PROGNOSTICATORS OF SURVIVAL IN DIFFERENTIATED THYROID CARCINOMA

Hemen K. Parikh¹, Raja S. Rao², S. S. Shrikhande³, Rohini Havaladar⁴,
Vinay H. Deshmane⁵, Deepak M. Parikh⁶

ABSTRACT : *Differentiated carcinoma of the thyroid has good prognosis, even in patients presenting in the late stage and with distant metastasis. In India, the incidence of papillary carcinoma and follicular carcinoma are in the ratio of 60:40. A retrospective study was carried out to determine the impact of patient and tumor factors on survival, and to develop a simple risk group staging system to predict survival in patients with differentiated thyroid carcinomas .*

Four hundred and seventeen (417) patients undergoing primary treatment at our hospital between 197-1985, were entered to the study. There were 198 follicular carcinomas and 219 papillary carcinomas. Impact of patient and tumor variables were studied by drawing Kaplan Meier curves and comparing them by the Chi Sq Test. Age ≤ 40 years ($p=0.00001$), tumor size < 5 cms ($p=0.01$), extrathyroidal spread ($p=0.001$) and distant metastasis ($p=0.00001$) had significant impact on survival. These findings were true for a subset analysis follicular and papillary carcinomas separately. A Cox Regression Analysis was also performed and this showed the above factors to impact significantly on survival. Basing on the regression analysis we devised a simple risk group system and classified the patients as high and low risk. Low risk group patients had a significant survival advantage. Our findings show that the incidence of follicular carcinoma is significantly high in India (48%) and that 65% of our patients are in the high risk group. Incidence of contralateral lobe disease on completion thyroidectomy is as high as 53%. Hence, a more aggressive treatment policy is warranted and total thyroidectomy is the appropriate treatment of choice in our patients.

INTRODUCTION

Differentiated thyroid carcinoma (DTC), consists of the papillary thyroid carcinoma (PTC) and the follicular thyroid carcinoma (FTC) and their variants. The disease has an indolent course and long term survivors are expected, even in patients with disseminated disease.

Debate regarding optimal surgical management for these tumors is still ongoing. Numerous risk group stratifications have been made based on the analysis of various prognostic variables. (1,2,3,4) Surgeons who advocate less than a total thyroidectomy as treatment, base their decision on the reduced morbidity of a conservative procedure. They specially cite recurrent laryngeal nerve injury and hypoparathyroidism as complications that justify a lesser procedure. It is also stated that there is no difference in long term survival, specially in the low risk group.

The goal of surgery in thyroid carcinoma is extirpation of the disease-primary and nodal, and subsequent appropriate postoperative treatment, namely radio-iodine therapy. The fears of residual disease, multicentric/multifocal disease, and the possibility of local recurrence of disease are strong

arguments favouring a total thyroidectomy (5,6). Clark (7) reported an 80% incidence of multicentricity or occult carcinomas in total thyroidectomy specimens and Mazzaferri and Young (8) reported a statistically significant reduction in recurrences in patients who underwent a total thyroidectomy.

A review of literature shows that the majority of large series, have papillary carcinoma as the predominant histologic type. The number of cases of follicular carcinoma in these studies range from 10%(5) to 28%(9).

The disease pattern differs in India, and it has been our experience that papillary and follicular thyroid carcinomas exist in nearly equal numbers. An analysis of our patients of DTC seen at our hospital between 1969 to 1993 shows that the ratio of PTC to FTC has remained largely unchanged over 25 years. (Table I)

Hence, to evaluate the disease in our population, we planned a retrospective study of our data with the aim :
a. To evaluate the survival patterns in PTC and FTC in our population.

¹Assistant Surgeon, ²Director and Chief of Surgery, ³Former Chief of Pathology, ⁴Biostatistician, ⁵Senior Research Fellow, ⁶Assistant Surgeon, Dept. of Surgery and Pathology, Tata Memorial Hospital, Dr. E. Borges Marg, Parel, Bombay - 400 012, India

Table -I**Distribution of Differentiated Thyroid Carcinoma : 1969-1993**

	Papillary	Follicular
1969-1978	223	249(53%)
1979-1988	755	487(40%)
1989-1993	458	254(36%)
Total	1436	990(40%)

- b. To define patient and tumor factors affecting survival.
- c. To formulate a risk group classification that could be simple, easy to use and applicable to both PTC and FTC. It was important that this risk grouping system was applicable in the preoperative stage-thus allowing for decision making.

MATERIALS AND METHODS

This is a retrospective study of 417 patients undergoing treatment for differentiated thyroid carcinoma at our hospital, between 1971-1985. All patients entered in this study fulfilled the following criteria —

- a. Patients referred primarily for treatment, without any prior intervention and had all their treatment completed at this hospital.:
- b. Patients who had some sort of biopsy/surgical procedure performed elsewhere and were then referred for further treatment. All these patients had further surgical and other adjuvant therapy at our hospital.
- c. All patients had their histology reviewed for classification to papillary or follicular carcinoma. [SSS] All patients with pure papillary, mixed papillary-follicular or papillary with follicular elements were classified as PTC. Patients of pure follicular and Hurthle cell carcinoma were classified as FTC. Any patient classified as a medullary carcinoma or anaplastic carcinoma, on review, were not included in this study.
- d. Only patients receiving definite surgical therapy at our hospital were included in this study.

Patient and tumor factors were evaluated for their impact on survival, which included : age of patient, sex, tumor type (histology), tumor size, node metastasis, extrathyroid spread and distant metastasis. Cut off points were assumed for our patients for age and tumor size, basing on the mean age and tumor size, which was 40 years and 5 cms respectively.

Table -II**Patient Distribution (n=417)**

Papillary	219
follicular	198

Age in years	Males	Females
0-20	16	18
21-40	59	107
41-60	70	98
>60	23	26
M:F	168	249

Survivals were studied by plotting Kaplan-Meier survival curves for each of the prognostic variable and comparing them by the Chi Sq. test (univariate analysis). A multivariate analysis of these factors was performed using the Cox Regression Model.

RESULTS

There were 219 cases of papillary carcinoma and 198 cases of follicular type. There was a preponderance of females in this study (M:F = 1:5). Patient ages ranged from 6 years to 83 years. (Table II) Twenty two percent (22%) patients had a surgical procedure performed elsewhere before being referred to our institution of further management. Largely these were hemithyroidectomies. The majority were referred on the basis of having a goitre/thyroid nodule for investigation and management.

Univariate analysis of patient and tumor factors was carried out by plotting the Kaplan-Meier survival curves.

1. Age : We adopted a cut-off age ≤ 40 years for **both** sexes. The survival curve shows a significant survival advantage ($p < 0.001$) for the younger age group. (Fig. I)
2. Sex : There was no survival difference between the genders (Fig. II)
3. Histology : The PTC seemed to do better than FTC in the univariate analysis (Fig. III), which did not reach significance on multivariate analysis.
4. Tumor size : was an extremely important prognostic factor, with smaller tumors > 5 cms doing significantly well - $p < 0.001$ (Fig. IV).
5. Node involvement: Did not have any significant impact on survival. (Fig. V)
6. Extrathyroidal spread : Patients without extrathyroidal spread had a distinct survival advantage over those

Fig. I : Survival curves for age.

Fig. V : Survival curves for nodal metastasis.

Fig. II : Survival curves comparing gender.

Fig. VI : Survival curves for extra-thyroidal spread.

Fig. III : Survival curves comparing histology.

Fig. VII : Survival curves for metastatic disease.

Fig. IV : Survival curves comparing tumor size <5 cm vs >5 cm

Fig. VIII : Survival curves comparing "Low Risk" and "High Risk" patients.

who had either microscopic or gross extrathyroidal extension. (Fig.VI)

7. Distant metastasis : Patients with distant metastasis had very poor survival (Fig.VII)

A multivariate analysis was performed, using the Cox Regression Model to evaluate the impact of the variables

on survival. The factors that were independently significant included : age $\leq$ 40 yrs, tumor size <5 cms, extrathyroidal spread and distant metastasis. (Table IV)

EVOLUTION OF PREDICTIVE "RISK GROUPS"

Based on the results of the regression analysis, we

Table -III
Multivariate Analysis

Variable	p-value
Age	<0.001
Sex	0.61
T-Size	0.0005
Histology	0.88
Node Metastasis	0.91
Extrathyroid spread	0.0013
Metastasis	0.0043

formulated risk groups as per the details below :

LOW RISK

- a. age ≤ 40 years and
- b. Tumor size < 5 cm. and
- c. Extra-thyroid spread - absent and
- d. Distant Metastasis - absent

HIGH RISK

- a. Age > 40 years or
- b. Tumor size > 5 cm. or
- c. Extra-thyroid spread - present or
- d. Distant Metastasis - present.

classification of our patients. If ALL the favourable criteria were found in a patient he/she was classified as "Low Risk". If EVEN ONE of the factors was unfavourable, the patient was classified as "High Risk". There were 144(34.5%) patients classified as low risk and 237 (65.5%) as high risk. Survival curves comparing these groups showed a significant survival difference, $p < 0.001$. (Fig.VIII)

DISCUSSION

In the management of cancer patients, it has been shown in recent times, less radical operations may achieve equivalent survival goals with reduced morbidity. This has been shown to be true for a variety of cancers and whether this truth could be applied to treatment of thyroid carcinoma has been a subject of debate for several decades. The advantages of a total thyroidectomy in treatment of differentiated thyroid carcinoma (DTC) has been strongly disputed. (2,3,10,11)

Hence, in an attempt to identify patients who would benefit from lesser procedures, numerous attempts have been made to formulate various risk group classifications. The E.O.R.T.C. Prognostic index was formulated for all histologies of thyroid carcinoma, by a complex scoring system which divided the risk groups from 1 to 5. (1)

This initial attempt was followed by a more elaborate staging from the Mayo Clinic, which was based on their experience with papillary carcinomas; resulting in the AGES classification(2). The AGES system was further modified since it was found that PTC could not be graded with certainty. The new scoring system proposed was the MACIS system, (4) which, once again is applicable to papillary carcinoma only.

The EORTC and AGES system were cumbersome and hence impractical to use in routine clinical practice, while the MACIS system required surgical intervention prior to allocation to a risk group. Cady (3), proposed the AMES scoring system, which was applicable for both PTC and FTC. In their series, the incidence of follicular carcinoma was only 26% and the overall incidence of patients in the high risk group was 16% Hay et al.(2), had 18% patients classified as high risk.

In analysing our results, we planned our cutoff values for age and tumor size based on the means of these values. As with other reports, (1,2,3,4,9,12) we found age at diagnosis one of the most important prognostic factors. The age cutoffs used in various series between 40 years to 50 years. Tumour size, extrathyroid infiltration and distant metastasis are other independently significant variables affecting survival. Our results are in agreement with other large studies. (2,3,4,9,13)

Female gender, histology and differentiation have been stated as important prognostic factors in some studies (9), however this was not seen in our study. Noguchi et al., did not find histology or differentiation as important prognostic factors on multivariate analysis.(14) Differentiation of tumor was not studied by us.

We simplified the formulation of our risk group staging (conforming largely with the AMES system) such that this could be applied preoperatively to DTC. The important features of this scoring system is that it uses a common cutoff age for both sexes and the presence of any one factor being unfavourable is considered high risk. This simplistic scoring system has been vindicated by the survivals seen in the high and low risk groups. This risk group classification system is easy to use in clinical practice and not cumbersome.

In our series, an inordinately large number of patients are in the high risk group(65%) and almost half our patients

belong to the follicular histology. Thus we have adopted an aggressive treatment policy in treatment of DTC. We routinely use radio-iodine ablation for all our patients who show a postoperative uptake of 5% or more. This allows ablation of any residual thyroid tissue, if any, and allows early metastasis to be picked up and treated. DeGroot et al. have shown a statistically significant reduction in recurrence and death in patients who underwent 1-131 ablation following a total thyroidectomy. (15) They support an aggressive treatment policy for tumors larger than 1 cm. Similar results have been reported by Emerick. (16)

Because of the high ratio of follicular carcinomas and high risk patients in our population, we recommend and practice a total thyroidectomy for DTC. It may be worthwhile studying, on a prospective basis, the role of conservative surgery for the low risk group; either in a clinical trial setting or by observing similar cohort of patients being treated elsewhere and comparing them with patients undergoing a more radical procedure.

CONCLUSIONS

Papillary carcinoma and follicular carcinomas are distinct histological entities. However, their biological behaviour is quite similar. The variables having independent significant impact on survival includes : age, tumor size, extra-thyroidal spread and metastasis. Our proposed risk group classification is easy to use in the preoperative evaluation of patients and assignation to risk groups, which is supported by the survival results in these groups.

We see a larger number of follicular carcinomas and the majority of our patients are in the high risk group. Hence, we recommend a total thyroidectomy for DTC, followed by radio-iodine ablation in all cases.

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Address for Correspondence :

Dr. Heman K. Parikh, Assistant Surgeon
Tata Memorial Hospital, Dr. E. Borges Marg, Parel,
Bombay - 400 012, India.