Overall Survival of Patients with Aggressive Thyroid Cancer on Fine-Needle Aspiration Biopsy Examination. A Tertiary Romanian Center Experience

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ABSTRACT

\textbf{Aim:} Anaplastic thyroid carcinoma (ATC), poorly differentiated thyroid carcinoma (PDTC) and lymphoma are aggressive forms of neoplasia. Although all carry a poor prognosis there is an important heterogeneity of overall survival (OS) between individual patients. The decision of total thyroidectomy is often based on fine-needle aspiration biopsy (FNAB) which has important limitations in this setting. Our aim was to assess the OS of aggressive thyroid cancer diagnosed on FNAB in a single university center.

\textbf{Methods:} We retrospectively reviewed all the ATC, PDTC and lymphoma cases diagnosed on FNAB during 2007-2013 (15 cases). All FNAB examinations were performed by the same specialized pathologist. Data on demographics, laboratory tests, imaging studies, FNAB/pathology reports, treatment and survival time were recorded. All patients had serum calcitonin levels under 5 pg/mL. Five patients had total thyroidectomy.

\textbf{Results:} The OS was 2.2 (0.6, 18.5) months. The survival rate at 3 and 12 months was 46.6% and 33.3% respectively. There were no significant differences between ATC and PDTC/lymphoma patients for age, TSH, largest tumoral diameter and cervical lymph involvement. Patients with ATC (8 cases) had a median OS of 0.8 months, significantly shorter than 6 months for patients with PDTC/lymphoma (7 cases). Patients treated with total thyroidectomy had a median OS of 20 months compared with 1.87 months for patients without surgical intervention (p=0.06).

\textbf{Conclusion:} The differences between groups and the heterogeneity of individual cases suggest that a diagnosis of aggressive thyroid cancer on FNAB should not preclude the surgical intervention. The decision to operate should be based on accurate imaging rather than on discouraging FNAB result.

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naplastic thyroid cancer (ATC) is a highly lethal form of thyroid neoplasia, accounting for 1-3% of all thyroid cancers (1,2). Although rare, it contributes to 14-50% of the annual mortality associated with thyroid cancer (1,2). Poorly differentiated thyroid carcinomas (PDTC) behave intermediate between differentiated and anaplastic thyroid carcinoma (3). Unlike differentiated forms of thyroid cancer, anaplastic thyroid cancer patients have a very low survival rate of only 20% at 1 year with a median of 5 months (4). Most PDTC are larger than 5 cm and invasive at diagnosis. PDTC is aggressive and often lethal. Metastases are common and 56% of patients die of their tumor within 8 years of initial therapy (5). A comparison between well-differentiated, poorly differentiated thyroid carcinoma (PDTC) and ATC performed in the Memorial Sloan Kettering Cancer Center with a median follow-up of 43 months showed 0% 5-year survival in ATC, unlike 91% in WDTC and 51% in PDTC. Lymph node metastases were present in all ATC patients compared with 47% in WDTC and 64% in PDTC (6).

ATC has been confused with lymphoma and poorly differentiated medullary thyroid carcinoma. These tumors, previously classified as small-cell ATC, carry a better prognosis and might account for the high survival reported in some ATC series (6). On fine-needle aspiration biopsy (FNAB) the differential diagnosis between PDTC and ATC is not straightforward. Although immunostaining of FNAB material could help to clarify the diagnosis it is not in widespread use (4).

Early recognition is probably important to an appropriate management of the disease. All patients require a multidisciplinary team composed of endocrinologist, surgeon, pathologist, radiation and medical oncologist and a palliation care specialist. There are very few guidelines available for the care of patients with ATC/PDTC, the latest being the American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer (4).

For patients with ATC surgical therapy consist of total thyroidectomy for those with resectable tumors and debulking palliative resection for patients with advanced stages of disease. Palliative management is meant to prevent death from asphyxiation. Airway management may be elective or emergent, depending on the patient’s presentation (4). In the case of PDTC total thyroidectomy and neck dissection followed by high-dose radioactive iodine remnant ablation is the standard treatment (7).

Chemotherapy and external radiation therapy are important options in advanced disease and in preventing the progression of the illness. Weekly administration of low-dose doxorubicin concurrently with radiation therapy showed an acceptable toxicity and may be a therapeutic option for patients with ATC (8). Combination chemotherapy with doxorubicin and cisplatin resulted in response rate of 33% in advanced thyroid cancer, producing considerable palliative effects (9). There are increasing interests in the use of taxanes for ATC, with an overall response rate of 53% in advanced ATC patients who were treated with a 96-hour infusion of paclitaxel (10). Postoperative radiotherapy improved survival of patients with disease extending to adjacent tissue, but it did not provide much benefit for patients with further extended disease or distant metastasis (11). The role of chemotherapy is controversial in PDTC patients because this kind of tumors frequently do not respond to cytotoxic agents either in vitro or in vivo (12). Chemotherapy may be indicated in patients with metastases that do not take up radioiodine (7).

Due to ambiguous result of FNAB and aggressive clinical behavior of PDTC and ATC these tumors are often managed alike. Unfortunately the surgical intervention is postponed or considered to have limited efficacy in the face of the dismal prognosis.

Our study aimed to assess the overall survival of aggressive thyroid cancer diagnosed on FNAB examination in a single university centre.

SUBJECTS AND METHODS

We retrospectively reviewed all the ATC and PDTC cases diagnosed on FNAB examination in an university clinic between 2007-2013. All FNAB examinations were performed according to the standard aspiration and staining technique by the same pathologist specialized in thyroid cytology and pathology. Data on demographics, ECOG (Eastern Cooperative Oncology Group), laboratory tests, imaging studies, FNAB/pathology reports, treatment and survival time for each individual patient can be found in Table 1. All patients had serum calcitonin levels under 5 pg/mL.
Five patients had total thyroidectomy in clinics experienced in thyroid oncologic pathology. Chemoradiation regimens and radiotherapy were performed in tertiary oncology centers. Concurrent chemoradiation regimens were 6 series of epirubicin 72 mg/m² plus cisplatin 72 mg/m² and then 4 series of paclitaxel 144 mg/m² plus a radiation dose of 50 Gy over 4 weeks for patient 2 and 10 series of paclitaxel 160 mg/m² plus a radiation dose of 50 Gy over 4 weeks for patient 4. The radiation regimen for patient 9 consisted of a 60 Gy dose over 5 weeks.

Overall survival (OS) was defined as the time from the first day of admission to the date of death from any cause.

Patients were divided in two groups: patients diagnosed with ATC on FNAB (patients 1, 4, 5, 7, 9, 10, 12, and 15) and patients diagnosed with PDTC/lymphoma at FNAB (patients 2, 3, 6, 8, 11, 13, and 14).

Data were expressed as median (25, 75 percentile) unless specified otherwise. Medcalc software (Medcalc version 8.0.0.1, Ostend, Belgium) was used to analyze the data.

### RESULTS

The median age at diagnosis was 73 years (63, 74) and the men/women ratio was 2:3.

Weight loss was a complaint in 37.5% of the patients, the average weight loss being 6.8 kg. TSH levels ranged between undetectable to 4.5 mU/L with a median of 1.1; 3 patients had a TSH value outside the normal range (lower than normal) (Table 2). Besides the large neck mass, the presentation complaints were dyspnea in 6 patients and dysphagia in 8 patients. The vocal cords were affected in 7 cases. Cervical lymph nodes involvement was found in 12 patients (80%) at presentation. Distant metastases (pulmonary, pleural, adrenal) were present in 11 patients (73.3%). The erythrocyte sedimentation rate (ESR) was high, with a median of 75 mm/h. 14 out of 15 patients had a ESR higher than 38 mm/h.

There were no significant differences between ATC and PDTC/lymphoma groups for age (72 vs. 73 years, p=0.6), TSH (1.3 vs. 1.1 mU/L, p=0.8), ESR (81 vs. 73 mm/h, p=0.6), largest tumoral diameter (83 vs. 68 mm, p=0.7) and cervical lymph involvement (100% vs. 57.1%, p=0.15).

The median overall survival was 2.2 (0.6, 18.5) months. The survival rate at 3, 6 and 12 months was 46.6%, 40.0% and 33.3% respectively.

Patients with ATC on FNAB (patients 1, 4, 5, 7, 9, 10, 12, 15) had a median OS of 0.8 months, significantly shorter than 6 months for

### TABLE 1. Main characteristics of individual patients.

<table>
<thead>
<tr>
<th>Pat. No.</th>
<th>Age (yrs)</th>
<th>Sex (M/F)</th>
<th>TSH (mU/L)</th>
<th>Maximal tumoral diameter (cm)</th>
<th>ECOG score</th>
<th>TNM</th>
<th>Stage</th>
<th>FNAB Pathology</th>
<th>Surgical treatment (y/n)</th>
<th>RxT (y/n)</th>
<th>ChT (y/n)</th>
<th>OS (mo)</th>
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<td>T4bN1bM0</td>
<td>IVb</td>
<td>ATC</td>
<td>y</td>
<td>n</td>
<td>n</td>
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</tr>
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<td>60</td>
<td>M</td>
<td>1.1</td>
<td>6.7</td>
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<td>T4aN1bM1</td>
<td>IVc</td>
<td>Lymphoma</td>
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<td>2</td>
<td>-</td>
<td>-</td>
<td>PDTC</td>
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<td>n</td>
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<tr>
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<td>F</td>
<td>2.5</td>
<td>6.4</td>
<td>1</td>
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<td>IVc</td>
<td>ATC</td>
<td></td>
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<td>PDTC</td>
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<tr>
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<td>PDTC</td>
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<td>6</td>
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<td>1.19</td>
<td>9.9</td>
<td>2</td>
<td>-</td>
<td>-</td>
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<td>Riedel thyroiditis</td>
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<td>ATC</td>
<td>-</td>
<td>n</td>
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ATC, anaplastic thyroid carcinoma; ChT, chemotherapy; EOG, Eastern Cooperative Oncology Group; FNAB, fine-needle aspiration biopsy; OS, overall survival; PDTC, poorly differentiated thyroid carcinoma; RxT, radiotherapy; TNM, tumor nodes metastasis classification; TSH, thyroid stimulating hormone.
OVERALL SURVIVAL IN AGGRESSIVE THYROID CANCER

DISCUSSION

Our study aimed to assess the overall survival of aggressive thyroid cancer diagnosed on FNAB examination in a single university centre. We included patients with both ATC and PDTC or lymphoma because in many centers the surgical intervention is a priori considered to have minimal efficiency and is often contraindicated for all these cancer types. Moreover, in these cases the diagnostic accuracy of FNAB is inferior to that reported for the more frequent papillary/follicular thyroid carcinomas (4). We tried to show that the prognosis and OS are not severe in all cases and that the FNAB result should not preclude the surgical intervention if this is technically feasible according to the results of preoperative radiologic exams.

Our group showed an OS of 2.2 (0.6, 18.5) months with a survival rate at 3 and 12 months of 46.6% and 33.3% respectively. The slightly higher rate of survival at 1 year in our group compared with ATC-only cohorts (33.3% vs. 20%) (4) is probably due to the inclusion of non-ATC cases in our group. However, the lower survival in our ATC group as compared with published ATC-only cohorts (0.8 months vs. 5 months) is probably due to the high proportion of untreated patients (62.5%, 5 out of 8 patients). As expected the PDTC/lymphoma group showed a longer OS compared with ATC group (6 months vs. 0.8 months).

Only 3 patients had radiotherapy and only 2 had chemotherapy (2 different regimens) so the efficacy of these treatments could not be assessed. Five patients had a total thyroidectomy but although the OS was longer (20 months vs. 1.87 months) the difference was not statistically significant, probably due to the small number of cases. However, it cannot be ruled out that only milder cases, those with a better prognosis per se and lower ECOG score (higher performance status), were operated.

Few cases are worth mentioning. Patient 2 was diagnosed with lymphoma on FNAB but the pathological examination of total thyroidectomy specimen suggested an ATC. Patient followed radiotherapy and chemotherapy and had an overall survival of 30 months. He died few hours after a laborious surgical intervention for a massive retroperitoneal metastasis. Patient 3 was diagnosed with PDTC on FNAB which proved to be an embryonal follicular adenoma. She was still alive at study completion (OS >22

patients with PDTC/lymphoma (log rank test p=0.03) (Figure 1A). Patients treated with total thyroidectomy (patients 1, 2, 3, 4, 9) had a median OS of 20 months compared with 1.87 months for patients without surgical intervention (log rank test p=0.06) (Figure 1B). However, patients treated with total thyroidectomy had also a lower ECOG score (better performance status) than patients without surgery (p=0.02).
months). Patient 4 had an ATC on FNAB which was confirmed on pathology. After total thyroidecotomy she followed chemo and radiotherapy and had an OS of 20 months. Patients 8 had a diagnosis of cystic and hemorrhagic goiter on FNAB but a lymphoma could not be ruled out. The open biopsy revealed a poorly differentiated solid carcinoma and she died after only 2 months. Patient 14 was diagnosed with PDTC/lymphoma on FNAB. The open biopsy showed a Riedel thyroiditis. The patient is still alive (OS >25 months).

The ESR was elevated in our patients 75 (56, 98) mm/h. There were no differences between ATC and PDTC group. The elevated ESR (14 out of 15 patients had an ESR higher than 38 mm/h) should be compared with that of papillary/follicular thyroid carcinoma where it is often normal.

The main limitation of our study is the small number of patients (15 cases). This is due to the low incidence of aggressive thyroid cancer. The lack of pathology reports for 8 patients (53%) is an obvious drawback but also points out that surgery/open biopsy is too often contraindicated based on clinical grounds and FNAB result. For 7 patients the pathology report was also available: 3 patients were diagnosed with ATC on FNAB and this was confirmed on pathology. A PDTC case proved to be an embryonal adenoma and the 3 lymphoma cases was diagnosed as an ATC, a poorly differentiated carcinoma and a Riedel thyroiditis respectively on pathology. The inconsistencies underline the difficulties of FNAB in non-WDTC tumors (4).

The differences between groups and the heterogeneity of individual cases suggest that a diagnosis of aggressive thyroid cancer on FNAB should not preclude the surgical intervention. The decision to operate should follow the advice of a multidisciplinary team be based on core biopsy and accurate imaging rather than on discouraging FNAB result.

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