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Follicular Thyroid Carcinoma: Disease Response Evaluation Using American Thyroid Association Risk Assessment Guidelines

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Key Words
Follicular thyroid carcinoma · Response evaluation · Risk assessment · Radioactive iodine · Thyroidectomy

Abstract
Objective: To evaluate the overall and progression-free survival for follicular thyroid carcinoma (FTC) based on the American Thyroid Association (ATA) staging system for recurrence risk assessment and the TNM staging system. ***Methods:*** A clinical review of FTC patients between 1995 and 2014 was conducted at a single center. The data was classified using the TNM staging system into low, intermediate, and high risk of recurrence as per the ATA risk assessment. ***Results:*** Over the course of 19 years, 114 (11.9%) of all of the thyroid cancer patients presenting to our hospital had FTC (i.e. 78 females and 36 males). The age range was 15–80 years. Ninety-four tumors were resectable and 18 were unresectable. Sixteen patients were excluded due to insufficient information on their recurrence risk. Based on the ATA categorization, 36 patients had a low recurrence risk. All patients were alive at the time of categorization, and 1 showed progressive disease. Thirty-eight patients had an intermediate recurrence risk. One patient died and 2 showed progression. Twenty-four had a high recurrence risk. Seven patients died and 6 showed progression. In terms of TNM stages, 2 (3.2%) stage I, 3 (17.6%) stage II, 1 (14%) stage III, and 2 (12.5%) stage IV patients died during follow-up. Both ATA risk classification and TNM staging were significant predictors of disease-free survival. On bivariate analysis, the ATA classification (HR 4.67; 95% CI 1.74–12.5, p = 0.002) was a better predictor of survival compared to the TNM classification (HR 1.26; 95% CI 0.98–1.62, p = 0.063). ***Conclusion:*** ATA risk stratification predicts the disease recurrence rate and survival better than TNM staging. Age does not have an association; the risk category with dynamic reassessment effectively better predicts the course of disease in FTC.

Introduction

Although most patients with follicular thyroid carcinoma (FTC) have a favorable prognosis [1], metastatic and recurrent tumors continue to pose a challenge. It is important to correctly determine the risk of recurrence and to follow patients according to their risk group with dynamic reassessment based on their clinical and biochemical status. The American Thyroid Association

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(ATA) recurrence staging system effectively predicts the risk of recurrence and persistent disease. In addition, follow-up data from the first 2 years after the diagnosis is used to categorize responses to therapy as excellent, acceptable, or incomplete [2]. An excellent response is considered as no evidence of disease on imaging, with stimulated and suppressed thyroglobin (Tg) <1 ng/ml. An acceptable response is defined as suppressed Tg <1 ng/ml, serum stimulated Tg levels of 1–10 ng/ml, or nonspecific changes in neck ultrasound or radioactive iodine-131 imaging. An incomplete response is defined as suppressed Tg ≥1 ng/ml, stimulated Tg ≥10 ng/ml, rising TG values, or persistent/newly identified disease on imaging.

The aims of this study were to evaluate the overall survival and compare the progression-free survival for FTC based on the ATA risk recurrence staging system versus the TNM staging system followed by a continuous risk assessment during the first 2 years.

Methods

Setting

This study was carried out in the Department of Nuclear Medicine of Shaukat Khanum Memorial Cancer Hospital and Research Centre, a 189-bed cancer specialist center in Lahore, Pakistan. The data of all FTC patients between 1995 and 2014 was collected retrospectively from the electronic medical record system.

The data was analyzed for basic demographic patterns and then classified based on TNM stage and ATA guidelines for risk of recurrence into one of the following 3 categories: low, intermediate, and high risk of recurrence. Disease behavior was compared using both of these classification systems to determine which one better predicted survival and progression. This study was approved by the institutional review board.

Management

Where possible, a complete thyroidectomy was performed, with neck dissection if there was evidence of nodal disease on MRI. Unresectable thyroid disease received external field radiation therapy. High-dose radioactive iodine (RAI) therapy was administered for remnant ablation, and patients were started on suppressive thyroxine doses. Subsequently, serum Tg and anti-Tg levels were monitored every 6 months for the first 2 years and yearly thereafter. In the case of tumor marker elevation, a whole-body RAI scan was obtained. If a site of uptake was identified, it was ablated with high-dose RAI therapy. Follow-up tumor marker levels and a low-dose RAI scan were obtained at 1 year. In patients with tumor marker elevation and no apparent disease on the low-dose RAI scan, a positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with a computed tomography (^{18}F-FDG PET/CT) was obtained. Disease identified on an ^{18}F-FDG PET/CT scan was either resected surgically or targeted with external beam radiation therapy.

Statistics

For disease-free survival, the data was analyzed via the Kaplan-Meier method using SPSS software. Differences between groups were evaluated using a log-rank test, and $p < 0.05$ was considered statistically significant. Multivariate analysis was performed with the Cox proportional hazards model using the Enter method, and $p < 0.05$ and was considered statistically significant.

Results

A total of 114 patients presented with FTC during the 19 years studied. During this period, 954 thyroid cancer cases were registered and FTC was present in 114 (11.9%) of all thyroid cancer patients. Of these patients, 78 (68%) were females and 36 (32%) were males. The age range was 5–80 years, with a mean of 40 years. Our youngest patient was a 5.5-year-old girl with an intermediate risk of recurrence at presentation.

At the baseline presentation, 94 tumors were deemed resectable on an MRI scan of the neck and 18 were unresectable due to invasion of either vascular or spinal structures on imaging. Two did not have adequate imaging.

During categorization based on the risk of recurrence, 16 patients were excluded due to a lack of data to perform analyses. These patients had had a surgical resection at an outside hospital. Each outside specimen was reviewed at our hospital to confirm the histopathological diagnosis of FTC; however, in some cases there was insufficient information regarding capsular invasion on the submitted blocks. The remaining 98 were classified as a low, intermediate, or high risk of recurrence. The details of demographics, data stratification by TNM stage, and ATA risk assessment are displayed in table 1 and figure 1.

No significant difference in mean age was seen among the 3 categories. The mean follow-up time was 5.2 years, with the shortest duration of follow-up being at least 1 year. All patients received at least 1 high dose of RAI for remnant ablation. During follow-up, 8 patients died due to thyroid cancer.

ATA Low Risk of Recurrence

Thirty-six of the 98 (36.7%) patients evaluated had a low likelihood of recurrence at presentation. In this group, there were 28 (77.7%) females and 8 (22.3%) males. Twenty-eight (77.7%) patients were under the age of 45 years. The baseline Tg level was elevated in 5 (13.9%) and invalid due to an elevated anti-Tg antibody level in 8 (22.2%) patients. Four (11.1%) patients were lost to follow-up after less than 1 year. The remaining 32 (88.9%) patients were alive at follow-up.

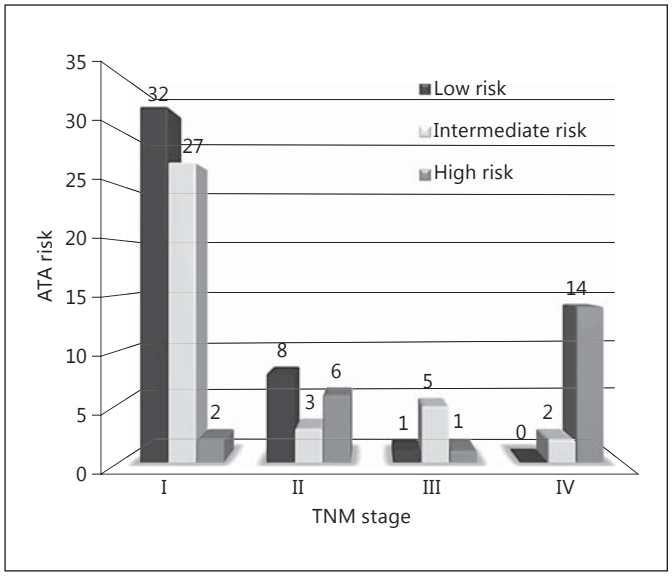

Fig. 1. Comparison of ATA risk groups and TNM stages.

Table 1. Patient characteristics

Total patients, n	114
Female:male ratio	2.5:1
Age range, years	5–80
TNM stage, n	
I	61
II	14
III	7
IV	16
ATA risk stratification, n	
Low	36
Intermediate	38
High	24

One patient progressed despite a total thyroidectomy at baseline and developed a noniodine avid Tg elevation 4 years after RAI therapy, indicating dedifferentiation. An ^{18}F-FDG PET/CT scan showed pulmonary metastases. Our patients with the longest survival was doing well after 10 years.

The average RAI dose received was 152.8 ± 100 mCi. Only 6 (16.7%) patients received more than 1 RAI dose. The highest cumulative dose received was 650 mCi. No patient required radiation therapy to the neck or to any distant metastases on follow-up.

According to the TNM staging system, 31 (86.1%) tumors were stage I, 4 (11.1%) were stage II, and 1 (2.8%) was stage III. The only patient in this low-risk group who showed progression was stage II at presentation. In this group, only 1 patient was stage III, and he was in remission with no evidence of disease after 3+ years of follow-up.

ATA Intermediate Risk of Recurrence

Thirty-eight (38.8%) patients had an intermediate risk of recurrence. At presentation, 24 (63.2%) were under the age of 45 years. The presurgical/baseline Tg level was elevated in 15 (39.5%) patients and invalid due to an elevated anti-Tg antibody level in 5 (13.2%). At baseline, 5 (13.2%) patients had nodal metastases. Five (13.2%) patients were lost to follow-up after less than 1 year. The average RAI dose received was 160 ± 111.4 mCi. Of the total number of patients, 7 (18%) received 2 or more RAI therapies. The highest cumulative dose for a single patient was 640 mCi. On follow-up, 4 (10.5%) patients became iodine-131 resistant after the first RAI therapy, and a subsequent ^{18}F-FDG PET/CT due to elevated Tg levels and iodine resistance revealed pulmonary and osseous metastases in 1 (2.6%) of them. Tg levels declined in the other 3 (7.9%) patients spontaneously.

Based on TNM staging, 28 (73.7%) patients were stage I, 3 (7.9%) were stage II, 5 (13.1%) were stage III, and 2 (5.3%) were stage IV. The single patient who passed away was stage I at presentation. He died 3 years after the diagnosis due to disease progression and metastases to the lungs and bones despite RAI and chemo- and radiation therapy. Of the 3 (7.9%) patients who progressed, 2 (5.3%) were stage I and 1 (2.6%) was stage IV. The patient with longest disease-free survival (i.e. 18 years) was stage III at presentation.

ATA High Risk of Recurrence

Twenty-four (24.5%) patients had a high risk of recurrence. In this group, there were 16 (66.7%) females and 8 (33.3%) males. At presentation, 9 (37.5%) patients were under the age of 45 years. The baseline presurgical Tg level was elevated in 12 (50%) patients and invalid due to an elevated anti-Tg antibody level in 3 (12.5%). At baseline, the thyroid was deemed unresectable in 13 (54.2%) patients and each received radiation therapy to the thyroid bed.

Seventeen (70.8%) patients had metastases at presentation, including nodal (n = 8), pulmonary (n = 6), osseous (n = 12), and cerebral (n = 2) metastases. The average RAI dose received was 378 ± 255 mCi. Ten (42%) patients received >2 RAI therapies, and the highest cumulative RAI dose given to a single patient was 760 mCi.

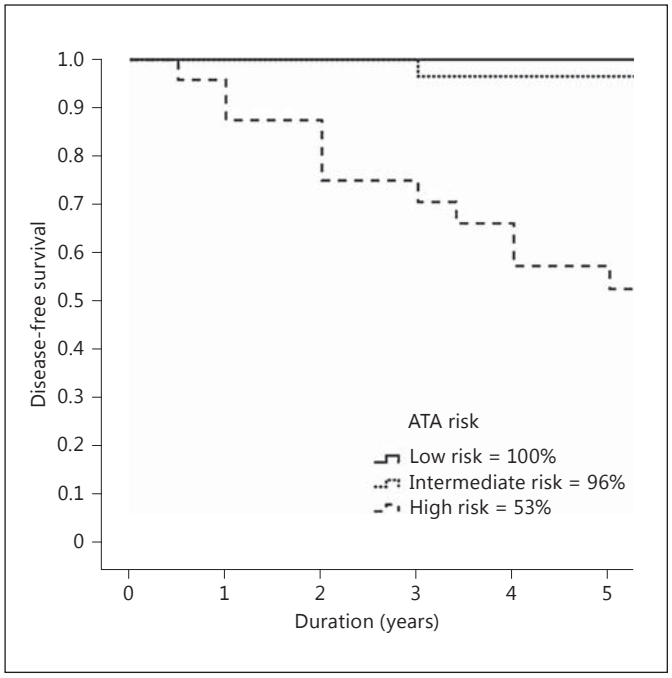

Fig. 2. Kaplan-Meier curve displaying the 5-year disease-free survival by ATA risk category (low, 100%; intermediate, 96%, and high, 53%). The log-rank test showed a significant difference in the percent survival of the ATA risk groups ($p < 0.01$).

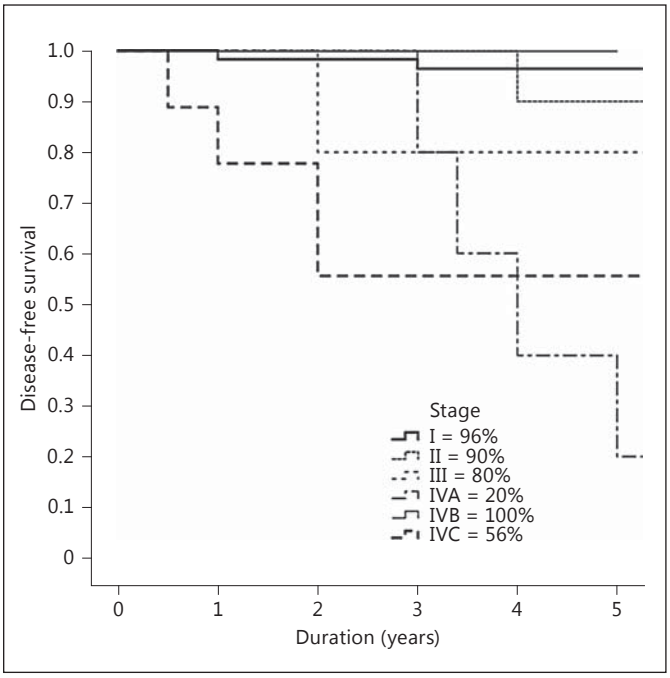

Fig. 3. Kaplan-Meier curve displaying the 5-year disease-free survival by TNM stage (stage I, 96%; stage II, 90%; stage III, 80%; stage IVA, 20%; stage IVB, 100%, and stage IVC, 56%). There was a significant difference in survival rate ($p < 0.01$).

Seven (29.2%) patients died and 6 (25%) others showed progressive metastatic disease. Four of the 7 patients who passed away were under the age of 45 years at presentation. The duration of the longest survival was 17 years. Two (8.3%) patients developed metastases on follow-up, and 4 (16.7%) showed progression of metastatic disease. An ^{18}F-FDG PET/CT scan performed in 2 (8.3%) patients with non-iodine-131 avid disease showed metastatic disease in both patients.

At baseline, 2 (8.3%) patients were stage I (1 died), 7 (29.2%) were stage II (3 died and 2 showed progression), 1 (4.2%) was stage III, and 14 (58.3%) were stage IV (2 died and 4 showed progression). The 5-year disease-free survival by ATA risk group is shown in figure 2.

Based on the TNM Staging System

In terms of TNM stages, 61 patients were stage I. Of these, 5 had unresectable tumors at presentation and 3 (5%) passed away during follow-up. The average RAI dose received was 143 ± 65 mCi. Fourteen patients had stage II tumors, and all were resectable, but 3 (21.4%) of these patients died. The average RAI dose received was 304 ± 254 mCi. Seven patients had stage III tumors. Of these, 2 were unresectable and 1 (14%) patient died during follow-up. The average RAI dose received was 255 ± 256 mCi. There were 16 stage IV patients. Ten of these had unresectable tumors at presentation and 4 (25%) died during follow-up. The average RAI dose received was 335 ± 247 mCi. The 5-year disease-free survival by TNM stage is shown in figure 3.

In terms of disease-free survival, univariate analysis revealed that both ATA risk classification ($p < 0.01$) and TNM staging ($p < 0.01$) were statistically significant. On bivariate analysis, ATA classification (HR 4.67; 95% CI 1.74–12.5, $p = 0.002$) was a better predictor of survival compared to TNM classification (HR 1.26; 95% CI 0.98–1.62, $p = 0.063$; table 2).

Reassessment during the First Two Years

Thirty-one (27%) patients had either biochemical or structural evidence of disease or both. In the low-risk group, an excellent response was seen in 86% of the patients, an acceptable response was observed in 5.5%, and the response was incomplete in 8.3%. There was biochemical evidence of disease in 2 patients and evidence of biochemical and structural disease in 3. In the intermediate

Table 2. Bivariate analysis of disease-free survival based on the ATA classification versus TNM staging

	Regression coefficient	Standard error	Wald test	Degrees of freedom	p value	HR	95% CI for the HR	Covariate mean
ATA risk	1.541	0.502	9.417	1	0.002	4.672	1.745–12.504	1.878
TNM stage	0.235	0.126	3.466	1	0.063	1.265	0.988–1.621	1.969

HR = Risk of death/progression according to the prognostic variables.

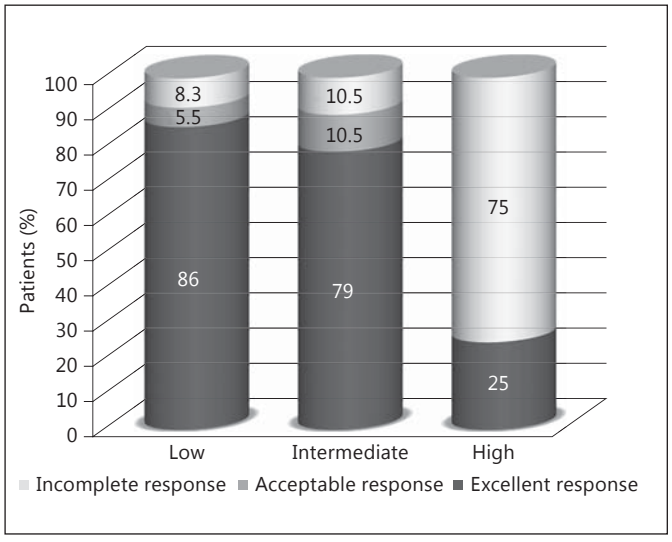

Fig. 4. Dynamic risk reassessment of ATA-based risk groups.

category, 79% of the patients had an excellent response, 10.5% had an acceptable response, and 10.5% had an unacceptable response. Of these, 1 subsequently died. In the high-risk category, 6 (25%) patients had an excellent response. Of these, 1 (16%) developed evidence of disease 16 years after the initial treatment and died. Eighteen (75%) patients had an unacceptable response, and on follow-up 6 (33%) of these patients died. The results of the dynamic risk assessment at 2 years are shown in figure 4.

Discussion

FTC is less frequent compared to papillary thyroid carcinoma. At our institution, only 11.9% of thyroid cancer patients were histologically proven to have FTC. This rate is higher than the reported trend in the USA, where 9% of thyroid carcinomas between 1973 and 2002 were follicular carcinomas [3]. In contrast, Balan et al. [4], in a study of 249 patients from 1967 to 1990, found that 32% had FTC. There was a female preponderance in our series, which is quite comparable to what is seen in the rest of the world (i.e. a 3:1 ratio in most populations).

Although the overall 5-year relative survival rate for papillary thyroid carcinoma and FTC is greater than 90% [8], FTC has a poorer prognosis compared to papillary thyroid carcinoma. The mortality rate ranges from 5 to 15% even if the disease is confined to the thyroid at the time of diagnosis [4, 5]. Minimally invasive FTC or tumors with microscopic capsular invasion have an overall worse prognosis than those with no invasion [6].

In our study, all patients received at least 1 high-dose RAI therapy remnant ablation. Upon classification by ATA risk stratification, we saw that the number of repeated doses administered for rising Tg or anti-Tg levels was directly proportional to the increase in the risk of recurrence. Patients with a low risk of recurrence received a smaller number of RAI therapies, and the cumulative dose was lower.

Podnos et al. [7] studied 2,112 FTC patients and found that iodine-131 provides a survival benefit for some patients, with the greatest improvements in those that have locoregional or distant disease spread. They also found that a tumor size <2 cm and an age <45 years provided a survival benefit. In our study, the largest proportion of patients under the age of 45 years was in the low-risk group, followed by the intermediate- and high-risk groups. However, there was no difference in the number of high-risk patients above or below 45 years of age who passed away.

The ATA risk staging system was a better predictor of disease-free survival and overall survival compared to the TNM staging system. After the initial assessment, a dynamic risk assessment during the initial 2 years allowed a more accurate risk assessment; this is in keeping with what was reported by Tuttle et al. [2]. The only exception was 1 patient with a low risk of recurrence at baseline with an acceptable response during the first 2 years. At the 4-year follow-up, the patient was found to have developed

rising Tg levels, and he was found to have noniodine avid pulmonary metastatic nodules on a PET/CT scan. At each follow-up visit, patients were reassessed based on the biochemical and structural disease status and managed accordingly.

Cano-Palomares et al. [8], in a study of 176 patients, reported that the response to the initial therapy system showed a negative predictive value of 97.7%, which is better than negative predictive values of the European Thyroid Association (ETA) and ATA systems (i.e. 93.9 and 94.9%, respectively). The ETA and ATA systems showed poor positive predictive values (i.e. 40.3 and 41%, respectively), while response to the initial therapy showed a positive predictive value of 70.8% [8].

Orlov et al. [9], in a study of 246 patients, found that age, primary tumor size, and pTNM staging did not predict the risk of residual/recurrent well-differentiated thyroid cancer, whereas extrathyroidal extension at the initial surgery was a better predictor.

Conclusion

ATA risk stratification predicts the disease recurrence rate and survival better than TNM staging. Age does not play a role; the risk category with dynamic reassessment effectively better predicts the course of disease in FTC.

Disclosure Statement

The authors report no conflict of interest.

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