

Clinicopathological Characteristics and Treatment Outcome of Patients with Metastatic Differentiated Thyroid Cancer

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Abstract

Background and Objective: Differentiated thyroid carcinoma (DTC) is a slow-growing tumour with 20% of the cases having distant metastasis. Its prognosis can vary by its histological characteristics, extension and spread. The data on metastatic DTC patients in Pakistan is scarce; therefore, the purpose of our study was to assess the clinicopathological characteristics and treatment outcomes of metastatic DTC in our population. **Methods:** This retrospective, single-centre study was carried out on 117 patients with metastatic DTC with their age at diagnosis, gender, tumour size and extent and spread of the tumour, and its histologic characteristic recorded. The treatment they received and the outcome in terms of status, at last, follow-up were also recorded. **Results:** The mean age of diagnosis was found to be 46.6 ± 17.2 years with an almost equal male to female ratio. The most common site of metastasis was the lung followed by bone. Papillary carcinoma was the most common subtype with 89.7% of the cases followed by follicular carcinoma occurring in 7.7%. The overall survival in years was found to be 5.6 ± 2.6 years. Ninety-six per cent had complete surgical resection followed by radioactive iodine (RAI) in 91.5%. **Conclusion:** Our study shows that the most significant factors in predicting the outcome in metastatic DTC are age, an extrathyroidal extension of the primary tumour and distant metastasis. However, further multicentric studies done on a much larger population will be needed to further support and strengthen our results.

Keywords: Differentiated thyroid carcinoma, metastasis, Pakistan

INTRODUCTION

Differentiated thyroid cancer (DTC) is a slowly growing cancer that carries a favourable long-term prognosis.^[1] In cases of well-differentiated thyroid carcinoma, 4%–20% develop distant metastases.^[2-4] These cancers generally present with neck lumps but metastasis to locoregional and distant sites may cause a constellation of symptoms depending on the site of distant spread.^[5] Usually, lungs and bones are the most common sites for metastasis; however, other sites including the brain and liver can also be involved in advanced cases. Bone involvement can lead to excessive morbidity and poor quality of life and lung involvement is the most common cause of death in these cancers leading to respiratory failure.^[6]

Prognosis becomes poor with distant spread and the 10-year survival rates decreased from over 95% for localized DTC to less than 50% for the metastatic disease.^[4] Treatment modalities for metastatic DTC include surgery, thyroxine suppressive therapy and radioactive iodine therapy.^[7,8] Tyrosine kinase inhibitors (TKIs) are considered for patients

with advanced disease refractory to surgery and remnant ablation.^[9]

Most of the studies which have been done previously belong to developed countries. To our knowledge, the clinical, pathological and treatment outcomes of metastatic DTC in our country have not yet been studied. It is therefore very important to determine the overall incidence of metastatic DTC and outcomes related to various treatment modalities so that better treatment guidelines for the population could be designed based on the study outcomes.

Therefore, the purpose of this study was to assess the clinical and pathological characteristics of patients with metastatic

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DTC in our population and at the same time to assess if the treatment outcomes and prognosis vary from other populations and countries.

METHODS

Study design and participant

This was a retrospective, real-world, single-centre study carried out on patients at a tertiary care hospital in Karachi, Pakistan between January 2000 and December 2020. Approval was taken from the Ethical Review Committee (ERC# 2021-6048-17255) of our institution and Health Information and Management Services (HIMS) was requested to provide the list of all patients with metastatic thyroid cancer during the said period. Out of 139 patients with metastatic DTC, 117 met the inclusion criteria.

The study included patients of either sex, 18 years and above age who had been diagnosed with metastatic DTC and had undergone treatment at our institution. Patients who were lost to follow-up and those with incomplete data were excluded. All the patients selected had confirmation of DTC by surgical biopsy. Non-probability convenience sampling technique was used to recruit the study participants. All the patients that fit this criterion had their age, gender, presenting symptoms at the time of diagnosis recorded along with the cervical and distant metastases of the tumour, the extent of extrathyroidal spread, the tumour size and the histological grade of the tumour. The treatment each patient underwent was also recorded, and the survival was calculated in terms of the status of the patient at their last follow-up visit.

Based on radiological (ultrasound neck/whole-body iodine scan) and biochemical (serum thyroglobulin levels) indicators, treatment outcomes were defined as follows:

1. Those with undetected stimulated serum thyroglobulin levels, ultrasound neck without any evidence of residual disease and/or negative whole-body iodine scan were labelled as disease-free patients.
2. Those with decreasing, unchanged or increasing stimulated serum thyroglobulin levels or/and positive radiological findings were further categorized as improving, stable and worsening persistent disease, respectively.

Statistical analysis

All statistical analysis was performed using the Statistical Package for Social Science SPSS (Release 19.0, standard version, copyright © SPSS; 1989-02) and MS-Excel 2016. A descriptive analysis was done with proportions calculated for categorical variables and mean \pm SD for continuous one. Multivariate linear regression analysis was performed to see the significance of possible predictive factors with a *P* value less than 0.05 taken as a greater significance.

RESULTS

Demographic data

The mean age of diagnosis was found to be 46.6 ± 17.2 years with the majority of cases being diagnosed in the third and

fourth decade. Out of 117 patients, 59 (50.4%) were female and 58 (49.6%) were male with no significant difference observed in the mean age of diagnosis in males (47.0 ± 17.4 years) and females (46.2 ± 17.2 years).

Characteristics of selected patients

It was seen that the primary complaint of most of the patients (114 (97.4%)) was a palpable neck swelling with the other major complaint (45 (38.5%)) being cough or shortness of breath. The presenting complaints about the patients are summarized in Table 1.

Histopathological characteristics

Table 2 summarizes the characteristic of 117 thyroid carcinoma with the majority of them (105 (89.7%)) being papillary carcinoma. Fifty-four (46.2%) were less than 4 cm while 63 (53.8%) were greater or equal in size to 4 cm. It was also found that 85 (72.6%) had cervical metastases while 64 (54.7%) had extrathyroidal extension outside the thyroid bed into the surrounding structures. It was also noticed that 15 (12.8%) had metastases to the lungs, 11 (9.4%) had metastases to the bone and 3 (2.6%) had metastases to the brain.

Management

Out of 117 patients, complete surgical resection was performed in 113 (96%) of the cases with 4 patients not operated on due to significant comorbidities, old age (>60 years) or a bad prognosis. Radioactive iodine (RAI) treatment was given to 107 (91.5%) of the patients with 65 being given a dose of 150 mCi, 38 given a dose of 100 mCi and 4 given a dose of 50 mCi. Adjuvant therapy was given to some patients as well

Table 1: Presenting complaints of metastatic differentiated thyroid cancer patients

Symptom	Frequency	Percentage
Palpable neck mass	114	97.4
Cough and/or shortness of breath	45	38.5
Haemoptysis	16	13.7
Respiratory failure	13	11.1
Pain due to bone metastasis	9	7.7
Pathologic fracture	2	1.7
Paralysis of the lower extremity	1	0.9

Table 2: Histopathological characteristics of metastatic differentiated thyroid carcinoma

	Frequency	Percentage
Histology		
Papillary carcinoma	105	89.7
Follicular carcinoma	9	7.7
Hurthle cell carcinoma	2	1.7
Diffuse sclerosing variant carcinoma	1	0.9
Size		
<4 cm	54	46.2
\geq 4 cm	63	53.8
Metastases		
Cervical metastases	85	72.6
Extrathyroidal extension	64	54.7

with 15 (12.8%) given external beam radiation and 18 (15.4%) given chemotherapy.

Treatment outcomes

Overall survival for these patients was measured from their time of diagnosis till their last follow-up, and the mean survival in years was found to be 5.6 ± 2.6 years (Range: 2–12 years). As seen in Table 3, it was found that 8 (6.8%) were disease-free, 66 (56.4%) had improved, 14 (12%) were stable, 16 (13.7%) had persistent disease, 4 (3.4%) showed worsening of symptoms while 9 (7.7%) had died due to the disease.

A multivariate logistic regression analysis was performed where male gender, age of diagnosis, tumour size, cervical metastases, extrathyroidal extension and distant metastases were entered as potential predictive factors for the outcome of the disease. Age, and extrathyroidal extension of the primary tumor, and distant metastases are the most significant factor in predicting the outcome. Table 4 displays the adjusted values for our analysis.

DISCUSSION

Over the years, a rising trend in DTC has been noticed in several countries, including Pakistan. However, the exact figures and trends concerning its rise in Pakistan are inconclusive due to the lack of extensive studies. It has been estimated that thyroid carcinoma represents 1% of total malignancies throughout the world.^[10] It was seen that the patients were younger at the time of diagnosis in our study with the mean age of diagnosis being 46.6 years which is almost similar to a study by Mishra *et al.*^[2] in which the mean age at diagnosis was 48.5 years. While in other studies by Nixon *et al.* and Lee *et al.*, the mean age at diagnosis was 59 and 58 years, respectively.^[11,12] In a study by Lee *et al.*, the female to male ratio was 2.03: 1,^[12] however in our selected population the number of males and

females was almost equal which might be attributed to the lower sample size.

In our study, we reviewed the features of metastatic DTC affecting patients seeking treatment at our institution over 20 years from 2000 to 2020. The most common histological subtype of metastatic DTC observed in our study was papillary carcinoma of the thyroid which affected 89.7% of the thyroid patients with the second most common being the follicular subtype affecting 7.7% of the patients while in another study the most common metastatic DTC was follicular thyroid carcinoma (50%).^[2] Only two patients reported with a Hurthle cell subtype and one with a diffuse sclerosing subtype.

The most common complaint at presentation was neck swelling affecting 97.4% of the presenting patients in our study, followed by cough or shortness of breath affecting 38.5% of the patients making symptoms due to the tumour mass in the neck the most common presenting complaints. A much lower percentage of our patients had complaints because of metastases of the primary tumour. The most common site of metastasis was the lung followed by bone in our study which is similar to other studies.^[13,14]

Despite only a few patients being disease-free at their last follow-up in our study, the overall prognosis of patients with metastatic DTC is positive with a low rate of mortality and most patients showing improvement of symptoms following therapy.^[15,16] Ninety-six per cent of the patients had gone through total thyroidectomy followed by an RAI therapy in 91.6% resulting in such a favourable outcome. This is in keeping with both American and international guidelines.^[17,18]

Nearly forty-six percent of cases in our study had a tumour size less than 4 cm with 72.6% having cervical metastases and around 54% having extrathyroidal extension outside the thyroid capsule and invasion into the surrounding structures. In our analysis, the factors shown to be of greater predictive significance when seeing if the patient had a positive outcome at the last follow-up were age, extrathyroidal extension and distant metastases. These results were supported by previous studies showing age, multifocality and extrathyroidal extension to be significant predictors of the patient being disease-free at the last follow-up.^[17,19]

Our study had several strengths and limitations. With the data regarding metastatic DTC in Pakistan being limited, this was the first study of its kind to look at the presenting symptoms, treatment method and outcomes for such patients over 20 years in a tertiary care centre where the treatment and care for DTC patients have been standardized according to international standards. It also has outcome data over a long period of follow-up, which previously has not been reported in a Pakistani population. However, being a retrospective review, not all data of the patients could be available and only a relatively small number of patients ($n = 117$) could be selected for our study.

Table 3: Status of the patients at the last follow-up

Status as the last follow-up	Frequency	Percentage
Disease-free	8	6.8
Improved	66	56.4
Stable	14	12.0
Persistent disease	16	13.7
Worse	4	3.4
Died of disease	9	7.7

Table 4: Multivariate analysis of demographic and histological factors for the outcome, at last, follow-up

Characteristics	Odds Ratio	P
Male gender	1.12 (0.38–2.1)	0.28
Age at diagnosis	1.18 (1.02–1.35)	0.005
Tumour size	2.84 (0.98–4.72)	0.36
Cervical metastases	1.98 (1.10–2.86)	0.33
Extrathyroidal extension	2.65 (2.24–3.07)	0.004
Distant metastases	3.01 (2.83–3.21)	0.005

CONCLUSION

Our study shows that metastatic DTC mostly affects patients in their third and fourth decade of life, with the most common complaints at a presentation being mass effects such as neck swelling or shortness of breath. The study also reveals that the most common variant of metastatic DTC is papillary carcinoma followed by follicular carcinoma. Age and extrathyroidal extension of the primary tumour and distant metastases are the most significant factors in predicting the outcome. However, further multicentric studies done on a much larger population will be needed to further support and strengthen our results.

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Conflicts of interest

There are no conflicts of interest.

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