Original Article

Marginal Treatment Benefit in Anaplastic Thyroid Cancer

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BACKGROUND: Because anaplastic thyroid cancer is a rare malignancy with a high mortality rate, the benefit of multimodality treatment was evaluated. **METHODS:** Overall survival was determined in the 2742 patients captured by the National Cancer Database who were diagnosed with anaplastic thyroid cancer between 1998 and 2008. Kaplan-Meier analysis and then Cox proportional hazard regression was performed, controlling for patient characteristics and treatment. **RESULTS:** Only older age (adjusted hazard ratio [AHR] for ≥ 85 years = 3.43, 95% confidence interval [CI] = 2.34-5.03; for 75-84 years, AHR = 2.85, 95% CI = 1.97-4.11; for 65-74 years, AHR = 2.20, 95% CI = 1.53-3.15; for 45-64 years, AHR = 2.08, 95% CI = 1.47-2.95) and omission of treatment were associated with greater mortality (omission of surgery: AHR = 1.79, 95% CI = 1.61-1.99; omission of radiation therapy: AHR = 1.56; 95% CI = 1.41-1.73; and omission of chemotherapy: AHR = 1.28, 95% CI = 1.15-1.43). In subgroup analysis of patients with American Joint Committee on Cancer stage IVA, IVB, and IVC anaplastic thyroid cancer, combination therapy with surgery, radiation, and chemotherapy was associated a difference in median survival of months. **CONCLUSIONS:** Multimodality management of anaplastic thyroid cancer results in a marginal treatment benefit. The poor overall survival of all anaplastic thyroid cancer patients, regardless of treatment, emphasizes the need for informed patients whose preferences are incorporated into treatment decision-making. ***Cancer*** **2013;119:3133-9.** © *2013 American Cancer Society.*

KEYWORDS: cancer; thyroid; treatment; anaplastic thyroid cancer; survival.

INTRODUCTION

Anaplastic thyroid cancer is a rare but deadly form of thyroid cancer. Even though it accounts for only 1% to 2% of the thyroid cancer cases each year, the relative 5-year survival of patients diagnosed with this cancer is a mere 7%.[1] Anaplastic thyroid cancer is more common in the elderly, and it almost always arises after preexisting well-differentiated thyroid cancer.[2,3]

Because anaplastic thyroid cancer is rare, there are very few studies with a cohort of patients large enough to adequately assess the effect of treatment on outcome. Several single-institution studies with small sample sizes (N = 25 to N = 134), have conflicting results.[4-6] There are international and Surveillance, Epidemiology, and End Results (SEER) studies,[2,7,8] but even with these studies, the largest cohort includes only 516 patients.[2] Recent clinical guidelines advocate combination therapy for stage IVA and IVB patients who want aggressive management,[9] but the benefit of this multimodality treatment is still unknown.

We used the National Cancer Database (NCDB), which includes 70% of all cancers in the United States,[10] to evaluate overall survival in the 2742 patients diagnosed with anaplastic thyroid cancer between 1998 and 2008. We hypothesized that there would be a statistically significant difference in survival with more intensive treatment but that the median difference in survival by months would be small and possibly clinically insignificant.

MATERIALS AND METHODS

Data Source and Study Population

The NCDB is a national cancer registry that is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. The NCDB captures 70% of all cancers in the United States, and all data are coded and reported according to nationally established protocols.[10] Data came from the NCDB Participant User File (PUF). Data

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from thyroid cancer cases were queried and International Classification of Diseases for Oncology (ICD-O) codes consistent with anaplastic thyroid cancer were used to identify this study cohort. The University of Michigan Institutional Review Board reviewed this proposal and because it involved research using publically available data sets, the Institutional Review Board felt approval was not required because the data cannot be tracked to human subjects.

The study cohort consisted of the 2742 patients diagnosed with anaplastic thyroid cancer between 1998 and 2008. Data was censored at death or a minimum of 2 years after diagnosis (December 2010). Median follow-up was 3.8 years. Prior to 2003, based on the fifth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, all anaplastic thyroid cancer patients were classified as AJCC stage IV. After 2003, the sixth edition of the AJCC Cancer Staging Manual added the following subgroups to the anaplastic thyroid cancer cohort: IVA, IVB, IVC.[11] Per the sixth edition of the AJCC Cancer Staging Manual, anaplastic thyroid cancers with intrathyroidal, surgically resectable tumors with or without lymph node involvement and without distant metastases are stage IVA. If the primary tumor is extrathyroidal and unresectable, with or without lymph node involvement and without distant metastases, the cancer is stage IVB. Any distant metastasis leads to categorization as stage IVC.[11] Given the change in staging categories, a separate subgroup analysis was performed using the more contemporary cohort (2003-2008) with AJCC stage categories IVA, IVB, and IVC.

Measures

Because anaplastic thyroid cancer is thought to develop after well-differentiated thyroid cancer,[3] we divided age into categories that are known to have survival implications for well-differentiated thyroid cancer: ≤ 44, 45-64, and ≥ 65 years. Due to the large number of patients ≥ 65 years, we subsequently divided this cohort into patients aged 65-74, 75-84, and ≥ 85 years. Because there were a small number of races other than black or white, the Asian, American Indian/Alaska Native, and Native Hawaiian and Pacific Islander categories were collapsed into an "other" race category. Ethnicity was divided into non-Hispanic and Hispanic. Persons of Hispanic origin could be any race and therefore race instead of ethnicity was included in the multivariable analysis. Insurance status was categorized as the following: Private/government, Medicare, Medicaid, Uninsured, or Unknown. By matching the ZIP code of the patient recorded at the time of diagnosis against files derived from year 2000 US Census data, income and education level less than a high school diploma were assigned to each patient. By matching the patient's state and county Federal Information Processing Standard code recorded at the time of diagnosis against files published by the US Department of Agriculture Economic Research Service, the rural-urban continuum variable was created. Treatment information included surgery (total thyroidectomy, lobectomy) or no surgery, use of radiation, and use of chemotherapy.

Statistical Analysis

Our outcome of interest was overall survival. Univariate analysis was performed using the Kaplan-Meier method with log-rank statistic to detect differences in overall survival.

Cox proportional hazard regression modeling was used for multivariable analysis. If the 95% confidence interval (CI) of the hazards ratio did not cross 1.00, then the relationship was considered statistically significant.

RESULTS

As shown in Table 1, the majority of patients with anaplastic thyroid cancer were women (61.9%) and 65 years or older (69.5%). The mean age of our sample was 70 ± 12.29 years. Eighty-six percent were white, 8.4% were black, and only 4.0% fell into the "other" race category. A small minority (6.0%) were Hispanic. Consistent with the older age of the cohort, 58.1% of patients had Medicare insurance. With respect to treatment, surgery was omitted in 47.8% of the patients, radiation therapy was omitted in 39.0%, and chemotherapy was omitted in 59.2%.

Kaplan-Meier curves (Fig. 1) illustrate survival in patients diagnosed between 1998 to 2008 based on treatment with surgery, radiation, and chemotherapy. The median survival with total thyroidectomy was 6.2 months versus 2.3 months without any surgery. Similarly, treatment with radiation was associated with an almost 5-month median survival versus close to 1.8 months without therapy. Chemotherapy improved median survival from 2.3 months to 5.9 months.

On univariate analysis, younger age, which was age ≤ 44 ($P < .001$), private insurance ($P < .001$), lower education ($P = .021$), and treatment with surgery ($P < .001$), radiation ($P < .001$), and chemotherapy ($P < .001$) were associated with improved survival. As demonstrated in Table 2, as age increased, the likelihood of death increased. In the adjusted model, only older age (adjusted hazard ratio [AHR] for age ≥ 85 was 3.43, 95%

TABLE 1. Characteristics of Patients Diagnosed With Anaplastic Thyroid Cancer Between 1998-2008 (N = 2742)

Characteristic	N (%)
Patient Characteristics	
Sex	
Male	1046 (38.1%)
Female	1696 (61.9%)
Age, years	
≤44	81 (3.0%)
45-64	754 (27.5%)
65-74	753 (27.5%)
75-84	834 (30.4%)
≥85	320 (11.7%)
Race	
White	2364 (86.2%)
Black	229 (8.4%)
Other	109 (4.0%)
Unknown	40 (1.5%)
Hispanic	
Yes	164 (6.0%)
No	2352 (85.8%)
Unknown	226 (8.2%)
Insurance	
Private/government	829 (30.2%)
Medicare	1592 (58.1%)
Medicaid	106 (3.9%)
Uninsured	87 (3.2%)
Unknown	128 (4.7%)
Income	
<$30,000	389 (14.2%)
$30,000-35,000	497 (18.1%)
$35,000-45,900	779 (28.4%)
$46,000+	962 (35.1%)
Unknown	115 (4.2%)
Education level less than high school diploma	
≥29%	476 (17.4%)
20%-28.9%	627 (22.9%)
14%-19.9%	632 (23.0%)
<14%	892 (32.5%)
Unknown	115 (4.2%)
Rural-urban continuum	
Metropolitan population	2076 (75.7%)
Other	527 (19.2%)
Unknown	139 (5.1%)
Treatment	
Surgery	
Total thyroidectomy	896 (32.7%)
Lobectomy	481 (17.5%)
No surgery	1310 (47.8%)
Unknown	55 (2.0%)
Radiation	
Yes	1596 (58.2%)
No	1070 (39.0%)
Unknown	76 (2.8%)
Chemotherapy	
Yes	1063 (38.8%)
No	1623 (59.2%)
Unknown	56 (2.0%)

CI = 2.34-5.03) and omission of treatment were associated with greater mortality (omission of surgery: AHR = 1.79, 95% CI = 1.61-1.99; omission of radiation therapy: AHR = 1.56, 95% CI = 1.41-1.73; and omission of chemotherapy: AHR = 1.79, 95% CI = 1.61-1.99). We had data on comorbidity from 2003 to 2008. When we re-ran the Cox proportional hazard regression with this smaller cohort and included comorbidity, having 1 comorbidity was associated with AHR = 1.31 (95% CI = 1.13-1.51) and having 2 or more comorbidities was associated with AHR = 1.63 (95% CI = 1.26-2.10). The addition of comorbidity did not change the relationship between the other patient and treatment variables and overall survival.

Figure 2 shows the Kaplan-Meier curves for the more contemporary cohort (2003-2008) with N = 699. Median survival of stage IVA anaplastic thyroid cancer was 9.0 months versus 4.8 months for IVB and 3.0 months for IVC.

In Table 3, we evaluated combination therapy in 244 patients with stage IVA anaplastic thyroid cancer, 242 patients with stage IVB anaplastic thyroid cancer, and 163 patients with stage IVC anaplastic thyroid cancer. The longest median survival in patients with stage IVA was 11.2 months in patients who received surgery, radiation, and chemotherapy ($P < .001$). Surgery and radiation, without chemotherapy, was associated with a median survival of 9.3 months. Patients with stage IVB had median survival of 9.9 months when they received surgery with radiation and chemotherapy and median survival of 5.9 months when they just received surgery and radiation ($P < .001$). Patients with stage IVC had a 4.9-month median survival if they received surgery, radiation, and chemotherapy and a 3.5-month median survival if they only received surgery and radiation ($P < .001$). Only 10 patients with stage IVC anaplastic thyroid cancer received surgery and chemotherapy (without radiation), but their median survival was 8.2 months.

DISCUSSION

In this large sample of patients treated across the United States, younger age and more intensive treatment were associated with improved survival in patients with anaplastic thyroid cancer. Within the subgroups of patients with stages IVA, IVB, and IVC cancer, more intensive treatment, specifically combination therapy, was associated with a statistically significant improvement in survival. However, the difference in median survival was consistently 9 months or less with the survival difference in the highest risk patients often differing by only a few months. This improved survival may be related to treatment selection bias, whereby the healthier patients with less aggressive tumor biology are more likely to receive treatment.

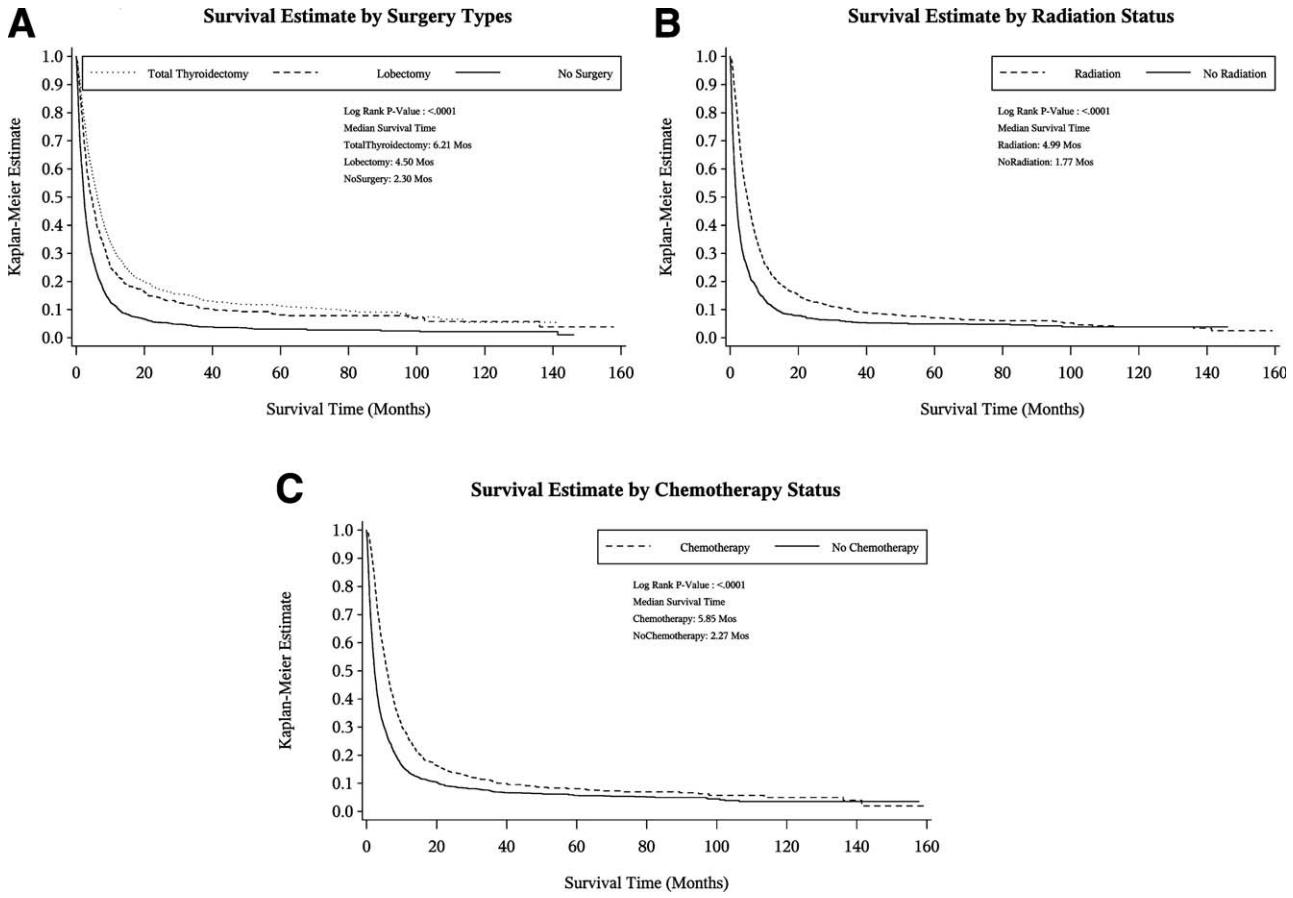

Figure 1. Kaplan-Meier curves show (A) overall survival of patients with anaplastic thyroid cancer undergoing total thyroidectomy versus lobectomy versus no thyroid surgery, and overall survival of patients with anaplastic thyroid cancer on the basis of receipt of (B) radiation and (C) chemotherapy.

Previous studies of anaplastic thyroid cancer have been limited by the small number of patients included in analyses.[3,5,6,12] The results of these prior studies have been conflicting, with some finding no survival benefit to intensive treatment[4] and others finding survival benefit with surgery plus radiation,[2,12,13] or a combination of surgery, radiation, and chemotherapy.[5,6]

Interestingly, in our entire cohort, the hazard ratios for the subgroups of age $>$ 44 years were greater than the hazard ratio for any individual treatment: surgery, radiation therapy, or chemotherapy. When we controlled for comorbidity in the contemporary cohort, the relationship between age and prognosis persisted. This emphasizes the relative importance of age at diagnosis in survival. Although significantly associated with survival in multivariable analysis, extent of surgery, use of radiation therapy, and use of chemotherapy were associated with a small absolute difference in survival (median survival closer to 6 months instead of near 2 months).

When we restricted the analyses to patients with AJCC stage IVA, IVB, and IVC cancer and looked at combination therapy, we found that combination therapy, typically comprising surgery, radiation, and chemotherapy, was associated with the longest median survival. The largest difference in median survival (9.3 months) was between the no-treatment versus multimodality treatment in the patients with stage IVA anaplastic thyroid cancer.

The survival benefit of these treatments should be taken in context of the risks. Weekly doxorubicin (10 mg/m^2) with radiation is the most commonly employed chemoradiotherapy regimen in the treatment of anaplastic thyroid cancer.[14] However, no randomized controlled trials are available to prove benefit for concurrent chemoradiotherapy over radiation alone. Justification for treatment is warranted, nonetheless, in an effort to save patients from the devastating complications of suffocation. The potential benefits, however,

TABLE 2. Cox Proportional Hazard Regression for Association of Patient Characteristics and Treatment With Overall Survival

Characteristic	N (%)	Median Survival, mo (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Patient characteristics				
Sex				
Male	766 (36.7%)	3.8 (3.4, 4.1)	0.95 (0.87, 1.05)	1.07 (0.97, 1.17)
Female	1319 (63.3%)	3.2 (2.9, 3.5)	-	-
Age, y				
≤44	56 (2.7%)	11.5 (8.8, 32.0)	-	-
45-64	571 (27.4%)	4.8 (4.0, 5.5)	2.25 (1.59, 3.17)	2.08 (1.47, 2.95)
65-74	567 (27.2%)	4.0 (3.5, 4.6)	2.48 (1.76, 3.50)	2.20 (1.53, 3.15)
75-84	637 (30.6%)	2.8 (2.4, 3.1)	3.44 (2.45, 4.84)	2.85 (1.97, 4.11)
≥85	354 (12.2%)	1.6 (1.2, 2.0)	4.85 (3.40, 6.92)	3.43 (2.34, 5.03)
Race				
White	1825 (87.5%)	3.5 (3.2, 3.7)	-	-
Black	175 (8.4%)	3.3 (2.0, 4.6)	1.08 (0.92, 1.27)	1.14 (0.96, 1.36)
Other	85 (4.1%)	2.8 (2.3, 4.1)	1.23 (0.98, 1.54)	1.16 (0.92, 1.46)
Insurance				
Private/government	664 (31.8%)	5.0 (4.4, 5.6)	-	-
Medicare	1274 (61.1%)	2.9 (2.7, 3.1)	1.41 (1.27, 1.55)	1.02 (0.89, 1.17)
Medicaid	81 (3.9%)	4.5 (2.2, 5.7)	0.99 (0.77, 1.28)	0.95 (0.73, 1.23)
Uninsured	66 (3.2%)	2.0 (1.4, 4.4)	1.30 (0.99, 1.71)	1.00 (0.76, 1.32)
Education level less than high school diploma				
≥29%	381 (18.3%)	2.9 (2.5, 3.6)	1.20 (1.05, 1.36)	1.10 (0.96, 1.26)
20%-28.9%	493 (23.6%)	3.2 (2.8, 3.7)	1.11 (0.99, 1.26)	1.13 (1.00, 1.28)
14%-19.9%	499 (23.9%)	3.0 (2.7, 3.6)	1.16 (1.03, 1.31)	1.14 (1.01, 1.29)
<14%	712 (34.1%)	4.1 (3.7, 4.7)	-	-
Rural-urban continuum				
Metropolitan population	1697 (81.4%)	3.5 (3.2, 3.8)	0.89 (0.80, 1.00)	0.92 (0.81, 1.03)
Other	388 (18.6%)	3.1 (2.8, 3.6)	-	-
Treatment				
Surgery				
Total thyroidectomy	686 (32.9%)	5.8 (5.1, 6.3)	-	-
Lobectomy	386 (18.5%)	4.5 (3.6, 5.2)	1.12 (0.98, 1.28)	1.01 (0.88, 1.15)
No surgery	1013 (48.6%)	2.3 (2.1, 2.5)	1.85 (1.67, 2.05)	1.79 (1.61, 1.99)
Radiation				
Yes	1259 (60.4%)	4.9 (4.6, 5.4)	-	-
No	826 (39.6%)	1.7 (1.5, 1.9)	1.77 (1.61, 1.94)	1.56 (1.41, 1.73)
Chemotherapy				
Yes	834 (40.0%)	6.0 (5.3, 6.4)	-	-
No	1251 (60.0%)	2.2 (2.0, 2.4)	1.65 (1.50, 1.81)	1.28 (1.15, 1.43)

Abbreviation: CI, confidence interval.

must be weighed against the toxicities from chemoradiation. Skin changes, pharyngoesophagitis and tracheitis have commonly been reported.[15] Toxicity can be lessened to a point when hyperfractionated radiotherapy is administered.[14,16] Daily radiation doses, exceeding 3 Gy, increase the risk for myelopathy. Hence, each patient's treatment plan must be tailored according to his or her performance status and other underlying comorbidities. Finally, malnutrition and weight loss are also of concern in patients with anaplastic thyroid cancer. In one institutional experience, 76% of treated patients experienced a median weight loss of 5% (range, 0%-20%) of initial body weight at the onset of chemoradiotherapy. Percutaneous endoscopic gastrostomy tubes were placed and were required over the long term in almost 30% of patients.[17]

A limitation of this current study is that it is a descriptive study and, unlike randomized controlled trials, does not allow for stratification according to factors that are associated with outcome. Although we did control for all known patient characteristics, it is still probable that the ability to resect the cancer correlates with both the likelihood of surgery and the likelihood of improved survival, thus leading to treatment selection bias. Related to treatment selection bias with resectability, it is also highly likely that patients who are more fit receive more intensive treatment and that their longer survival is related to their health status rather than or in addition to the treatment modalities received. Additional limitations of this study are that intent of therapy, ie, curative versus palliative, are not clearly defined when using data from a large national registry and that income and education level can only be

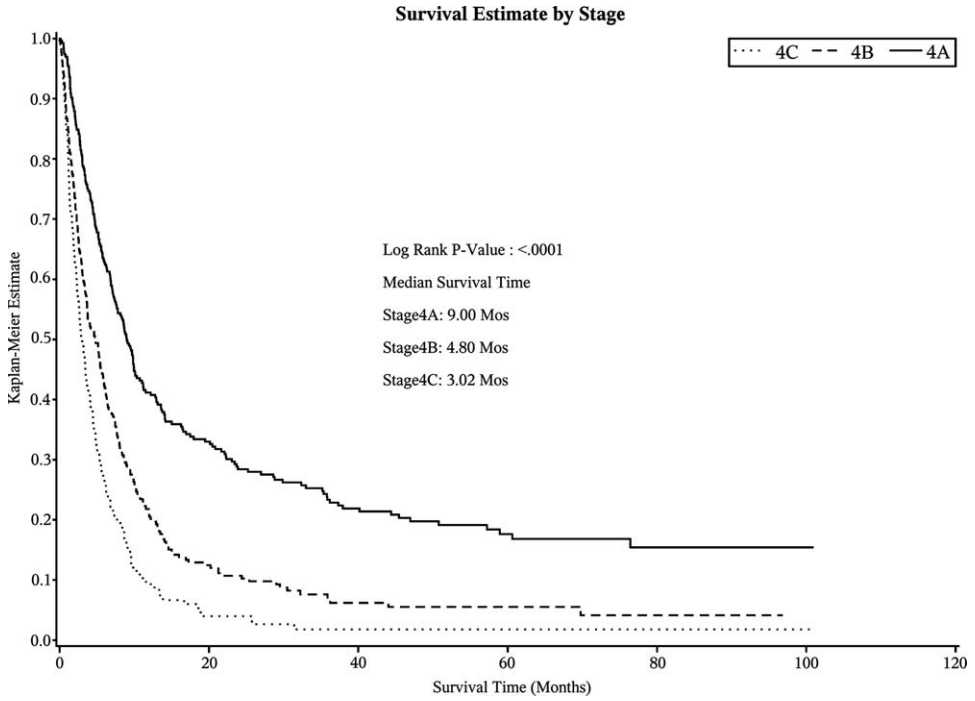

Figure 2. Overall survival is shown for patients with anaplastic thyroid cancer who had American Joint Committee on Cancer stage IVA, IVB, and IVC cancer.

TABLE 3. Stage-Stratified Survival Analysis of Anaplastic Thyroid Cancer by Treatment for Patients Diagnosed Between 2003 and 2008

Stage	N (%)	Median Survival, mo (95% Confidence Interval)
Stage IVA		
No treatment	8 (3.3%)	1.9 (0.3, 9.1)
Surgery only	70 (28.7%)	4.3 (3.1, 7.4)
Surgery + radiation	55 (22.5%)	9.3 (5.9, 17.5)
Surgery + chemotherapy	7 (2.9%)	6.4 (1.9, 37.3)
Surgery + radiation + chemotherapy	96 (39.3%)	11.2 (8.3, 15.0)
Stage IVB		
No treatment	19 (7.9%)	0.9 (0.5, 2.4)
Surgery only	72 (29.8%)	2.1 (1.3, 2.5)
Surgery + radiation	39 (16.1%)	5.9 (3.7, 8.1)
Surgery + chemotherapy	10 (4.1%)	5.7 (1.5, 12.0)
Surgery + radiation + chemotherapy	79 (32.6%)	9.9 (6.4, 12.9)
Stage IVC		
No treatment	18 (11.0%)	0.8 (0.4, 1.3)
Surgery only	41 (25.2%)	1.8 (1.3, 2.4)
Surgery + radiation	17 (10.4%)	3.5 (1.6, 8.6)
Surgery + chemotherapy	10 (6.1%)	8.2 (1.8, 18.9)
Surgery + radiation + chemotherapy	41 (25.2%)	4.9 (3.4, 6.3)

The table illustrates the survival benefit of the addition of surgery followed by adjuvant therapy with radiation and chemotherapy. Due to small numbers, radiation only, chemotherapy only, and radiation plus chemotherapy are not included in the table.

categorized by ZIP code/census data. However, previous work has found that use of census-based socioeconomic status is valid.[18]

By evaluating this large cohort of patients with anaplastic thyroid cancer, we demonstrated a statistically significant improvement in survival with more intensive therapy. However, overall survival of all patients with anaplastic thyroid cancer is dismal, and more intensive therapy leads to only small differences in median survival. This study has implications for patients and providers. The results call attention to the need for shared decision-making with informed patient participants. The risks and morbidity associated with each treatment (surgery, radiation, and chemotherapy) and the marginal expected improvement in survival should be explained to the patient.[19] Some patients and providers may decide that a 2-month prolongation of life approaches futility.[20] The aggressiveness of cancer care near the end of life has increased in recent years,[21] and yet a previous study evaluating other advanced cancers found that many patients receiving chemotherapy for incurable cancers do not understand that the chemotherapy is unlikely to be curative.[22] It is not known whether patients with anaplastic thyroid cancer understand that in most patients with the disease, the likelihood of cure with any treatment modality is low. For some patients, the chance of an improved median survival by 1 to 9 months may be worth any risk; for other patients, this marginal treatment benefit may not be worth

the risks.[23] The poor overall survival of all patients with anaplastic thyroid cancer, regardless of treatment, emphasizes the need for informed patients whose preferences are incorporated into treatment decision-making.

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CONFLICT OF INTEREST DISCLOSURE

F. Worden has provided expert testimony and has acted as a member of the Speakers Bureau for and received travel support from Bristol-Myers Squibb.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program. www.seer.cancer.gov. Accessed November 1, 2011.
2. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer*. 2005;103:1330-1335.
3. Venkatesh YS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA. Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer*. 1990;66:321-330.
4. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery*. 2001; 130:1028-1034.
5. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer*. 2001;91: 2335-2342.
6. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid*. 2011; 21:25-30.
7. Kim TY, Kim KW, Jung TS, et al. Prognostic factors for Korean patients with anaplastic thyroid carcinoma. *Head Neck*. 2007;29: 765-772.
8. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. *Cancer*. 1997;79:564-573.
9. Smallridge RC, Ain KB, Asa SL, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012;22:1104-1139.
10. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683-690.
11. American Joint Committee on Cancer. Comparison guide: cancer staging manual, fifth versus sixth edition. www.cancerstaging.org/products/ajccguide.pdf. Accessed November 1, 2012.
12. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid*. 2011;21:1183-1189.
13. Chen J, Tward JD, Shrieve DC, Hitchcock YJ. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983-2002. *Am J Clin Oncol*. 2008;31:460-464.
14. Tennvall J, Lundell G, Wahlberg P, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *Br J Cancer*. 2002;86:1848-1853.
15. Kim JH, Leeper RD. Treatment of anaplastic giant and spindle cell carcinoma of the thyroid gland with combination Adriamycin and radiation therapy. *A new approach. Cancer*. 1983;52:954-957.
16. Tennvall J, Lundell G, Hallquist A, Wahlberg P, Wallin G, Tibblin S. Combined doxorubicin, hyperfractionated radiotherapy, and surgery in anaplastic thyroid carcinoma. Report on two protocols. The Swedish Anaplastic Thyroid Cancer Group. *Cancer*. 1994;74: 1348-1354.
17. Sherman EJ, Lim SH, Ho AL, et al. Concurrent doxorubicin and radiotherapy for anaplastic thyroid cancer: a critical re-evaluation including uniform pathologic review. *Radiother Oncol*. 2011;101:425-430.
18. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82:703-710.
19. Smith TJ, Hillner BE. Explaining marginal benefits to patients, when "marginal" means additional but not necessarily small. *Clin Cancer Res*. 2010;16:5981-5986.
20. Kadakia KC, Moynihan TJ, Smith TJ, Loprinzi CL. Palliative communications: addressing chemotherapy in patients with advanced cancer. *Ann Oncol*. 2012;23(suppl 3): 29-32.
21. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol*. 2004;22:315-321.
22. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med*. 2012; 367:1616-1625.
23. Wright AA, Mack JW, Kritek PA, et al. Influence of patients' preferences and treatment site on cancer patients' end-of-life care. *Cancer*. 2010;116:4656-4663.