemotherapy, RT, and surgical resection.[18,33] In an earlier retrospective study, initial intensive multimodal therapy appeared to be associated with improved survival, even in patients with late-stage disease, with more aggressive RT (doses of 46-70 Gy) associated with improved survival outcomes.[32] The pattern of failure for these studies tended to be DM, which is consistent with the findings of the current study and suggests that aggressive local therapy with surgery and RT provides adequate local control.

The importance of RT was demonstrated further by a recent National Cancer Data Base analysis of >1200 patients with ATC, which found a positive RT dose-survival correlation among the entire study cohort, those with stage IV disease, and among patients receiving chemotherapy.[34] The correlation for patients receiving 60 to 75 Gy versus 45 to 59.9 Gy was confirmed by propensity score matching and correlated with OS. It is interesting to note that the 1-year OS rate was only 11% in this study. These data support the findings of the current study that high-dose RT is associated with improved outcomes within the context of multimodal therapy. However, the differences in the median OS noted among the patients receiving ≥60 Gy was 10.6 months, compared with 3.6 months among patients receiving <60 Gy. This suggests that the difference in outcomes may be associated with patient comorbidity.

The frequency and mutations observed in the current study cohort were comparable to the historical literature with regard to the higher frequency of mutations in *TP53*, *TERT*, and the PI3K, AKT, and mTOR pathway effectors.[35] In the current study, a longer

TABLE 3. Toxicities[a]

	Baseline		Acute: 0 to 3 Months		Subacute: 3 to 6 Months		Late: 3 to 6 Months	
	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
CTCAE Grade	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
General								
Fatigue	5 (5%)		74 (71%)	8 (8%)	26 (25%)	3 (3%)	31 (30%)	4 (4%)
Nausea	3 (3%)		58 (56%)	1 (1%)	10 (10%)		12 (12%)	
Vomiting	1 (1%)		33 (32%)	1 (1%)	8 (8%)		8 (8%)	
Skin								
Dermatitis	1 (1%)		40 (38%)	21 (20%)	13 (13%)		15 (14%)	
Head/neck								
Mucositis	1 (1%)		52 (50%)	13 (13%)	14 (13%)		12 (12%)	1 (1%)
Xerostomia	1 (1%)		52 (50%)		11 (11%)		12 (12%)	
Dysphagia	4 (4%)		66 (63%)	8 (8%)	19 (18%)		20 (19%)	
Voice changes	2 (2%)		49 (47%)	2 (2%)				
Taste	1 (1%)		48 (46%)		2 (2%)		2 (2%)	

Abbreviation: CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
[a]Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

median OS was observed in the small group of patients treated with systemic therapy based on molecular profiling. Further study of these mutations may lead to the development of more targeted therapies for selected patient populations.

However, because the current study was a retrospective study, the results herein were subject to the effect of stage migration wherein improvements in diagnosis, workup, and imaging may lead to changes in diagnosis patterns.[36] Selection bias among patients considered suitable for trimodal therapy was another possible limitation of the current study.

The prognosis of patients with ATC remains poor despite aggressive multimodal therapy. There are numerous ongoing clinical trials investigating various combinations of targeted therapies and immunotherapies for patients with ATC.[11-17] Various RT modalities and fractionation schedules also are being actively investigated.

The current large-scale, single-institution, 33-year experience with patients with ATC has identified several factors associated with statistically significant improvements in LPFS and OS for RT dose ≥60 Gy, improvements in LPFS for trimodal therapy, and improvements in OS for the absence of metastatic disease prior to RT on multivariate analysis, suggesting that high doses of RT can be effective in select patients. The current practice at the study institution is the administration of 69.96 Gy in 33 fractions for patients with macroscopic disease and 59.40 Gy in 33 fractions for individuals with microscopic disease.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Dan Fan: Data curation, investigation, methodology, project administration, supervision, validation, writing–original draft, and writing–review and editing. **Jennifer Ma:** Data curation, investigation, writing–original draft, and writing–review and editing. **Andrew C. Bell:** Data curation, investigation, and writing–original draft. **Andries H. Groen:** Formal analysis, methodology, and writing–review and editing. **Kyrie S. Olsen:** Visualization and writing–review and editing. **Benjamin H. Lok:** Conceptualization, methodology, project administration, supervision, and writing–review and editing. **Jonathan E. Leeman:** Methodology, formal analysis, project administration, supervision, and writing–review and editing. **Erik Anderson:** Methodology, project administration, and writing–review and editing. **Nadeem Riaz:** Methodology, supervision, resources, and writing–review and editing. **Sean McBride:** Methodology, supervision, resources, and writing–review and editing. **Ian Ganly:** Conceptualization, methodology, supervision, resources, and writing–review and editing. **Ashok R. Shaha:** Conceptualization, methodology, supervision, resources, and writing–review and editing. **Eric J. Sherman:** Conceptualization, methodology, supervision, resources, and writing–review and editing. **C. Jillian Tsai:** Conceptualization, formal analysis, funding acquisition, resources, software, supervision, validation, and writing–review and editing. **Jung J. Kang:** Conceptualization, methodology, supervision, resources, and writing–review and editing. **Nancy Y. Lee:** Conceptualization, formal analysis, funding acquisition, resources, software, supervision, validation, and writing–review and editing.

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