Aggressive Palliation and Survival in Anaplastic Thyroid Carcinoma

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**IMPORTANCE** Anaplastic thyroid carcinoma is an undifferentiated aggressive tumor with a high rate of regional and distant spread and a grave prognosis (median survival, 3 months) with no standardized treatment.

**OBJECTIVE** To review the effect of an active treatment policy on the outcome of anaplastic thyroid carcinoma.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective comparative study of all patients diagnosed as having anaplastic thyroid carcinoma and undergoing treatment from January 1, 2008, through December 31, 2013, in a tertiary university-affiliated medical center. Data were collected by medical record review. Final follow-up was completed on November 30, 2014. Data were analyzed from December 1 to 3, 2014.

**INTERVENTIONS** Treatment options included surgery and adjuvant concomitant radiotherapy and chemotherapy with doxorubicin hydrochloride or paclitaxel for local disease; full-dose chemoradiotherapy (70 Gy to the gross tumor) for local disease when surgery was not feasible; aggressive palliative radiotherapy (50 Gy to the gross tumor) for metastatic disease; and palliative radiotherapy (≤ 30 Gy) for metastatic disease with a low performance status.

**MAIN OUTCOMES AND MEASURES** Survival time and quality of life.

**RESULTS** Of the 26 patients (including 15 women) who met the inclusion criteria, 11 underwent radiotherapy with curative intent. These patients included 5 who underwent curative surgery (5 with chemotherapy) and 6 who received primary chemotherapy. Nine patients received aggressive palliative radiotherapy, and 3 received palliative radiotherapy. The remaining 3 patients were not treated. Curative radiotherapy was associated with a significantly longer overall median (95% CI) survival time (11 [8.1-13.9] months) than aggressive palliative radiotherapy (6 [3.1-8.9] months), palliative radiotherapy (3 [0.0-7.8] months), and no treatment (1 month) (P < .001). Chemotherapy in 10 patients had a significant effect on survival (mean [95% CI], 11 [1.2-6.8] vs 4 [8.1-13.9] months for patients who did not receive chemotherapy; P = .01). Among the patients who underwent surgery and curative radiotherapy, 3 were alive after more than 3 years of follow-up. No association of survival with patient sex (median [95% CI] survival for men and women, 9 [3.6-14.4] and 5 [0.3-9.7] months, respectively; P = .54) or a history of thyroid disease (median [95% CI] survival for those with and without, 4 [1.0-6.9] and 9 [5.4-12.5] months, respectively; P = .15) was found.

**CONCLUSIONS AND RELEVANCE** Anaplastic thyroid carcinoma has a grave prognosis, but an aggressive approach, including surgery, chemotherapy, and radiotherapy, seems to improve survival. Higher doses of radiotherapy may have a survival benefit in candidates for palliative treatment and may be considered for patients with extensive disease.

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Anaplastic thyroid carcinoma (ATC) accounts for only about 5% of all thyroid tumors. Nevertheless, ATC is responsible for more than half of all deaths attributed to thyroid cancer each year. Patients with ATC are usually older, and some have a history of thyroid disease. The tumor characteristics have been well documented; therefore, patients are automatically classified at presentation as having stage IV disease (A, B, or C) according to the American Joint Committee on Cancer TNM system. No standardized treatment exists for ATC; different studies suggest surgery, radiotherapy with or without chemotherapy, or only palliative, symptomatic treatment. None of these modalities has demonstrated a clear effect on outcome. The aim of the present study was to evaluate our active institutional treatment policy for ATC and its effect on outcome.

Methods

Design and Setting
We used a retrospective comparative study design. The cohort consisted of all patients with ATC who received a diagnosis, treatment, and follow-up at a tertiary university-affiliated medical center from January 1, 2008, through December 31, 2013. Final follow-up occurred on November 30, 2014. The study was approved by the institutional ethics committee of the Rabin Medical Center, and patient data were deidentified. The histologic findings were examined by a pathologist to exclude possible cases of poorly differentiated carcinoma.

Active Institutional Treatment Policy
Patients underwent staging according to the TNM system and 1 of the following 4 treatment options offered by our department, based on disease stage and general performance status:

1. For local resectable disease and Eastern Cooperative Oncology Group (ECOG) Scale performance status of less than 2 (range, 0 [normal activity] to 4 [completely bedridden]), surgery and adjuvant concomitant chemotherapy and radiotherapy.

2. For local disease when surgery was not feasible or could not be tolerated by the patient, chemotherapy with doxorubicin hydrochloride (Adriamycin), 10 mg/m² weekly, or paclitaxel, 70 mg/m² weekly, and concomitant radiotherapy at a dose of 70 Gy to the gross tumor volume and 56 to 63 Gy to the clinical target volume;

3. For metastatic disease and good ECOG performance status (<2), aggressive palliative radiotherapy at a dose of 50 Gy to the gross tumor volume and further biological treatment with sorafenib tosylate (Nexavar).

4. For metastatic disease and poor ECOG performance status (>2), palliative radiotherapy only at a dose of no greater than 30 Gy. Radiotherapy was administered during a period of 4 weeks using a hypofractionated regimen with an intensity-modulated technique. In patients with localized disease, the radiotherapy field included the tumor bed and bilateral neck at levels 2 to 6. In all other patients, the radiotherapy field included the tumor bed with a planning target volume of a 1-cm margin.

A computed tomography simulator was used to plan treatment in all cases. Tumor volumes were outlined, and a computed tomography-based display of the isodoses was recorded to confirm adequate target exposure. Multisegmental intensity-modulated radiotherapy was used.

Study Procedure
The medical records were reviewed for patient age and sex, presenting symptoms, histologic diagnosis, treatment modalities, and survival. Outcome measures were patient survival and quality of life and tumor-specific mortality.

Statistical Analysis
Data were analyzed from December 1 to 3, 2014 with SPSS statistical software (version 17.0; SPSS, Inc). Survival was calculated using the Kaplan-Meier product limit estimate method. A P value of less than .05 was considered statistically significant.

Results

Clinical Findings
Twenty-six patients, including 15 women (58%) and 11 men (42%), met the inclusion criteria. Neck mass was the most prevalent presenting symptom (19 patients [73%]), followed by dysphagia (12 patients [46%]) and hoarseness (8 patients [31%]). Other symptoms included otalgia, throat pain, and a globus sensation (8 patients [31%]). Nine patients had a history of papillary thyroid carcinoma (PTC). The diagnosis was confirmed by fine-needle aspiration biopsy findings in 22 patients (85%) and open biopsy findings in 4 patients (15%). Tumor resectability and the presence of distant metastases were assessed by computed tomography of the head, neck, and chest region.

Treatment Protocol and Survival Rate
The overall median survival time for the whole group was 6 (95% CI, 2.1-9.8) months. Five patients were alive at 1 year, for a survival rate of 19%. Eleven patients with local disease were treated with radiotherapy with curative intent (dose range, 60-70 Gy). This group included 5 patients who underwent curative surgery (complete resection in 3 and tumor-debulking surgery in 2) and adjuvant chemotherapy and 6 patients who received primary chemotherapy. All 11 patients received further chemotherapy and radiotherapy at a dose of 70 Gy to the neck region. Nine patients with metastatic and extensive neck disease and an initial good performance status received aggressive palliative radiotherapy at a dose of 50 Gy. Three patients with metastatic disease and a low performance status received palliative radiotherapy at a dose of no greater than 30 Gy. Thus, a total of 23 patients (88%) received radiotherapy. Five patients (19%) underwent surgery and 11 (42%) underwent chemotherapy. The remaining 3 patients were deemed unsuitable for any type of oncologic treatment.
Median (95% CI) survival time was 11 (8.1-13.9) months in the 11 patients treated with curative radiotherapy, 6 (3.1-8.9) months in the patients given aggressive palliative radiotherapy, 3 (0.0-7.8) months for patients receiving palliative radiotherapy (PAR), and 1 month for patients receiving no RT.

Further analyses of the 11 patients who received chemotherapy (5 after surgery and 6 primarily) revealed that 6 were treated with doxorubicin and 5 with paclitaxel or a combination of paclitaxel and carboplatin. Their median (95% CI) survival time was 11 (95% CI, 1.2-6.8) months compared with 4 (8.1-13.9) months for patients who did not receive chemotherapy. This difference was statistically significant (P = .01). Survival times by administration of chemotherapy (yes/no) are summarized in Figure 2.

Eleven patients required supportive treatment with gastrostomy (n = 7) or tracheostomy (n = 9) during the course of the disease. The lowest rate of these procedures was found in the curative radiotherapy group (2 of 7 patients undergoing gastrostomy [29%] and 2 of 9 patients undergoing tracheostomy [22%]). The findings are detailed in the Table.

To evaluate the effect of disease origin on outcome, we divided the patients into those with de novo ATC (n = 16) and those with a history of PTC (n = 10). Median (95% CI) survival was 9 (5.4-12.5) months in the de novo ATC group and 4 (1.0-6.9) months in the patients with a history of PTC. The difference was not statistically significant (P = .15). The findings are summarized in Figure 3. We found no statistically significant difference in overall survival between men (median [95% CI],

Discussion

The present study evaluated the effect of our institutional treatment protocol for ATC, based on disease and disease-related characteristics, on patient outcome. According to the guidelines of the National Comprehensive Cancer Network, the accepted treatment of ATC is surgical resection and adjunct therapy. When the disease is unresectable (most cases), patients may be referred to a clinical trial, given external beam radiotherapy with or without chemotherapy, or provided the best supportive care. So far, studies of the benefit of treatment in general and treatment optimization in particular in the medical literature have yielded unclear results, and repeated attempts to improve patient survival with these and other modalities have been made, as discussed below. However, the rarity of the disease combined with its aggressive nature and dismal prognosis make randomized clinical trials difficult.

The present study revealed significant differences in the survival of patients with ATC by type of treatment. A better outcome was noted in the patients given higher doses of radiotherapy as a curative dose or an aggressive palliative dose (50-70 Gy), with no adverse events and no deaths due to local disease progression. Our protocol is similar to the 2012 guidelines of the American Thyroid Association on ATC treatment, which recommend surgery and curative chemoradiotherapy for stage IVA disease and resectable stage IVB disease and aggressive or palliative treatment for unresectable or metastatic disease. Accordingly, our findings show that aggressive or palliative treatment can improve survival even in the presence of metastatic disease.

In an earlier retrospective study of 75 patients with ATC treated with radiotherapy, Swaak-Kragten et al reported an
Overall median survival time of 5.4 months in those who received a total dose of more than 40 Gy compared with 1.7 months in those who received at total dose of less than 40 Gy. A positive correlation between radiotherapy dose and survival was also observed by others.12-14 Chen et al15 analyzed the outcomes in 261 surgically treated patients with ATC retrieved from the Surveillance, Epidemiology, and End Results (SEER) database from 1983 to 2002. Overall median survival was 4 months. The addition of radiotherapy to surgery improved survival in patients with extensive disease into adjacent structures. However, restriction of the study group to patients who underwent surgery may have led to a selection bias for patients with less advanced disease, leading to better results. In another study based on the SEER database, Kebebew et al16 reviewed the outcomes of 516 patients with ATC treated from 1973 to 2000. Nearly two-thirds received external beam radiotherapy. The authors found that combined use of surgery and external beam radiotherapy was an independent predictor of lower cause-specific mortality.

Tennvall et al17 compared 3 ATC protocols of combined surgery, chemotherapy (doxorubicin), and hyperfractionated radiotherapy of no more than 46 Gy. The protocols differed in the number and timing of the fractions. All were associated with poor survival (median, 2.0-4.5 months). By contrast, we used hypofractionated radiotherapy at a curative dose of 70 Gy, which is the highest suggested dose. We found that prognosis was better for patients who received the curative dose (median survival, 11 months), with no grade 3 or grade 4 adverse events. However, this finding may be attributed in part to the fact that these patients initially had a better prognosis owing to their limited disease and good performance status.

The treatment of stage IVB or stage IVC ATC with extensive disease involves particular medical and ethical challenges, specifically in terms of the role of local radiotherapy. Wang et al18 treated patients with aggressive ATC with radical, once- or twice-daily fractionated radiotherapy at a dose of more than 40 Gy and those with distant metastases or poor performance status with palliative radiotherapy at a dose of less than 40 Gy. Half of the patients received the lower dose, and two-thirds of the patients had stage IVB disease. Median overall survival was 5.6 months. Patients treated with the palliative dose had a median survival of 3.2 months compared with 10.1 months in the patients treated with the radical protocol. Lowe et al19 studied 20 patients with ATC, of whom 6 were treated with palliative radiotherapy and the remainder with surgery and radiotherapy. The respective median survival times were 59 and 176 days. Bhatia et al20 described their experience with palliative intensity-modulated radiotherapy at a median dose of 45 Gy compared with 3-dimensional radiotherapy at 30 Gy. The median disease-specific and overall survival times were 1.5 months.

In a series of 47 patients with ATC, Chang and colleagues21 found that those with unresectable disease had a median survival of 2 to 3 months, and those who underwent complete tumor resection combined with chemoradiotherapy had a median survival of 6 months. The difference in survival time was not statistically significant. Indeed, most of the patients had rapid disease progression, with a mean survival of 4.3 months. The authors concluded that ATC has a poor prognosis regardless of the type of treatment. Levy et al22 assessed the effect of radiotherapy with fludeoxyglucose F 18–labeled positron emission tomography. They reported higher rates of local recurrence in patients in whom the relative standardized uptake value (a marker of tumor response to treatment) decreased less than 20%. In the present study, 9 patients with metastatic disease or low performance status were given aggressive palliative radiotherapy at a dose of 50 Gy followed by biological treatment with sorafenib. The median overall survival time was 6 months, but only 4 of these patients required tracheostomy and 3 required placement of a percutaneous endoscopic gastrostomy tube.

We sought to determine whether patients with a known history of PTC have a different prognosis from patients with de novo ATC. Some cases of ATC develop in long-standing goiters or from the transformation of preexisting, incompletely treated, differentiated thyroid cancers.23-24 Reports suggest that the larger the component of ATC in differentiated thyroid cancer, the worse the outcome will be.25 We noted a shorter median survival time in patients with a history of PTC than in patients with de novo ATC, which may indicate that the presence of PTC in patients with ATC implies a worse prognosis. However, the difference was not statistically significant (P = .15).

Table. Supportive Treatment According to Radiotherapy Protocol

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<tr>
<th>Radiotherapy Protocola</th>
<th>Supportive Treatment, No. (%) of Patients</th>
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<tbody>
<tr>
<td></td>
<td>Gastrostomy (n = 7)</td>
</tr>
<tr>
<td>No radiotherapy (n = 3)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Palliative radiotherapy (n = 3)</td>
<td>33</td>
</tr>
<tr>
<td>Aggressive palliative radiotherapy (n = 9)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Curative radiotherapy (n = 11)</td>
<td>2 (18)</td>
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* Described in the Active Institutional Treatment Policy subsection of the Methods section.
The main disadvantages of radiotherapy are minimal long-term patient gain, a long duration to completion of treatment, and the risk for adverse events. Our study demonstrates that although survival continues to be poor, it may be prolonged with local radiotherapy. Radiotherapy also decreases tumor-specific mortality and apparently prevents death from hemorrhage and suffocation (which did not occur in any of our patients). By applying a 4-week hypofractionation regimen using an intensity-modulated technique, we were able to minimize adverse events. We found no grade 3 or 4 events, and none of the patients required hospitalization for severe mucositis or esophagitis. These findings are in line with the study by Stavas et al., who demonstrated the safety and feasibility of hypofractionated radiotherapy in the treatment of ATC in 17 patients. In our cohort, aggressive palliation improved survival even in patients with extensive or metastatic disease in whom surgery was impossible. The low rates of insertion of percutaneous endoscopic gastrostomy tubes and tracheostomy suggest an improved quality of life for the patient and his or her family.

Conclusions

Survival continues to be poor in patients with ATC. Local control, even in the presence of distant metastases, improves survival and quality of life and decreases tumor-specific mortality. Further studies are needed to develop optimal radiotherapy and chemotherapy protocols.

REFERENCES