

Original Article

Pattern of metastasis in differentiated thyroid carcinoma

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Abstract:

Total 60 patients were selected as per described criteria from the department of Otolaryngology and head neck surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2005 to October 2006. In this study of 60 patients of differentiated thyroid carcinoma (DTC), majority of the patients are within 31-50 yrs age group with female predominance. Papillary carcinoma was more common in 31-40 yrs age group and follicular carcinoma was more common in 41-50 years. Thyroid swelling was the most common presenting symptom of DTC (91.66%), followed by cervical lymphadenopathy (33.33%). Among the 60 DTC patients, papillary carcinoma was commoner (73.33%) than follicular carcinoma (26.67%). Overall female-male ratio for these 60 patients of DTC was 1.72: 1, but in papillary type the ratio was 1.44:1. and for follicular carcinoma was 3:1. Out of 44 papillary carcinoma patients 18 patients had cervical lymph node metastasis (40.90%), and out of 16 follicular carcinoma patients 2 had cervical lymph node metastasis (12.50%); $P < 0.05$. Among the 44 papillary carcinoma patients only 1 had distant metastasis (2.27%), and among the 16 follicular carcinoma patients 4 had distant metastasis (25%); $P < 0.05$. 85% of the patients were presented with unilateral and 15% were presented with bilateral lymph node metastasis. In this series, distant metastasis was found in bone and lung, Maximum lymph node metastasis was found in level II (42.10%), level III (57.89%) and level IV (42.10%).

Finally the Chi-square (χ^2) significance test was performed according to above described findings and it was found that there is significant difference in the pattern of lymph node metastasis and of distant metastasis between papillary and follicular type of DTC ($P < 0.05$).

Key words: Thyroid carcinoma, Metastasis.

Introduction:

Clinically recognized thyroid carcinoma constitutes less than 1% of human malignant tumours¹. Among them differentiated thyroid carcinoma is the most common variety.

There are two types of differentiated thyroid carcinoma. Papillary and follicular carcinoma. The incidence of thyroid carcinoma varies in different series². The presence of a solitary thyroid nodule is a risk factor for malignancy. The incidence of malignancy within a solitary thyroid nodule is approximately 10%³. The reported incidence of carcinoma in solitary nodule

varies from 2-20%^{4,5}. Among the thyroid swelling 9.89% cases were reported to be carcinoma and most of which were papillary type⁶.

Metastasis of differentiated thyroid carcinoma occur in two different ways lymphatic and haematogenous. Nodal metastasis occurs in 40% of papillary carcinoma and 4% of follicular carcinoma. On the other hand blood borne metastases are twice as common in follicular carcinoma than papillary group⁷.

Young patients with differentiated thyroid carcinoma typically present with regional lymph node involvement. Distant metastasis and extremes of age has poor prognosis. Distant metastasis is an aggressive with lethal consequence. Distant metastases are the principle cause of death from papillary and follicular carcinoma¹. By multivariate analysis, any age at the time of diagnosis of distant metastasis ($p < 0.0001$) and involvement of multiple organ sites ($p < 0.0003$) were independently associated with cancer mortality. The highest risk of cancer death (92% at 5 years) was found in the 14

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patients (any age), who at the time of first diagnosis of metastasis had multiple organ involvement⁸.

Lungs and bone are the commonest sites of distant metastasis⁹. At time of diagnosis of distant metastasis only lung 53%, bone 20% and multiple organ 16% were involved¹⁰.

Tumor Staging and Prognostic Scoring Strategies: Several staging and clinical prognostic scoring strategies use patient age over 40 as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma. When applied to the papillary carcinoma data from the Mayo Clinic, four of the schemes using age (EOTRC-European Organization for Research and Treatment of Cancer, TNM/tumor characteristics, lymph node involvement, and distant metastatic lesions, AMES/age of patient, presence of distant metastatic lesions, and extent and size of the primary cancer, and AGES/patient age and tumor grade, extent, and size), were effective in separating low-risk patients, in whom the 20 year cancer-specific mortality was 1%, from high-risk patients, in whom the 20 year cancer-specific mortality was 30% to 40%, with incrementally worsening metastasis, age, completeness of resection, invasion, and size (MACIS) scores of less than 6; 6 to 6.99; 7 to 7.99; and 8+; the 20-year survival rates were progressively lower: 99%, 86%, 59%, and 24%, respectively.

The American Joint Commission on Cancer (AJCC) TNM staging approach, which is perhaps the most widely used schemes, classifies tumors in all patient under age 45 as stage I and stage II (i.e., low risk), even those with distant metastases. Although, it has been widely verified to predict cancer mortality, TNM staging does not forecast the high number of recurrences that occur in patients diagnosed before age 20, which is true of all prognostic scoring systems that lend heavy weight to age¹⁰.

In the Otolaryngology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka, we define low and high risk in following order. Here, in papillary carcinoma a low risk patient means a case which has got, a) age between 15 to 40 years, b) intrathyroidal growth, c) tumor size less than 4 cm. and d) no nodal or distant metastasis; and a high risk patient means a case having a) age below 15 year and over 40 years, b) extra thyroid growth, c) tumor size 4 cm. or more and d) with nodal or distant metastasis. All follicular carcinoma are kept in high

risk group irrespective of age of patient, extent & size of tumor and metastasis. The above criteria has a close similarity with NCCN (National comprehensive cancer network, USA) criteria in regard to papillary carcinoma but different to NCCNs low and high risk types, we categorize all follicular carcinoma as high risk ones¹.

Prognostic importance of regional lymph node metastasis is controversial. In some study lymph node metastasis are not associated with worse prognosis¹¹. But in others it is important especially in elderly patients.

But there are many studies where recurrence of diseases is higher in cervical lymph node metastasis that may be a marker for more aggressive differentiated thyroid carcinoma.

The associated cervical lymph node metastasis with an increase recurrence rate, a more aggressive differentiated thyroid carcinoma, low operative and radioiodine related morbidity support an aggressive approach for management of differentiated thyroid carcinoma with lymph node metastasis.

In contrast to squamous cell carcinoma of head & neck, distant dissemination is not a death sentence for differentiated thyroid carcinoma. Long term survival of the patient with distant metastasis is quite satisfactory, in one study 43% overall survival compared with 80% survival in patient without distant metastasis¹¹.

Few cases were also reported to involving brain, mediastinum, skin, liver, eye, Kidney and other organs¹².

So pattern of metastasis is important in overall management of differentiated thyroid carcinoma.

Aims and Objectives

General

To find out the relative frequency of both locoregional and distant metastasis in patients with differentiated thyroid carcinoma.

Specific

- To find out the age and sex distribution.
- To find out the relative frequency of papillary and follicular type.
- To find out the pattern of metastasis.

Methods:

A detailed clinical history was taken from each patients about the thyroid swelling and its duration, any other neck swelling, neck pain, dysphagia, respiratory distress, cough, hoarseness of voice and any other body swellings. Any previous thyroid disease or surgery of the head neck, previous irradiation was also discussed during history taking process. A full head and neck examinations with special attention to thyroid region and cervical lymph nodes was noted. A brief general examination was also performed. A examination of larynx was also performed thoroughly with indirect or fiberoptic laryngoscopy. Then FNAC examination from the thyroid and neck node, ultrasonography, scanning examination, thyroid hormone levels were also performed.

Some of the patients were also investigated radiologically in the form of x-ray neck, chest, affected bones. CT scan and MRI were also performed in some of the patients for precise detection of spread of the disease.

Surgery was performed to the patients and the choice of surgery was detected by stage of the disease and others risk factors. During surgery under general anesthesia, neck palpation was also performed to detect metastatic lymph nodes. After performing surgery, the surgically excised thyroid and lymph node, some soft tissue were examined histopathologically. Most of the patients after surgery were followed up for 2/3 visit in an average of one month. Four patients with distal metastasis were treated with radio iodine ablation procedure.

Findings of every patients were documented as per data form. After compiling the results, they had been arranged and presented in various tables and figures. On the basis of this results the significance of this study was tested statistically by using the Chi - Square test (χ^2). χ^2 value was compared with corresponding probability value.

Observations and Results:**Table-I***Age distribution of patients of DTC (N = 60)*

Age (Years) Groups	Total Number of Patients	Percentage
0-10	6	10
11-20	3	5
21-30	7	11.66
31-40	18	30
41-50	16	26.66
51-60	6	10
61-70	4	6.66

Most of the patients are between 30-50 years of age group. Mean -37 years.

Table-II*Age distribution of both papillary and follicular type of DTC.*

Age(Years)	Papillary		Follicular	
	N = 44	%	N=16	%
0-10	6	13.63	0	0
11-20	2	4.55	1	6.25
21-30	4	9.09	3	18.75
31-40	16	36.37	2	12.50
41-50	10	22.73	6	37.50
51-60	2	4.55	4	25.00
61-70	4	9.09	0	0

Papillary thyroid carcinoma (PTC) type is more frequent in 31-40 years. age group (36.37%) followed by Follicular thyroid carcinoma (FTC) type which is more frequent in 41-50 years. age group (37.50%).

Table-III*Presenting symptoms of patients on admission. (N = 60)*

Symptoms	Average duration (months)	Number	Percentage (%)
Thyroid Swelling	5	55	91.66
Cervical Lymphadenopathy	3	20	33.33
Dysphagia	1	3	5.00
Pain in Neck	1	5	8.33
Bony Swelling	1	2	3.33

Table-IV
Histological type of DTC (Done by postoperative Histopathology)

Type of Malignancy		Number		Percentage (%)
Total		60		100%
Papillary	Pure papillary	40	44	73.33%
	Mixed papillary follicular	3		
	Follicular variant	1		
	Pure Follicular	15		
Follicular	Hurthle cell variant	1	16	26.67%
Overall ratio	-	Female : Male	=	1.72 : 1
For Papillary	-	Female : Male	=	1.44 : 1
For Follicular	-	Female : Male	=	3 : 1

Table-V
FNAC of finding of DTC (from thyroid) (N = 60)

Type of Malignancy	Result		
	Malignant	Adenoma	Suspicious
Papillary	40	0	4
Follicular	0	12	4

Table-VI
FNAC Finding of neck node in DTC. (N = 60)

No. of patients	FNAC Positive for malignancy	FNAC Negative for malignancy	Suspicious
20	14	2	4

Table-VII
Cervical lymph node metastasis in DTC. (N = 60)

Type of DTC	Number	Metastatic cervical lymph node present	No Cervical metastasis	Percentage (%) of lymph metastasis
Papillary	44	18	26	40.90
Follicular	16	2	14	12.50

Table-VIII
Distance metastasis in DTC (N = 60)

Type of DTC	Number	Metastatic cervical lymph node present	No Cervical metastasis	Percentage
Papillary	44	1	43	2.27
Follicular	16	4	12	25

Table-IX
Overall metastasis in DTC. (N = 60)

Type of DTC	Number	Metastatic present	Metastasis absent	Percentage (%)
Papillary	44	16	28	43.18
Follicular	16	6	10	37.50

Table-X
Cervical lymph node metastasis in DTC (N = 20)

Cervical lymph node metastasis	Number	Percentage (%)
Unilateral	17	85
Bilateral	3	15

Table-XI
Distant involvement in DTC. (N = 60)

DTC type	Number of Patients	No. of Patients with distant metastasis		Total
Papillary	44	Bone	Lungs	1
		0	1	
Follicular	16	Skull	1	4
		Sternum	1	
		Humerus	1	

Table-XII
Levels of cervical lymph node involvement in DTC (N = 20)

Level of Lymph node	Pattern of involvement	Number of involved patient	Percentage of involvement
I	Only level-I	0	5.26
	Level-I+II	1	
II	Only level –II	4	42.10
	Level-II+III+IV	4	
III	Only level-III	4	57.89
	Level-III+II+IV+V	7	
IV	Only level-IV	3	42.10
	Level-IV+III+V+VI	5	
V	Only level-V	0	21.05
	Level-V+III+IV+VI	4	
VI	Only level-VI	2	21.05
	Level-VI+III	2	

20 Patients out of 60 DTC patients had cervical lymph node involvement from level I to VI. The most frequently involved levels are II (42.10%), III (57.89%), IV (42.10%), V (21.05%), VI (21.05%). Most of the patients involved more than one lymph node levels.

Table-XIII
Local findings during thyroid surgery (N = 20)

Group	Surgery done	Total	Operation findings	No local invasion
			Local invasion	
Papillary	44	44	2	42
Follicular	16	15	4	11

Local invasion by thyroid carcinoma is a frequent finding. In this study local extension carcinoma was found in 2 PTC patients and 4 FTC patients during surgery.

Table- XIV
Local invasion findings during thyroid surgery.

Type of DTC	No. of patients with invasion	Organ/structure	No.
PTC	2	Strap muscles	1
		Larynx	1
FTC	4	Trachea	1
		Oesophagus	1
		Rec. laryngeal nerve	1

Local invasion by thyroid carcinoma to local structures is a frequent finding in this study larynx, trachea, oesophagus, rec. laryngeal nerve, strap muscles are the structures found involved by thyroid carcinoma.

Discussion:

Carcinoma of the thyroid gland is an uncommon Cancer, 0.6% and 1.6% of all cases of malignant neoplasia in men and women respectively¹³, but is the most common malignancy of endocrine system. Among them the differentiated tumors (papillary and follicular) are highly treatable and have a good prognosis. The incidence of this malignancy has increasing over the last decade. In a series of DTC cases in BSMMU Dhaka it has been shown that the incidence of DTC is increasing, like 3 cases in 1985 to 23 cases in 2000¹. The cause this may be due to modern diagnostic techniques and increased cancer consciousness among the people. Yet this has been associated with a significant fall in mortality rate in some countries¹.

The incidence of thyroid cancer in Bangladesh is not known. One study at INM & thyroid clinic in Institute of Post-graduate Medicine & Research (IPGMR) Dhaka reviewed 2629 thyroid patients from January 1994 to June 1995 and found thyroid carcinoma in 2.58%¹⁴.

The American cancer society estimates that 20700 new cases of thyroid cancers are diagnosed in 2002 in USA and that 1300 thyroid cancer related death occur annually¹⁵(AACE- 2001).

In this prospective study of 60 cases of DTC we have tried to see mainly the pattern of metastasis in DTC, along with others variables like age, sex, operation findings etc.

In this series the high incidence of DTC is found in the 30 - 50 years age group. This result correlates with that of Watkinson, 2000³ where it was stated that although thyroid cancer can occur at any age, the

majority of patients specially those with DTC are elderly. In adolescence and young adult thyroid cancers is predominantly of the well differentiated type. The peak incidence of the disease is in 4th decade in papillary and 5th decade in follicular.

It is predominantly a disease of women. The female to male ratio is 2.5:1 in a study¹⁶. In another study¹⁷, the female to male ratio is 3:1 and is related to patient's age. In this study shows a clear predominance of female over male in DTC. It is shown that overall female to male ratio is 1.72:1, for papillary it is 1.44:1 and for follicular it is 3:1.

In this study it is shown that out of 60 DTC cases 73.33% are of papillary & 26.67% are of follicular type, confirmed by postoperative histopathology. It shows a clear predominance of papillary over follicular carcinoma. According to the study³, frequency of PTC is 80% and that of FTC is 10%. Another study¹⁶ shows that Papillary carcinoma comprises about 60% of all thyroid cancers, and follicular carcinoma comprises 18% of all malignant thyroid neoplasm¹⁸. Histological subtypes of both PTC and FTC were also found in this study. Out of 44 PTC patients, 40 were pure papillary, 3 were mixed papillary-follicular and 1 was follicular variant of PTC. Out of 16 FTC patients, 15 were of pure follicular variety and only 1 was Hurthle cell carcinoma.

The age distribution both for papillary and follicular variety in this study it is shown that, the peak incidence of papillary carcinoma in 31-40 years group and that of follicular in 41-50 years group. In other study¹⁷, it was stated that thyroid carcinoma is common in all age groups with FTC tends to occur more frequently in older adults than papillary carcinoma.

DTC may present in a variety of way, like that of primary site, local extension and that of local and distant metastasis. In this study it is shown that the main

and frequent presenting way of DTC is thyroid swelling (91.66%). According to the study¹⁷ the most common presentation of thyroid cancer is an asymptomatic thyroid mass. A study¹⁶ stated that thyroid neoplasm either benign or malignant present in the early phase as solitary nodule. Another study¹⁸ by Krukowski, in 2005 stated that the most common presenting symptom of thyroid cancer is a thyroid swelling.

Like all other malignancies DTC also metastasize to regional lymph nodes, to distance organs like bones, lungs and infiltrates to local structures. This study shows a 40.90% of lymph node metastasis in papillary and 12.50% in follicular type of DTC. These result shows a statistical difference. In one review, nodal metastasis were found in 36% of 8029 adults with papillary DTC and 17% of 1540 patients with follicular DTC. The study¹⁸, shows lymph node metastasis rate in PTC is 35% and in FTC is 13%. The study¹⁶ stated that bilateral spread to the neck node is found in about 8% of papillary defends this study. An enlarged cervical lymph node may be the only sign of thyroid carcinoma. In this patients multiple nodal metastasis either unilateral or bilateral are usually found at surgery. In the study¹⁹ contralateral cervicolateral and upper mediastinal lymph node metastasis were rare. Here it is also found that the more frequent lymph nodes involved are in level- II, III, IV by 42.10%, 57.89% and 42.10% respectively. This results also nearly similar to that of study²⁰, who states that patient of papillary DTC have metastasis in anterolateral group (Level II, III, IV), with level III nodes consistently the most frequently involved. In his study of 75 papillary DTC he found only 3 patients have level 1 involvement.

In this study incidence of distant metastasis is found as 2.27% for PTC and 25% for FTC. Distant metastasis are the principal cause of death from DTC. About half of these metastasis are present at the time of diagnosis. The sites of distant metastasis among 1231 patients in 13 studies were lung 49%, Bone 25%, Both lung & bone 15% and the central nervous tissue or other soft tissue 10% as described in the study¹. Distant metastasis to kidney, cerebellum and oesophagus have also been reported^{21,22,23}.

Other reports of unusual distant metastasis also need to be express here. In one report²⁴ shown unusual metastasis of papillary thyroid carcinoma to larynx and hypopharynx (not local extension). In other report²⁵ five documented brain metastasis with DTC out of 400 cases of thyroid cancer between 1972-1993. In another

report²⁶ skull metastasis from thyroid follicular carcinoma with difficult diagnosis of the primary lesion. In a study²⁷ reported a case of solitary metastasis at right petrous apex, from occult follicular carcinoma of thyroid mimicking trigeminal neuralgia. In another study of 101 patients, has shown that the incidence of pulmonary metastasis is lowest in patient with papillary carcinoma (9%), compared with that of follicular carcinoma (13%). Involvement of recurrent laryngeal nerve, larynx, pharynx, trachea and oesophagus occur due to direct infiltration²⁸. A direct associations between presence of externodal spread and occurrence of distal metastasis has also been reported in the series²⁹.

In this study only 5 patients have distant metastasis out of 60 patients. This small number of patient is not enough to reflect the actual picture shown in other studies.

Up to 10% of differentiated thyroid carcinomas grow directly into surrounding tissues, increasing both morbidity and mortality. The invasion may be microscopic or gross and can occur with both papillary and follicular carcinomas. Recurrence rates are two times higher with invasive than noninvasive tumors. Up to one-third of patients with invasive tumors die of cancer within a decade¹.

Local invasion by both type of DTC shows that structures involved by PTC are strap muscles and laryngeal extension. Structure involved by FTC are trachea, oesophagus, rec. laryngeal nerve and strap muscles.

Conclusion:

It may be concluded from the present series that proper diagnosis and accurate staging of patients of DTC should be done in a early stage, using different investigations like FNAC, histopathology, ultrasonography, CT Scan and MRI. Emphasis should also to be given in frozen section during surgery. Early and effective treatment for DTC make give good life expectancy, also in some cases reduce the mortality and morbidity. Further studies involving large number of patients and a long term follow-up are necessary to have more definite conclusion.

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