

# Distant metastasis as the sole initial manifestation of well-differentiated thyroid carcinoma

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**Abstract** Thyroid carcinoma usually presents as a neck lump. Distant metastasis as the sole initial manifestation of well-differentiated thyroid carcinoma (WDTC) is rare and little is known about these patients. The aim of this study is to characterize patients who present with distant metastasis as the sole initial manifestation of WDTC. Retrospective review of case records of WDTC seen at the National Cancer Centre Singapore from 2002 to 2015 was performed. Patients with no prior complaint of neck swelling and whose first presentation was distant metastatic WDTC were included. Patient demographics, disease characteristics, radiological imaging, histopathology, types of treatment administered, and survival outcomes were examined. Nineteen out of seven hundred and thirty-two cases fulfilled inclusion criteria. Mean age was 65.4 years. All patients presented with osseous (36.8%), pulmonary (31.6%), cerebral metastases (5.3%), or a combination of two out of three aforementioned sites (26.3%). Follicular thyroid carcinoma was most common (47.4%), followed by papillary (36.8%) and medullary (15.8%). More than two-thirds of patients had multiple metastatic foci. Thirteen out of nineteen patients (68.4%) underwent total thyroidectomy with or without neck dissection and adjuvant RAI, while the rest declined surgery. The mean length of follow-up was  $40.1 \pm 5.1$  months and 5-year disease-specific survival was  $48.0 \pm 17.2\%$ . Distant metastasis without a history of neck swelling as the initial presentation of WDTC is extremely rare. Osseous metastasis and follicular thyroid carcinoma are the most common metastatic site and etiology,

respectively. Disease-specific survival at 5-year post-diagnosis is lower compared to patients with thyroid carcinoma diagnosed with distant metastasis on further work-up.

**Keywords** Thyroid carcinoma · Metastasis · Survival · Atypical presentation

## Introduction

Thyroid carcinoma is the most common endocrine malignancy and generally presents as an enlarging neck lump. Ninety percent (90%) of thyroid malignancies are well-differentiated forms (papillary, follicular or medullary) and they are usually associated with an indolent clinical course and a good prognosis [1, 2]. Distant metastasis is generally regarded as a prognosticator of poor survival in most malignant neoplasms. In contrast, distant metastasis in well-differentiated thyroid carcinoma has been found to have better survival rates compared to other cancers. A 1986 study by Schlumberger et al. reported survival rates (from the time of discovery of distant metastases) in patients with well-differentiated thyroid carcinoma to be 53% at 5 years and 38% at 10 years [3]. In 2009, Mihailovic et al. similarly reported promising survival rates of 58% at 5 years for patients with distant metastatic well-differentiated thyroid carcinoma [4]. This is partially attributed to the widespread use of highly effective multimodality treatment such as surgery, adjuvant radioactive iodine, radiotherapy, and metastasectomy depending on the site and type of distant metastasis [3, 5]. It should be noted that the majority of thyroid carcinoma metastases are asymptomatic and discovered only on systemic surveillance or a full-body metastatic work-up of a malignant thyroid nodule. Symptomatic distant metastasis

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as the sole initial presentation, in the absence of a neck swelling, is extremely rare. The disease course and survival rates in this group of patients are not well known. Hence, we have conducted this review, looking at patients whose the initial presentation was solely distant metastasis in the absence of a neck swelling and who were then retrospectively diagnosed with thyroid carcinoma. Patient characteristics, disease pathology, treatment course, and survival records were investigated.

## Methods

The study was approved by the SingHealth Centralized Institutional Review Board. A retrospective review of case records of all patients with thyroid carcinoma seen at the National Cancer Centre Singapore from January 2002 to December 2015 was performed. Diagnosis of well-differentiated thyroid carcinoma was confirmed with cytological and/or histopathological examination of tissue samples. Patients with no prior complaint of neck swelling and whose first presentation was distant metastasis due to thyroid carcinoma were included. Locoregional cervical lymph node metastasis was not considered as distant metastasis. Data pertaining to patient demographics, radiological imaging, histopathology, treatment course, and survival duration were examined.

The diagnosis of distant metastasis was based on positive findings on radiography (e.g., computed tomography scans, magnetic resonance imaging, positron emission topography imaging, and radioactive iodine uptake scans) and/or tissue biopsy. Apart from patient demographics and type of thyroid carcinoma, data on the types of distant metastasis were reviewed and classified by location (bony, lungs, and cerebral) and plurality (single or multiple sites).

All patients were discussed at the National Cancer Centre Singapore multidisciplinary Tumor Board. Surgery in the form of total thyroidectomy with or without neck dissection was offered to patients who were surgically fit. All patients were considered, with no prejudice apart from physical fitness and amenability of disease, for multidisciplinary management with adjuvant radioactive iodine, radiotherapy, and metastectomy. Survival data and death records were reviewed and patients were classified as having died of thyroid carcinoma if this was stated as the primary cause of death or as a contributing cause of death in the death certificate.

All statistical analyses were performed using SPSS v20.0 software package (SPSS, Inc., an IBM Company, Chicago, IL, USA). Groups were compared using Fisher's exact *t* test and the  $\chi^2$  test as appropriate.

## Results

A total of 732 patients were diagnosed with well-differentiated thyroid carcinoma (papillary, follicular, and medullary types) at the National Cancer Centre Singapore from January 2002 to December 2015. Nineteen patients (2.6%) fulfilled inclusion criteria of having distant metastasis as the sole initial feature, without a history of thyroid or neck lump (Table 1). The mean age at presentation was 65.4 (31–81) years. Seventeen out of these nineteen patients were clinically symptomatic at the point of initial presentation. Investigation of their presenting complaints led to a final diagnosis of metastatic well-differentiated thyroid carcinoma. Two out of nineteen patients (10.5%) were asymptomatic at presentation. Instead, they had incidental pulmonary lesions detected on health screening. All 19 patients had either osseous (36.8%), pulmonary (31.6%), cerebral metastases (5.3%), or a combination of two out of three aforementioned sites (26.3%). In patients with osseous metastases, axial ( $n=5$ ) and appendicular ( $n=5$ ) patterns of metastasis were equally common. In addition, two patients had concomitant axial and appendicular bony metastases. Accordingly, the three most common symptoms that symptomatic patients presented with were (1) bone pain and/or pathological fractures, (2) shortness of breath, and (3) neurological deficits such limb weakness, etc.

Follicular thyroid carcinoma was the most common (47.4%) followed by papillary (36.8%) and medullary (15.8%). Thirteen out of nineteen patients (68.4%) underwent surgery for the primary thyroid tumor and adjuvant radioactive iodine while the rest declined intervention for the primary thyroid tumor. Surgery for the primary thyroid tumor involved total thyroidectomy with or without neck dissection depending on the presence of metastatic cervical lymphadenopathy. Several patients also underwent metastasectomy if deemed surgically resectable after multidisciplinary Tumor Board discussion (Table 1).

On histopathological examination, the mean size of the largest tumor focus in thyroidectomy specimens was  $28.6 \pm 23.2$  mm. Lymphovascular and extrathyroidal extension was present in 76.9 and 61.5% of thyroidectomy specimens, respectively.

The overall length of survival is illustrated in Fig. 1. The mean length of follow-up was  $40.1 \pm 5.1$  months and disease-specific survival (DSS) was  $48.0 \pm 17.2\%$  at 5-year post-diagnosis. More than two-thirds of patients had multiple metastatic foci at point of diagnosis. At the point of last follow-up, 9 out of 19 patients had demised, with 7 patients (77.8%) having their cause of death attributed to metastatic thyroid carcinoma. The other two patients (22.2%) died of unrelated causes (Table 1).

**Table 1** Patients with distant metastases as the initial manifestation of well-differentiated thyroid carcinoma

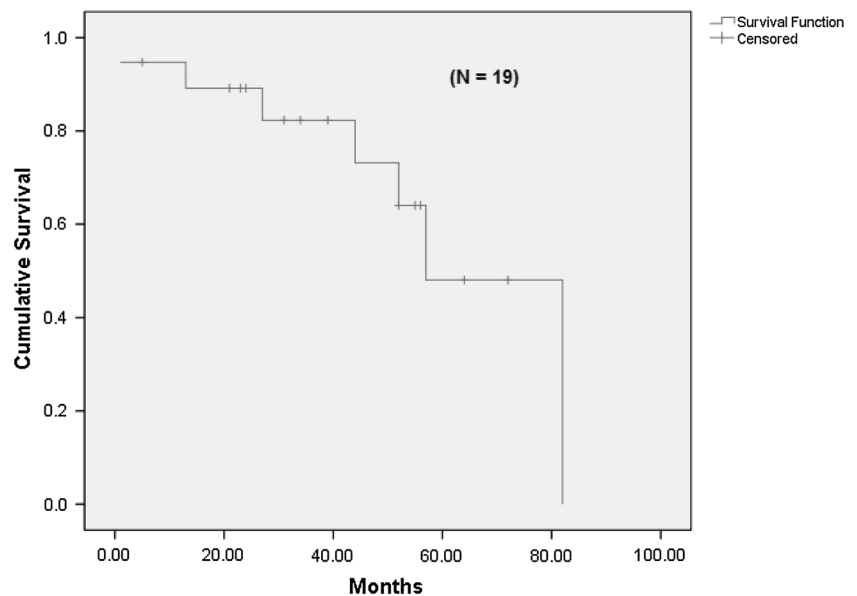
Patient	Presentation	Type of thyroid carcinoma	Metastasis	Management	Outcome/survival status	Cause of death
1. 62/F	Right thigh pain	Follicular	Bony	TT, adjuvant RAI	Alive	NA
2. 81/M	Right hip pain	Follicular	Bony	TT, adjuvant RAI, palliative RT to bony metastasis	Alive	NA
3. 62/F	Bilateral lower limb weakness	Follicular	Bony	Declined intervention for primary tumor, underwent palliative RT and RAI to vertebral metastases	Demised at 57 months	Metastatic thyroid carcinoma
4. 58/M	Left back lump	Follicular	Bony, lungs	TT, metastasectomy, adjuvant RAI	Alive	NA
5. 57/F	Right shoulder lump	Follicular	Bony, lungs	TT, adjuvant RAI, palliative RT, intramedullary humerus fixation	Demised at 52 months	Metastatic thyroid carcinoma
6. 79/M	Hemoptysis	Follicular	Lungs	Declined intervention	Demised at 13 months	Pneumonia and metastatic thyroid carcinoma
7. 75/F	Right hemiparesis	Follicular	Cerebral	Declined intervention	Demised at 27 months	Metastatic thyroid carcinoma
8. 66/F	Left hip pain	Follicular	Bony, lungs	TT, adjuvant RAI	Alive	NA
9. 62/F	Neck pain	Follicular	Bony	TT, adjuvant RAI	Alive	NA
10. 79/M	Shortness of breath	Papillary	Lungs	Declined intervention	Demised at 5 months	Gastric carcinoma
11. 71/F	Prolonged cough	Papillary	Lungs	TT, adjuvant RAI	Demised at 24 months	Myocardial infarction
12. 64/M	Back pain	Papillary	Bony, lungs	TT, right lung lower lobectomy, adjuvant RAI and RT	Demised at 82 months	Metastatic thyroid carcinoma
13. 63/M	Asymptomatic (found on imaging surveillance for nasopharyngeal carcinoma)	Papillary	Lungs	TT, right lung lower lobectomy, adjuvant RAI	Alive	NA
14. 65/F	Right gluteal pain	Papillary	Bony	TT	Demised at 1 month (post-operatively)	Metastatic thyroid carcinoma with post-operative sepsis and thyroid storm
15. 85/F	Right hip pain	Papillary	Bony, lungs	TT, adjuvant RAI, palliative RT to right acetabular bony metastasis	Alive	NA
16. 75/F	Shortness of breath	Papillary	Lungs	Declined intervention	Demised at 44 months	Metastatic thyroid carcinoma
17. 57/M	Asymptomatic (raised carcinoembryonic antigen during health screening)	Medullary	Lungs	TT, left modified radical ND and left tracheoesophageal groove clearance, adjuvant RAI and RT	Alive	NA
18. 50/F	Shortness of breath	Medullary	Bony	Declined intervention for primary tumor, underwent palliative RT for vertebral metastases	Alive	NA

**Table 1** (continued)

Patient	Presentation	Type of thyroid carcinoma	Metastasis	Management	Outcome/survival status	Cause of death
19. 31/M	Chest lump	Medullary	Bony	TT, left ND (levels II–VI), anterior mediastinal metastasectomy and anterior chest wall reconstruction, adjuvant RAI	Alive	NA

TT total thyroidectomy, ND neck dissection, RAI radioactive iodine, RT radiotherapy

**Fig. 1** Disease-specific survival of patients who present with distant metastasis as the sole initial manifestation of WDTC



## Discussion

Well-differentiated thyroid carcinoma confined to the thyroid gland is associated with excellent long-term survival, with a 10-year cancer-specific survival of up to 90% [6]. Even with distant metastasis, it has been reported to have better survival than other metastatic malignancies [2–4]. The incidence of distant metastasis at presentation in well-differentiated thyroid cancer is reportedly 1–4% [7, 8]. In a recent comprehensive Surveillance, Epidemiology, and End Results (SEER) database study between 1988 and 2009, a total of 1291 patients with metastatic DTC at diagnosis were identified, amounting to a prevalence rate of 2.2% [9]. Patients with thyroid carcinoma typically present with a neck lump and distant metastatic disease may be diagnosed on the initial full-body work-up or during follow-up, most commonly with the use of systemic radioactive iodine. The former and latter are often considered together and comparisons are made with thyroid carcinoma with no distant metastatic disease [10, 11]. However, some studies have suggested that the

prognosis in patients who present initially with metastases versus those who subsequently develop metastases may be different and that these two groups should be considered separately [12–14]. This is because patients with distant metastasis at presentation are ‘treatment-naïve,’ in particular with respect to radioactive iodine [15]. We wish to highlight that in the former, a further subset exists—patients who present only with distant metastasis without any neck lumps and are diagnosed retrospectively with well-differentiated thyroid carcinoma.

Due to its rarity, little is known about this group of patients. In 1997, Shaha et al. described a series of 44 patients, over a period of 55 years, with distant metastases as the initial presenting symptom of well-differentiated thyroid carcinoma [8]. Literature concerning this subtype of thyroid carcinoma patients has remained scarce after his study. We aim to provide updated insights with this report. Shaha et al. noted that patients generally had “acceptable long-term survival with adequate primary tumor treatment and aggressive radioactive iodine for distant metastases”. A similar management approach was observed in our study.

We found remarkable heterogeneity in our patients, despite its rare occurrence at only 2.6% of all WDTC diagnosed at our institution over a 14-year period. Our results also revealed that majority of these patients had multiple sites of metastasis, suggesting that with this atypical presentation, the tumor was likely undetected for a long time, allowing it to spread systemically.

Congruent with existing literature, our study found that the most common thyroid malignancy associated with distant metastasis was follicular thyroid carcinoma, which has a propensity for hematogenous spread [8, 16]. Papillary thyroid carcinoma was the most common type of thyroid malignancy observed in patients with multiple foci of metastasis.

Taking 40 years old as the cutoff, Mazzaferri et al. found that young patients had a significantly lower risk of developing distant metastasis compared to old patients [17]. Similarly, we found that the mean age at diagnosis in our study population was high at 65.2 years and only one patient was younger than 40 years old.

In existing literature, 5-year DSS probability in patients with distant metastasis from well-differentiated thyroid carcinoma has been reported to be about 60% [3, 4, 18]. However, in our study, we found a slightly lower 5-year DSS probability of 48.0%. This may be attributed to the fact that the patients in our study presented initially with distant metastasis as the sole manifestation of thyroid carcinoma. The presence of a swelling at the neck, an easily observable and palpable part of the body, would normally have prompted patients to seek medical attention. In our study, due to the atypical presentation, these patients do not usually present initially to the head and neck surgeon and may instead be seen at other specialist departments for complaints such as bone pain, hemoptysis, or neurological deficits, etc., providing the disease time to metastasize and hence adversely impacting DSS.

The American Thyroid Association guidelines are frequently adopted in management of non-metastatic thyroid disease. However, no widely-accepted guidelines exist on the management of metastatic thyroid carcinoma. This is further complicated by heterogeneity in this patient group, as alluded to earlier. A multidisciplinary discussion at Tumor Board, as was the practice in our study, should be advocated for all patients with this atypical and rare presentation as management should be individualized.

We recognize several limitations in our study, including its retrospective nature in a single institution, and small study population. Due to the small number, we are unable to identify statistically significant prognosticators and risk factors. In addition, we did not analyze the histological subtypes of thyroid carcinoma and could not identify patients that had tumors with more aggressive behavior (e.g., tall cell variant and insular variant), which may have yielded

their own impact on survival and plurality of metastases. However, keeping in mind that this study examines a little-known and rare occurrence, we believe that the characterization of patient and disease features achieved through this report will provide a foray into further investigation of the risk factors and prognosticators in this unfortunate group of patients, who, despite having a malignancy generally regarded as “favorable”, may have a poor clinical course.

#### Compliance with ethical standards

This study did not receive any funding.

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed were in accordance with the ethical standards of the SingHealth Centralised Institutional Review Board (IRB) standards. Informed consent was waived as per SingHealth Centralised IRB permission as data were reviewed retrospectively and in anonymity with no patient contact.

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