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Survival advantage of chemoradiotherapy in anaplastic thyroid carcinoma: Propensity score matched analysis with multiple subgroups

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Abstract

Background: We compared overall survival (OS) between radiation therapy (RT) and chemoradiotherapy (CRT) in patients with anaplastic thyroid carcinoma (ATC) using a large database.

Methods: The National Cancer Data Base was queried for ATC patients diagnosed between 2004 and 2013 who received RT or CRT. Groups were balanced by propensity score matching (PSM) on nine relevant variables. OS was also examined in five paired subgroups given known patient heterogeneity.

Results: Of 858 total patients, 575 received CRT and 283 received RT. CRT was associated with decreased risk of death (hazard ratio [HR] 0.66, $P < .001$), 1-year OS 25.5% vs 14.3%. A survival advantage to CRT was seen using PSM cohorts (HR 0.75, $P = .006$). Those receiving definitive surgery saw the greatest benefit to CRT over RT (HR 0.65, $P = .009$), 1-year OS 39.6% vs 20.4%.

Conclusions: CRT is associated with decreased risk of death in ATC; the magnitude of CRT vs RT benefit varied by subgroup.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords

anaplastic thyroid carcinoma; chemoradiation; chemotherapy; national cancer data base; radiation therapy

1 | INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is a rare malignancy with an estimated 500 annual cases in the United States, accounting for 1% to 2% of thyroid cancers.¹ Prognosis is poor; median overall survival (OS) ranges 3 to 6 months despite aggressive treatment as both local and distant failure are common.²

For patients who wish to undergo definitive-intent treatment, surgery and radiation therapy (RT) are recommended. However, the role of chemotherapy is unclear. Professional societies have not routinely recommended adding chemotherapy to surgery and RT. The National Comprehensive Cancer Network (NCCN), the American Thyroid Association (ATA), and the American College of Radiology (ACR) all support maximum safe resection with preoperative or postoperative RT.^{2–4} These guidelines reflect the inconsistent outcomes with respect to chemotherapy and survival. Select single arm series have demonstrated favorable outcomes and long-term survival with combined modality therapy including surgery, radiation, and chemotherapy.^{5–8} In these series, small sample size, selection bias, patient, and treatment heterogeneity are outstanding concerns. Additionally, many reports have found no improvements in survival from the addition of chemotherapy.^{9–12}

Given the rarity of ATC, a large administrative database approach may be informative in the absence of randomized data. The purpose of this study was to compare survival outcomes between patients receiving RT with or without chemotherapy, such that specific populations that substantially benefit from treatment intensification may be identified.

2 | METHODS

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, and includes 1500 accredited cancer program registries which allows for acquisition of information regarding 70% of new cancer diagnoses in the United States.¹³ Access to de-identified patient data and the corresponding data files was provided to the authors as part of the NCDB Participant Use File program. The current study was exempted from requiring institutional review board approval.

ATC was defined within the thyroid cancer user file by the *International Classification of Disease for Oncology*, 3rd edition (ICD-O-3) topography code C739, the use of morphology code 8021 (anaplastic histology), and the intersection of anaplastic grade with morphology codes 8010–8015, 8070–8078, and 8140–8147. Patients who were treated with RT with or without chemotherapy as the first course of treatment were included. RT was defined by external beam radiation therapy to the head and neck and thyroid regions. Patients who received radioactive implants or radioisotopes as their sole radiation modality were

excluded. Patient who received RT alone defined the RT cohort; those who received RT and chemotherapy defined the chemoradiation (CRT) cohort.

Patients with a history of prior malignancy, unknown T classification, missing survival outcomes, and those who received all treatment outside of the reporting institution were excluded (Figure 1). Demographic factors including sex, age Charlson-Deyo comorbidity score, year of diagnosis, race, insurance status, census tract region, and treatment facility type were examined. Given considerable patient heterogeneity, five paired subgroups were defined to better detail outcomes by treatment group. The five subgroups were based on extent of surgery, T and M classifications, tracheal extension, and RT dose. Extent of surgery was defined by RX_SUMM_SURG_PRIM_SITE codes: 0, 13, 20–23, and 25–27 (non-definitive, ie, local tumor excision, lobectomy, etc.) vs 40, 50, and 80 (definitive, ie, near total, total thyroidectomy). Tracheal extension was mapped by CS_extension codes 550, 650, and 730. Timing of chemotherapy and RT delivery was evaluated by simultaneously using the respective time to treatment from diagnosis variables; treatments started within 30 days of each other were considered concurrent.

To minimize the effect of selection bias, traditional 1:1 propensity score matching (PSM) was performed using a greedy match algorithm. Propensity score models allow analysis from an observational study to reflect results one would expect from a randomized study, by balancing on a propensity score. Propensity scores are derived from a multivariable logistic regression model predicting probability of treatment group fit as a function of key prognostic factors. RT and CRT groups were then matched by the propensity score derived from that model to create balanced groups. Variables used for propensity analyses were: age at diagnosis as a continuous variable, sex, Charlson-Deyo (C-D) comorbidity score (0 vs 1–2), T classification (T4a vs T4b), N classification (N0 vs N1), M classification (M0 vs M1), type of surgery (definitive vs non-definitive), tracheal extension, and year of diagnosis. Balance between matched groups was performed using mean standardized differences.

OS was defined as time from last treatment started to death or last follow-up, where those alive were censored at last follow-up. Survival was estimated using the Kaplan-Meier (K-M) method, and distributions were compared using log-rank tests. Characteristics of treatment groups were compared using chi-squared tests or ANOVA, where appropriate. Univariate Cox proportional hazards models were fit for each model variable: treatment group, surgery type, surgical margins, M classification, T classification, N classification, tracheal extension, Charlson-Deyo score, year of diagnosis, dose, and age at diagnosis. K-M curves were generated for the overall and matched cohorts. K-M curves were also generated as stratified by the variables listed earlier. Cox models were fit for propensity score matched groups. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina); the significance level was 0.05.

3 | RESULTS

The NCDB was queried for patients diagnosed with thyroid cancer diagnosed from 2004 to 2013, identifying 309 923 patients. After relevant exclusion criteria were applied, 858 patients who were treated with RT or CRT were included for analysis. Two hundred eighty-

three (33%) patients were treated with RT, and 575 (67%) received chemoradiation. The majority (89.7%) of patients received concurrent chemoradiation. The median age at diagnosis was 68 years; the median length of follow-up was 30.2 months. A total of 45.6% were male, 77.4% of patients had a Charlson-Deyo score of 0, and 60.4% had non-metastatic disease. Two hundred thirty-six (27.5%) received definitive intent surgery; other demographic, disease and treatment characteristics are summarized in Table 1. Those receiving chemoradiation were younger; the median age was 66 vs 73 years ($P < .001$). They were also more likely to be male (50.4% vs 35.7%, $P < .001$), with fewer comorbidities (C-D score of 0 in 79.7% vs 72.8%, $P = .024$). They were also more likely to have received definitive surgery, diagnosed in a more recent era, and had private primary insurance coverage. Total radiation dose received varied among patients, and is summarized in Table S1.

Treatment with CRT compared with RT in all patients was associated with decreased risk of death; hazard ratio (HR) was 0.66 (95% CI 0.57–0.77, $P < .001$). Median OS was 2.6 vs 4.7 months; 1-year and 5-year OS were 14.3% vs 25.5% and 6.9% vs 10.2% (RT vs CRT, Figure 2). The longer survival associated with CRT over RT was also seen in the propensity-matched cohort with 416 patients (HR 0.75, $P = .006$). The median, 1-year and 5-year OS were 2.8 vs 4.2 months, 13.6% vs 22.4%, and 6.6% vs 8.6% (RT vs CRT).

Survival outcomes for CRT vs RT were evaluated in five paired subgroups. A significant benefit to CRT was not observed across all subgroups. CRT was associated with decreased risk of death regardless of the type of surgery (Figure 3). However, a substantial portion of the benefit appeared confined to patients who underwent definitive surgery. In patients who received definitive surgery median OS was 5.1 months vs 7.6 months (RT vs CRT); 12-month OS was 20.4% vs 39.6% and 5-year OS was 10.6% vs 22.3% (HR 0.65, $P < .01$). For those receiving non-definitive surgery, 12-month OS was 12.5% vs 19.3%, and 5-year OS was 5.9% vs 5.5% (RT vs CRT, HR 0.69, $P < .01$). Absolute differences in OS between RT and CRT were 19.2% vs 6.8% at 1-year (definitive vs non-definitive surgery groups); and 11.7% vs 0.4% at 5 years. Subgroups based on T classification showed similar benefits to the addition of chemotherapy (Figure 4). In patients with T4a disease, median and 1-year OS were 2.9 vs 5.9 months and 20.7% vs 33.1% (HR 0.67, $P = .003$). In patients with T4b disease, median and 1-year OS were 2.2 vs 4 months, and 10% vs 21% (HR 0.65, $P < .001$). CRT was associated with decreased risk of death in both subgroups based on M classification (Figure 5). Absolute differences in OS between RT and CRT were 12.5% vs 6.6% at 1-year (non-metastatic vs metastatic). The addition of chemotherapy to RT was associated with a significant improvement in OS only in patients without tracheal extension (Figure 6). The advantage of CRT over RT was modulated by RT dose. Superior OS was limited to patients receiving radiation of 30 Gy or higher (HR 0.73, $P < .001$). Median and 1-year OS were 3.5 vs 5.3 months, and 18.9% vs 28.6%. In the lower dose subgroup, differences in survival endpoint comparing RT vs CRT were negligible (Figure 7).

4 | DISCUSSION

The current study represents the largest known cohort examining survival after RT or chemoradiation in patients with ATC. Treatment with CRT was associated with longer OS in

unadjusted, and propensity-score matched cohorts. Five paired subgroups were defined to address the addition of chemotherapy discretely across each subpopulation. Significant disparities were identified. Meaningful benefits appeared confined to patients who had been treated with definitive-intent surgery, had non-metastatic disease, and received RT dose of 30 Gy. Some subgroups with marginal and likely clinically irrelevant differences showed statistical significance due to relative cohort size. For example, the absolute OS benefit for chemotherapy in the non-definitive surgery and metastatic groups was approximately 7% at 12 months. Additionally, stratification by surgical status gave estimates of the value of CRT in patients with medically or technically inoperable disease, which constituted the majority of our study population.

Glaser et al queried the NCDB for patients with ATC diagnosed between 1998 and 2012.¹⁴ A total of 3552 patients were included to identify patterns of care and prognostic factors. Using an unadjusted multivariable Cox proportional hazard model, the authors identified 11 patients, disease or treatment factors related to survival. Absence of chemotherapy use was associated with increased risk of death (HR 1.32, $P < .0005$), and RT, when dose was greater than 36 Gy was also associated with decreased risk of death (HR 0.58 for 36.1–59.3 Gy, HR 0.41 for 59.4 Gy). After additional statistical refinements were applied, only high-dose radiotherapy use remained significant. Differences between its sample size and the 858 patients reported here may be partially accounted by the absence of exclusion criteria applied to the total ATC NCDB population. Thus, median follow-up for the entire cohort was 3.5 months (30.2 months in current study).

Haymart et al analyzed the impact of each treatment modality (surgery, radiotherapy, and chemotherapy) and combinations thereof in ATC, as stratified by group stage, based on patients captured from 1998 to 2002.¹⁵ Actuarial survival endpoints agree well with those reported here. Median OS was 2.3 vs 5.9 months (no use vs use of chemotherapy), compared with median OS of 2.6 vs 4.7 months from the unadjusted cohort reported here. Similarly, the authors found a survival benefit to the addition of chemotherapy regardless of group stage. Agreement in subgroups is also noted. Median OS was 5.9 vs 9.9 months (surgery + RT with or without chemotherapy) for stage IVB disease; here, we reported median OS of 4.7 vs 7.9 months for the subgroups receiving definitive surgery + RT +/- chemotherapy. Finally, Pezzi et al evaluated the impact of radiotherapy dose in a primarily unresected ATC population.¹⁶ Higher radiotherapy dose was significantly linked to longer OS in a multivariable model; and also demonstrated in PSM-cohorts comparing 45–59 Gy vs 60–75 Gy. The risk of death associated with high-dose (60–75 Gy) radiotherapy (HR 0.419) was in excellent agreement with values previously reported.

The use of large-scale data allowed several key refinements that are not typically feasible with smaller-scale institutional data, where selection bias is particularly concerning. First, we identified notable imbalances in variables relevant to prognosis between treatment groups. Patients who had received CRT were more likely male, younger, had a lower Charlson-Deyo score, received definitive intent surgery, and treated in a more recent era. These covariates were all balanced between groups in the propensity score matched analysis. Adjusting by year of treatment takes into consideration technical changes in radiotherapy delivery and preferred regimens for systemic therapy. Patients receiving CRT were

associated with a higher likelihood of having a private primary payor. This was not included in the PSM model as it is not clear that type of insurance directly impacts survival independently of access to treatment. Other variables captured by the NCDB, but have no implications on treatment allocation or survival, such as level of education and median income quartiles were reviewed and excluded from PSM. Notably, the median time to treatment from diagnosis was similar between RT and CRT groups (0.72 vs 0.79 months). To account for potential bias due to differences in treatment duration between CRT and RT groups, OS was measured from the start of the last treatment course.

The NCDB is an important tool for capturing outcomes data for patients treated outside of academic medical centers. Reports from high-volume institutions may represent preselected populations whose outcomes may not be applicable to the population at large. In the current study, just over half of patients were treated outside of academic centers. Historical series have varied widely when reporting survival, even when considering only patients treated with surgery followed by chemoradiation. Median OS ranges from 7 months to 60 months.^{6,17} Few studies have isolated the effect of chemotherapy in addition for surgery and RT; combined modality strategies are largely supported by single arm studies. Regimens using doxorubicin, combination chemotherapy of doxorubicin and cisplatin, or single agent paclitaxel have been reported.^{5,18–20} These agents have typically been combined with hyperfractionated RT, in preoperative and postoperative settings, or definitively. Two large database studies on postoperative radiation utilizing SEER (Surveillance, Epidemiology, and End Results) did not include chemotherapy as a variable.^{21,22} The results here support several smaller institutional experiences. A series of 83 patients treated over 25 years at Memorial Sloan Kettering Cancer Center included 59 patients who received surgery and postoperative radiation with or without chemotherapy.²³ The addition of chemotherapy was associated with superior 1-year disease-specific survival of 52.6% vs 8.3% for surgery and postoperative radiation ($P = .002$). In the multivariable analysis, single-modality treatment was associated with increased risk of death (HR 2.996, 95% CI 1.2–7.1, $P = .013$). A smaller series from Israel of 26 patients, evaluating three different RT dose levels showed similar results.²⁴ Longer median OS was seen with the use of chemotherapy vs none (11 vs 4 months, $P = .01$), and treatment with chemoradiation vs aggressive palliative RT dose vs conventional palliative RT (11 vs 6 vs 3 months, $P < .001$). The agents used were either weekly doxorubicin 10 mg/m² or paclitaxel 70 mg/m². The use of chemoradiation was also supported by a report on 44 patients by Siironen et al, in which longer median survival was seen with both the use of chemotherapy (8.5 vs 1.3 months, $P = .002$) and chemoradiation (10.6 vs 1.4 months, $P = .003$).²⁵

There were several limitations to the current study. Large databases are valuable by virtue of using aggregate data for rare diagnoses; however, not all variables of interest are routinely captured. The NCDB does not include information on disease status and interventions after the initial course of treatment. Information on cause of death, time to disease progression, patterns of failure, and salvage treatments are not typically captured. Patient-level treatment data that would be expected in the setting of a prospective study are also not included. The NCDB does not record details on number of chemotherapy cycles or radiation target volumes. The majority (72.5%) of patients were treated with non-definitive surgery, when defined as procedures not meeting the criteria of subtotal, near total, or total thyroidectomy.

Given this patient composition, which reflects the overall operability of ATCs, a portion of patients likely received palliative-intent or suboptimal treatment. Overall, 20.6% received RT dose of less than 30 Gy. With regard to chemotherapy intent, as specific agents, chemotherapy dose, and number of cycles is not routinely captured, this remains a known limitation of the NCDB. Propensity-score matching minimizes bias by balancing confounders based on observed characteristics. It does not eliminate the possibility that outcomes are influenced by unobserved, and thus potentially unbalanced, covariates.²⁶ For example, patients with metastatic disease were not balanced by the extent of metastatic involvement. Those with a single metastatic focus, or oligometastatic disease, are more likely to be selected for more aggressive approaches. These reasons, among others, may have accounted for some of the observed differences between CRT vs RT in the metastatic cohort. Finally, the population captured in this study largely predates the approval and use of targeted agents such as dabrafenib and trametinib, which have shown significant clinical activity in V600E-mutated ATC patients.²⁷

Quality of life metrics is critical in the setting of aggressive treatment rendered for diseases with very limited prognosis. Unfortunately, they are not within the scope of the NCDB. RT in the definitive dose range of 60–66 Gy given with concurrent systemic therapy is associated with considerable morbidity. Accordingly, quality of life concerns must be weighed against marginal improvements in life expectancy and disease control in the decision-making process. The NCCN, ATA, and ACR have all emphasized the importance of addressing end-of-life issues after an assessment of traditional prognostic factors such as age, sex, extent of tumor involvement, and stage. The ATA makes a number of recommendations, including drafting an advanced directive, naming a surrogate decision maker, and declaring end-of-life preferences. All three highlight the importance of early counseling on expectations of treatment and the integration of palliative care and supportive care services within a multidisciplinary approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Selection diagram detailing the relevant inclusion/exclusion factors identifying the analysis population

FIGURE 2.

Kaplan-Meier curves for overall survival in unmatched and matched cohorts of patients, stratified by treatment group

FIGURE 3.
Kaplan-Meier curves for overall survival stratified by treatment in subgroups defined by the extent of surgery

FIGURE 4.
Kaplan-Meier curves for overall survival stratified by treatment in subgroups defined by T classification

FIGURE 5.
Kaplan-Meier curves for overall survival stratified by treatment in subgroups defined by M classification

FIGURE 6.
Kaplan-Meier curves for overall survival stratified by treatment in subgroups defined by tracheal extension

FIGURE 7.
Kaplan-Meier curves for overall survival stratified by treatment in subgroups defined by radiation dose

TABLE 1

Demographic, disease, and treatment characteristics of all patients, and by treatment group

Characteristic	All (N = 858)	CRT (N = 575)	RT (N = 283)	P-value
Age				
Median (SD)	68 (11.8)	66 (10.88)	73 (12.75)	<.001
Sex				<.001
Male	391 (45.6%)	290 (50.4%)	101 (35.7%)	
Female	467 (54.4%)	285 (49.6%)	182 (64.3%)	
Race				.526
White	734 (85.5%)	491 (85.4%)	243 (85.9%)	
Black	77 (9%)	55 (9.6%)	22 (7.8%)	
Other	47 (5.5%)	29 (5%)	18 (6.4%)	
Charlson-Deyo score				.024
0	664 (77.4%)	458 (79.7%)	206 (72.8%)	
1, 2	194 (22.6%)	117 (20.3%)	77 (27.2%)	
T Classification				.464
T4	30 (3.5%)	17 (3%)	13 (4.6%)	
T4a	304 (35.4%)	206 (35.8%)	98 (34.6%)	
T4b	524 (61.1%)	352 (61.2%)	172 (60.8%)	
N Classification				.133
N0	304 (39.7%)	193 (37.4%)	111 (44.4%)	
N1	141 (18.4%)	93 (18%)	48 (19.2%)	
N1a	59 (7.7%)	45 (8.7%)	14 (5.6%)	
N1b	262 (34.2%)	185 (35.9%)	77 (30.8%)	
Missing	92	59	33	
M Classification				.104
M0	504 (60.4%)	348 (62.4%)	156 (56.5%)	
M1	330 (39.6%)	210 (37.6%)	120 (43.5%)	
Missing	24	27	7	
Surgery type				
Definitive	236 (27.5%)	173 (30.1%)	63 (22.3%)	.016
Non-definitive	622 (72.5%)	402 (69.9%)	220 (77.7%)	

Characteristic	All (N = 858)	CRT (N = 575)	RT (N = 283)	P-value
Surgical margins				
Positive	203 (66.6%)	143 (65.9%)	60 (68.2%)	.702
Negative	102 (33.4%)	74 (34.1%)	28 (31.8%)	
Missing	553	358	195	
Tracheal extension				.749
Yes	126 (14.7%)	86 (15%)	40 (14.1%)	
No	732 (85.3%)	489 (85%)	243 (85.9%)	
Median time from diagnosis to treatment in months (SD)	0.79 (0.86)	0.79 (0.84)	0.72 (0.9)	.942
Year of diagnosis				.007
2004–2006	203 (23.7%)	125 (21.7%)	78 (27.6%)	
2007–2009	275 (32.1%)	174 (30.3%)	101 (35.7%)	
2010–2013	380 (44.3%)	276 (48%)	104 (36.7%)	
Facility type				.071
Community cancer Program	84 (9.9%)	55 (9.7%)	29 (10.4%)	
Comp. community cancer program	303 (35.7%)	188 (33%)	115 (41.4%)	
Academic program	414 (48.8%)	294 (51.7%)	120 (43.2%)	
Integrated network cancer program	46 (5.4%)	32 (5.6%)	14 (5%)	
Primary Payor				<.001
Government	507 (59.1%)	312 (54.3%)	195 (68.9%)	
Private insurance	292 (34%)	217 (37.7%)	75 (26.5%)	
Not insured/unknown	59 (6.9%)	46 (8%)	13 (4.6%)	
Facility location				.513
New England	48 (5.7%)	28 (4.9%)	20 (7.2%)	
Middle Atlantic	147 (17.3%)	104 (18.3%)	43 (15.4%)	
South Atlantic	161 (19%)	104 (18.3%)	57 (20.4%)	
North Central	232 (27.4%)	164 (28.8%)	68 (24.4%)	
South Central	122 (14.4%)	83 (14.6%)	39 (14%)	
West	138 (16.2%)	86 (15.1%)	52 (18.6%)	

Abbreviations: CRT, chemoradiotherapy; RT, radiation therapy.