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RESEARCH COMMUNICATION

Threshold Primary Tumour Sizes for Nodal and Distant Metastases in Papillary and Follicular Thyroid Cancers

Maseeh uz Zaman[1], Nosheen Fatima[2], Zafar Sajjad[1], Jaweed Akhtar[1], Najmul Islam[1], Qamar Masood[1], Asma Ahmed[1]

Abstract

Background: In papillary and follicular thyroid cancers (PTC, FTC), nodal and distant metastasis are generally considered important determinants of recurrence and survival, respectively. However, there is no consensus about the threshold primary tumour size (PTS) for these determinants. The aim of this study was to assess size relationships for developing nodal, pulmonary, bone and overall distant metastases. Methods: This prospective study covered 139 (93 females and 46 males) consecutive biopsy proven patients with PTC (114/139, mean age 41.0 ±15.7 years, M: F, 35%:65%) and FTC (25/139, mean age 39.2 ± 14.3 years, M: F: 24%:76%). Results: Average primary tumor size was 23.4 ± 11.1 mm and 26.5 ± 13.1 mm for PTC and FTC respectively (p value=0.223). Nodal metastasis was found more common in PTC than FTC (49% vs 28%, p value <0.05), whereas overall distant metastasis was approximately the same (13% and 24%, p value =0.277); however, bone metastasis was significantly higher in FTC than PTC (24% vs 5%, p value <0.05). Cumulative risk for nodal and distant metastases for FTC and PTC starts at PTS <20 mm and may indicate an unusual aggressive tumor behavior in the studied population. Highest cumulative risk for nodal and pulmonary metastases in PTC and for bone metastasis in FTC was found to be ≥50 mm PTS. Conclusion: We conclude that a PTS of <20 mm may indicate an unusual aggressive tumor behavior with highest cumulative risk for nodal and pulmonary metastases in PTC and for bone metastasis in FTC with a cutoff of ≥50 mm.

Keywords: Thyroid cancer - papillary - follicular - metastasis - tumour size

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Introduction

Well differentiated thyroid cancer (WDTC) which includes papillary (PTC) and follicular thyroid cancers (FTC) is an uncommon malignancy with a reported worldwide incidence of 0.5-10/100,000 population (Franceschi and Vecchia, 1994). These tumors have an indolent clinical course with late relapse. The outcome of patients with WDTC has been determined by multiple factors. It has been reported that higher recurrence is closely linked to lymph node metastasis (Coburn and Wanebo, 1992). Increasing primary tumor size (PTS) has been found to have correlation with an increased risk of extrathyroidal growth and distant metastasis (Machens et al., 2005). However, the single most important determinant of survival in this condition is distant metastasis [worse with bone metastasis] (DeGroot et al., 1990) with the median survival of 4.1 years (Shoup et al., 2003). A PTS of > 2 cm has been considered as a threshold for distant metastasis and as a demarcation between T1 and T2 lesions by American Thyroid Association (ATA) in its recent guidelines (Cooper et al., 2009).

The aim of this study was to find out threshold primary tumour sizes for developing nodal, pulmonary, bone and over all distant metastasis.

Materials and Methods

This is a prospective study which included 139 (93 females and 46 males) consecutive biopsy proven patients with WDTC who attended nuclear medicine section of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan for radioiodine-131 (^{131}I) treatment from January 2005 till July 2011. These patients were referred from The Aga Khan University Hospital (AKUH), Karachi, Pakistan. The study was duly approved by the ethical committee of the Institute. We included only those patients who had complete information of PTS as mentioned in their histopathology reports, ultrasound neck, serum TSH >30 IU/ml, stimulated thyroglobulin level with antibodies, ^{131}I ablation and a post therapy whole body iodine scan (WBIS). Patients with no information about tumor size in histopathology reports and histopathology other than PTC, follicular variant of PTC and FTC (like Hurtle cell, tall, columnar, sclerosing or insular type or well differentiated tumor of unknown malignant potential) were excluded. For confirmation of nodal metastasis histopathology was used as gold standard while ^{131}I avid distant metastases (lung, bone or soft tissue) seen on WBIS were confirmed by imaging modalities like ultrasound, CT and MRI.

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Table 1. Patients' Demographics

	Papillary Thyroid Carcinoma (PTC) (114)	Follicular Thyroid Carcinoma (FTC) (25)	p value
Age (mean± SD) years	40.96 ± 15.7	39.16 ±14.29	0.588
Male	40 (35%)	06 (24%)	0.409
Female	74 (65%)	19 (76%)	
Primary Tumor Size			
Mean ± SD in mm	23.4 ± 11.1	26.5 ± 13.1	0.223
Post-op Thyroglobulin			
Median (range) ng/dl	14 (0.15-12000)	77 (3.5-6900)	0.194
Pot-op TSH			
Median (range) IU/L	60 (2.25-100)	50 (5-100)	0.138
Nodal Metastases	56 (49%)	7 (28%)	0.046*
Distant Metastases			
Overall	15 (13%)	6 (24%)	0.277
Bone	06 (5%)	6 (24%)	0.006*
Pulmonary	10 (9%)	2 (8%)	0.818

SD, Standard Deviation; TSH, Thyroid Stimulating Hormones; *p<0.05 (statistically significant)

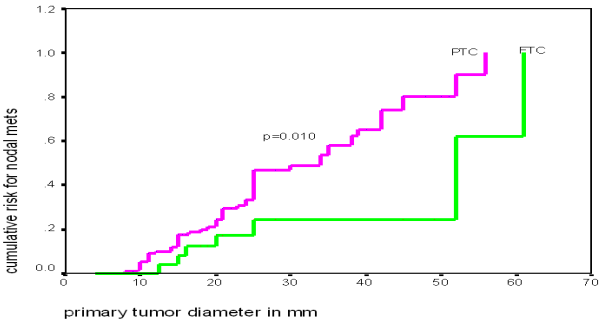

Figure 1. Cumulative Frequency Risk for Nodal Metastasis with Relation to Primary Tumor Size of Papillary and Follicular Thyroid Cancers

Statistical Analysis

Categorical and continuous data were tested on univariate analysis using the two-tailed Chi Square test. For comparative analysis of cumulative risks between both tumor entities, the Kaplan–Meier method (log-rank test) was used. The level of significance was set at P< 0.05. Commercial statistical software packages (SPSS version 12 and MedCalc®) were used.

Results

We included biopsy proven 114/139 (82%) patients (mean age 40.96 ±15.7 years, M: F, 35%:65%) of PTC and 25/139 (18%) cases (mean age 39.16 ± 14.29 years, M: F: 24%:76%) of FTC. Out of these 139 patients, 103 had total thyroidectomy, 36 had completion thyroidectomy and in 63 patients nodal dissection was also performed (Table 1). Average primary tumor size was 23.4 ± 11.1 mm and 26.5 ± 13.1 mm for PTC and FTC respectively (p value=0.223). Nodal metastasis was found more common in PTC than FTC (49% Vs 28%, p value <0.05). Cumulative frequency risk for nodal metastasis in PTC rises linearly with PTS (starting at a PTS of 8-10 mm) (Figure 1). For FTC, cumulative frequency risk for nodal metastasis increases with a PTS between 12-25 mm followed by a plateau up to 50 mm and then an exponential rise is seen after > 50 mm PTS (p value <0.05; Log rank). Incidence of overall distant metastasis was same for PTC and FTC (13% and

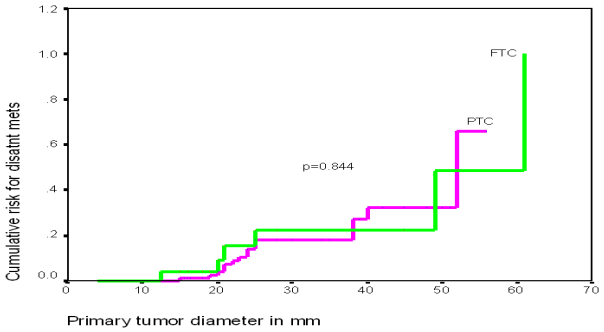

Figure 2. Cumulative Frequency Risk for Overall Distant Metastases with Relation to Primary Tumor Dize of Papillary and Follicular Thyroid Cancers

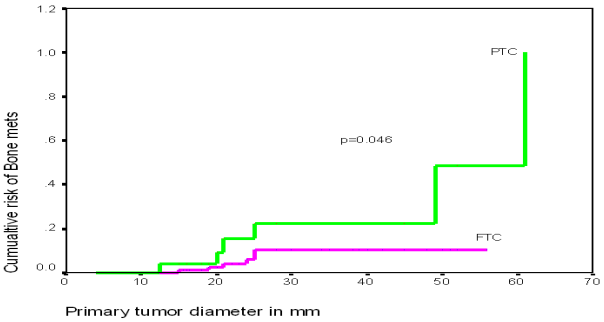

Figure 3. Cumulative Frequency Risk for Bone Metastasis with Relation to Primary Tumor Size of Papillary and Follicular Thyroid Cancers

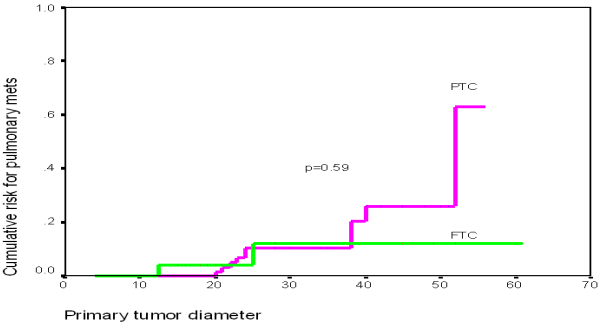

Figure 4. Cumulative Frequency Risk for Pulmonary Metastasis with Relation to Primary Tumor Size of Papillary and Follicular Thyroid Cancers

24%, p value=0.277, Table 1) with a congruent cumulative frequency risk for PTS in FTC and PTC (p value = 0.844; log rank, Figure 2) however, bony metastasis was significantly higher in FTC than PTC (24% Vs 5%, p value <0.05, Table 1). For FTC cumulative frequency risk for bony metastasis was started at PTS of 12 mm or more in a linear trend up to 25 mm followed by constant response between 25-50 mm when an exponential rise was noted at 50mm (p value <0.05; Log rank, Figure 3). For PTC, the cumulative risk for bone metastasis shows progressive rise for a PTS of 15-25 mm then followed by plateau in rest of its course. Similarly, the incidence of pulmonary metastasis was same (p value=0.818, Table 1). In PTC the cumulative frequency risk for pulmonary metastasis showed an initial linear relation at PTS 20-25 mm then a constant response between 25-38 mm followed by an exponential ascend. In FTC the cumulative frequency risk for pulmonary metastasis was observed at PTS of 12 mm with a slight rise till 25 mm and then it followed a constant response (p value = 0.59; Log rank, Figure 4).

Discussion

According to various reports patients with FTC are on average 3-6 years older and have larger PTS than PTC (Mazaferri and Jhiang 1994; Hölzer et al., 1996; Hundahl et al., 1996). A delay in diagnosis due to inability of fine needle aspiration (FNA) to delineate between adenoma and carcinoma (Cerutti et al., 2004) is supposed to be one of the major factors. However, in this study PTS and mean age of patients with FTC and PTC were marginally different (non-significant p values). The most plausible explanation for this fact might be an early referral and proactive approach employed in patients with thyroid nodule resulted in early diagnosis of follicular neoplasm.

Cumulative risk for nodal metastasis for PTC was higher than FTC due to early and predominant nodal spread of PTC as indicated by steeper curve for PTC. However, position of anchoring points on the ordinate (x intercept) of the curves showed a threshold PTS of 8-10 mm for PTC and 12-14 mm for FTC. This is an important finding in this study as thyroid nodules <20mm size are considered low risk and TNM classification has used 20 mm demarcation between T1 and T2 lesions (Sobin and Wittekind, 2002). Exponential rise in nodal metastasis in FTC after 50mm PTS may be explained by higher degree of invasion associated with larger tumor size (Asari et al., 2009). Incidence of nodal metastasis in PTC in this study is 56% which coincides with reported incidence of 23-56% (Grebe and Hay, 1996; Shaha, 1998) but incidence of nodal metastasis in FTC in our study (28%) is higher than the reported incidence of 5-13% (Soh and Clark, 1996). Higher incidence of nodal metastasis in FTC and at a PTS <20 mm (both FTC and PTC) in this study indicate a possible aggressive behavior of disease in studied population which needs further studies for precise evaluation.

In our study the incidence of distant metastasis overall was statistically not significant between PTC and FTC and this is in contrary to most of the published studies which show higher incidence in FTC (Shaha et al., 1997). This fact may be explained by small sample size of FTC cohort. Another possible explanation might be an unusual aggressive nature thyroid cancer in our region as depicted by an appreciable number of nodal metastasis with small PTS and congruent cumulative risk for distant metastasis overall with respect to PTS. Higher incidence of bone metastasis in FTC with a linear cumulative frequency risk with respect to PTS is explained by hematogenous spread of tumor (Schlumberger, 1998) and this correlates well with the reported incidence (Durante et al., 2006). However, there are reports which found no difference between PTC and FTC for cumulative risks of distant metastasis to the bone (Machens and Wanebo, 2005). The cumulative frequency risk of PTC shows a relatively persistent and low risk for bony metastasis for increasing PTS and this could be explained by well known predominant nodal route of dissemination of PTC. However, FTCs show an exponential rise in risk of bone metastasis for PTS >50 mm (approaching almost 100%) which denotes threshold PTS > 50 mm as an important predictor of bone metastasis in FTC. The incidence of pulmonary metastasis in FTC and PTC are statistically similar (non significant p value) and this is concurred with published data (Machens and Wanebo, 2005). The cumulative frequency risk of FTC for pulmonary metastasis shows a low but appreciable risk even for tumor size between 10-20 mm which draws attention towards a possible aggressive tumor nature in studied population. The cumulative risk of pulmonary metastasis for PTC shows a progressive increase and an exponential rise (>60%) for a PTS >50 mm (threshold size to predict pulmonary metastasis for PTC). We don't have any plausible explanation for predilection of PTC for pulmonary metastasis and FTC for bone metastasis for a threshold PTS of 50 mm and needs more studies to probe this aspect of pathogenesis.

We conclude that (1) Cumulative risk for nodal and extra-nodal metastases for FTC and PTC starts at PTS <20 mm and may indicate an unusual aggressive tumor behavior in studied population; (2) highest cumulative risk for nodal and pulmonary metastases in PTC and for bone metastasis in FTC was found to be ≥50 mm PTS.

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