

Clinical characteristics and disease outcome of patients with non-medullary thyroid cancer and brain metastases

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Received September 10, 2016; Accepted September 22, 2017

DOI: 10.3892/ol.2017.7325

Abstract. Brain metastases from non-medullary thyroid carcinoma (NMTC) are rare, with a reported frequency of ~1%, and patient survival time is <1 year after diagnosis. The optimal management of brain metastases in this setting continues to be debated. The aim of the present study was to evaluate a series of patients with brain metastases from NMTC attending a single tertiary medical center. The electronic database of Rabin Medical Center was reviewed for all patients with NMTC and distant metastases who were diagnosed and treated between 1970 and 2014. Those with brain metastases were identified and formed the study group. Data were collected from medical records comprising clinicopathological characteristics, time intervals for diagnosis and treatment, treatment modalities and outcome. Of the 172 patients with NMTC and distant metastases, 10 possessed brain metastases. These included 6 females and 4 males of median age 53.5 years (range, 18-81 years). All patients had lung metastases and 7 demonstrated bone metastases. The median interval between the diagnoses of NMTC and brain metastases was 40 months (range, 9-207 months). Of the 10 patients, 1 presented with brain metastases at primary diagnosis. Treatment of the brain metastases consisted of surgery, radiotherapy (external beam, stereotactic), and radioiodine, alone or in combination. A total of 2 patients received tyrosine kinase inhibitors. The median overall survival time from diagnosis of brain metastasis was 15 months. A total of 2 patients remained alive at the last follow-up (32 and 300 months, respectively). The present study demonstrated that brain metastases may occur in ≤6% of patients with NMTC and distant metastases. Brain metastases rarely present at diagnosis of NMTC and are associated with metastases in

other distant sites. Systematic screening for brain metastases requires consideration in all patients with NMTC and distant metastases. Some patients show an indolent evolution with overall survival of >2 years, supporting an aggressive treatment approach.

Introduction

Non-medullary thyroid carcinoma (NMTC) originating from thyroid epithelial cells accounts for >90% of all thyroid malignancies (1). Patients with NMTC usually demonstrate a good prognosis, with a 10-year survival rate of 80-95% (2). However, 4-23% of patients will present with distant metastases (DM) at the time of diagnosis or over the course of their disease (3-8). Our previous study reported a 6.8% rate of DM for all patients with NMTC who were treated and followed-up at our institution (9). The presence of DM is associated with a poor prognosis, constituting the most frequent cause of thyroid cancer-associated mortality (8-10). The most common sites of DTC metastases are the lungs and the bones, followed by the brain and the liver (11). While the 10-year survival rate in the whole population of NMTC patients with DM may reach ~50% (12), intracranial DM are associated with a median survival time of <1 year (13,14). Data on the optimal management of brain metastases in this setting and the factors affecting outcome remain limited. In potentially curable patients with isolated brain metastases, surgical excision is indicated, while the administration of ¹³¹I-iodine therapy for radioiodine-responsive disease and external-beam radiation therapy (EBRT) may partially control disease progression in selected patients. Data regarding the role of systemic therapy with kinase inhibitors are limited (15).

Furthermore, rates of brain metastases occurrence may be underestimated. While patients may present with headaches or various neurological symptoms, intracranial metastasis may be asymptomatic. According to a previous study, asymptomatic brain metastases were diagnosed incidentally during systemic brain imaging prior to prescription of tyrosine kinase inhibitors in 15.4% of patients with NMTC and distant metastases (13). De Figueiredo *et al* (13) suggested, in agreement with others (16-19), that surgical intervention, EBRT and

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Key words: thyroid cancer, non-medullary, distant metastases, brain metastases, disease outcome

stereotactic radiosurgery (SRS) may prolong survival in this group of patients.

The aim of the present study was to evaluate a series of patients with NMTC-associated brain metastases who were treated and subsequently followed-up at a single tertiary medical center.

Patients and methods

The electronic database of the Rabin Medical Center Thyroid Cancer Registry and the Head and Neck Tumor Unit, Beilinson Hospital (Petach Tikva, Israel) was searched for all patients diagnosed and treated for NMTC with distant metastases between 1970 and 2014. A total of 10 patients with brain metastases, confirmed by computerized tomography or magnetic resonance imaging, were identified and formed the study group. Patients with anaplastic cancer were excluded. The medical records of the eligible patients were reviewed for data on clinical characteristics, histological type of primary tumor, sites of distant metastases, diagnosis and treatment of brain metastases, time intervals for diagnosis and treatment of the brain metastasis, disease outcome and tumor-node-metastasis staging of the thyroid cancer, according to the American Joint Committee on Cancer (seventh edition) (20). The study protocol was approved by the Institutional Ethics Board of Rabin Medical Center, Beilinson Hospital.

Statistical analysis. Categorical variables are presented as numbers and percentage, and continuous variables as means and standard deviations or medians with ranges. Categorical variables were compared using χ^2 test, and continuous variables using unpaired Student's t-test or Mann Whitney U-test, as appropriate. The product-limit estimate method (Kaplan-Meier) was used to estimate survival in the cohort of patients with distant metastases, and the log-rank test was used to compare survival curves. P<0.05 was considered to indicate a statistically significant difference. All analyses were conducted using SAS Software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline patient characteristics and clinicopathological findings. Clinicopathological characteristics of patients are presented in Table I. Of the 172 patients diagnosed and treated for NMTC with distant metastases during the study period, 10 (5.8%) possessed brain metastases. This included 6 female and 4 male patients with a median age of 53.5 years (range, 18-81 years). The median follow-up time from primary diagnosis was 84 months (7 years; range, 1-25 years). Histological analysis of the primary tumor revealed papillary thyroid carcinoma (PTC)-classical variant in 3 patients, and PTC-follicular variant in 3 patients. The remaining 4 patients exhibited an aggressive variant, including poorly differentiated and follicular in 2, tall cell in 1, and insular in 1 patient. Tumor stage was determined to be pT4 in 5 patients, pT3 in 2 patients, pT2 in 2 patients and unknown in the remaining patient (20). Extra-thyroidal extension was documented in 7/9 patients (78%). A total of 6 patients (60%) demonstrated nodal involvement, and 5 (50%) possessed distant metastases at diagnosis.

Table I. Baseline features and clinicopathological findings in patients with non-medullary thyroid carcinoma-associated brain metastases.

Patient no.	Sex	Age, years	Histopathology	Thyroidectomy	RAI	Tumor size, mm	ETE	NI	MI	Sequence of metastasis
1	F	64	PTC	Yes	Yes	55	Yes	Yes	No	Lung>brain
2	M	56	PTC-FV	Yes	Yes	20	No	Yes	Lung	Lung>bone, brain
3	F	30	PTC-FV + poorly diff.	Yes	Yes	75	Yes	No	Lung, bone, liver	Lung, bone, liver>brain
4	F	32	Tall cell	Yes (hemi)	Yes	29	Yes	Yes	No	Lung>bone>brain
5	F	60	PTC-FV + poorly diff.	Yes	Yes	35	Yes	No	Bone, lung	Lung>bone>brain
6	M	36	PTC-FV	Yes	Yes	Uk	Yes	No	No	Lung>bone>brain
7	F	18	PTC-FV	Yes	Yes	35	Yes	Yes	Lung, brain	Lung>brain>bone
8	M	48	Insular	Yes	Yes	35	No	No	No	Lung>bone>brain
9	M	81	PTC	Yes	Yes	32	Yes	Yes	Lung, bones	Lung>bone>brain
10	F	55	PTC	Yes	Uk	Uk	Uk	Yes	No	Lung>brain

diff., differentiated; ETE, extrathyroidal extension; FV, follicular variant; PTC, papillary thyroid carcinoma; Uk, unknown; RAI, radioactive iodine therapy for initial treatment of NMTC; NI, nodal involvement at initial presentation; MI, distant metastases at initial presentation.

Table II. Diagnosis and management of brain metastases from non-medullary carcinoma.

Patient no.	Symptoms	Features	Thyroglobulin, ng/ml	Treatment				TKI	RAI	TKI	Treatment sequence	Overall follow-up, months	Follow-up since BM, months	Last status
				Surgery	RT	EBRT	SRS							
1	Hemiparesis	>1 cm	<0.2 Ab-positive	Yes	EBRT	Yes	No	Yes	No	RAI>surgery>RT	32	24	DOD	
2	None	>1 cm	1,258	No	EBRT + SRS	Yes	No	Yes	No	RT>RAI	60	26	DOD	
3	None	>1 cm, Mf, Bi	143,751	No	SRS	Yes	Yes	Yes	Yes	RT>RAI>TKI	36	2	DOD	
4	Diplopia	>1 cm, Mf, Bi	521	No	EBRT + SRS	No	Yes	No	Yes	RT>TKI	108	4	DOD	
5	None	<1 cm, Mf, Bi	1,496	No	SRS	No	No	No	No	RT	240	32	AWD	
6	Nausea	>1 cm, Mf, Bi	Uk	Yes	SRS	No	No	No	No	Surgery>RT	264	18	DOD	
7	Hemiparesis	Uk	Uk	Yes	EBRT	Yes	No	Yes	No	Surgery>RAI>RT	300	300	AWD	
8	Hemiparesis	>1 cm	2,182	Yes	EBRT	Yes	No	No	No	Surgery>RT	48	15	DOD	
9	Delirium	>1 cm	2,800	No	No	No	No	No	No	None	12	2	DOD	
10	Vertigo, vomiting	>1 cm	4.2 Ab-positive	No	EBRT	No	No	No	No	RT	120	12	DOD	

Ab, anti-thyroglobulin antibody; AWD, alive with disease; Bi, bilateral; BM, brain metastasis; DOD, succumbed to disease; EBRT, electron beam radiotherapy; Mf, multifocal; surgery, brain metastasectomy; RAI, adjuvant radioactive iodine therapy; RT, radiotherapy; TKI, tyrosine kinase inhibitor; Uk, unknown.

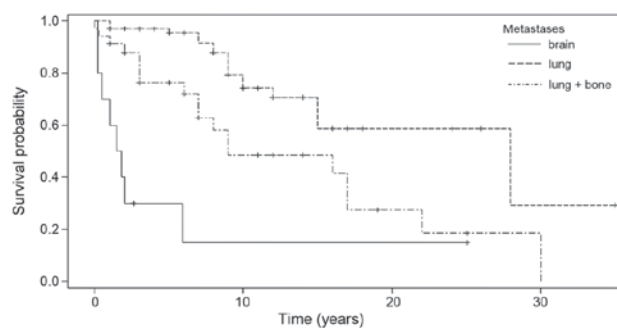


Figure 1. Product-limit estimates of OS following diagnosis of distant metastases from non-medullary thyroid carcinoma. Mean OS was 2.5 years in patients with brain metastases compared with 20.6 years in patients with only lung metastases ($P<0.0001$) and 13.6 years in patients with lung and bone metastases ($P=0.98$). OS, overall survival.

All 10 patients exhibited associated lung metastases, which preceded the brain metastases in 9 cases and occurred synchronously with the brain metastases in 1 case. A total of 7 patients (70%) demonstrated bone metastases, which preceded the brain metastases in 5 cases, was synchronous in 1 case and was metachronous in 1 case. In 1 patient with lung and bone metastases, liver metastases were also detected, all of which were identified at initial diagnosis.

Clinical, biochemical and radiological characteristics of brain metastases. Data on the diagnosis and management of brain metastases from non-medullary carcinoma are presented in Table II. The median interval from thyroidectomy to diagnosis of brain metastases was 40 months (range, 9-207 months). Brain metastases were detected at initial presentation in 1 patient.

A total of 7 patients presented with neurological symptoms, primarily motor deficits, followed by nausea, headaches and delirium. The remaining 3 patients were asymptomatic and the brain metastases in these cases were diagnosed incidentally by computed tomography or magnetic resonance imaging during systemic evaluation of other distant metastases. Additionally, 4 patients exhibited >1 brain lesion. Macroscopic lesions (≥ 1 cm) were identified in 8 patients and bilateral lesions were detected in 4 patients (3 with macroscopic lesions). Brain imaging results from 1 patient (treated in 1990) were unknown. A total of 6 patients presented with high thyroglobulin levels (threshold value, >0.2 ng/ml) at diagnosis of the brain metastasis (mean, $1,496\pm 874$ ng/ml). Positive anti-thyroglobulin antibodies limited the accuracy of thyroglobulin measurement in 2 patients, and the data were missing in the remaining 2 patients.

Treatment of brain metastases. The data on treatment and prognosis of brain metastases are presented in Table II. Treatment for NMTC consisted of thyroidectomy (total or hemi) and subsequent radioactive iodine (RAI) in all patients. No information on RAI were available in the medical chart of patient no. 10 operated at another hospital. In 4 patients, EBRT was delivered to the primary tumor bed. Treatment of the brain metastases consisted of surgery in 4 patients, radiotherapy delivered directly to the lesion in 8 patients and RAI in 4 patients, alone or in combination. Surgery was combined

with EBRT in 1 patient, with SRS in 1, and with EBRT and RAI in 2. One patient each underwent only EBRT or SRS, and 1, ERBT + SRS and RAI. Patient no. 3 received tyrosine kinase inhibitors in combination with SRS and RAI, and patient no. 4 in combination with radiotherapy. In patient no. 9, the brain metastases were not treated due to a poor performance status. The thyroid was confirmed by histology to be the origin of the brain metastases in 4 patients following surgical resection.

Disease outcomes. Median overall survival time following diagnosis of brain metastasis was 15 months (range, 2-59 months). A total of 6 patients survived for >12 months, of whom 2 remained alive at their last follow-up (duration of follow-up from brain metastases diagnosis, 32 and 300 months, respectively). Mortality in the remaining patients was due to progression of the brain lesions in 5 patients and worsening of pulmonary metastases in 3 patients.

Median survival time was markedly increased in patients who underwent surgical resection and/or external radiotherapy (28 months) compared with patients who did not (4 months). The small sample size of the study precluded an analysis of survival by type of treatment. Mean survival time in the patients with brain metastases (2.5 years) was significantly decreased compared with the other patients with NMTC with distant metastases only in the lungs (20.6 years; $P < 0.0001$) (Fig. 1).

Patient no. 7 (Tables I and II) was the only patient in whom brain metastasis was diagnosed prior to diagnosis of the primary tumor. Following total thyroidectomy and radioiodine treatment, the patient underwent five neurosurgeries followed by EBRT. Despite severe disability, the patient received a bachelor's degree in social work and, at the age of 41 years, successfully gave birth by caesarean section. She remains alive, after a follow-up of 25 years.

Discussion

The present study demonstrated that the brain is a relatively frequent site of secondary metastases in patients with NMTC and distant metastases, reaching rates of ~6%. This finding is in agreement with previous studies comprising large cohorts of >600 patients with NMTC (21-25), including our previous study (9). In the present study, all the patients exhibited lung metastases and the majority also possessed bone metastases. Hematogenic spread of tumor cells may explain the association observed between intracranial involvement and lung metastases. Notably, a high rate of extrathyroidal extension (78%) was observed in this cohort of patients. As such, clinicians should consider this risk and investigate the possibility of intracranial involvement as early as possible in patients with NMTC and distant metastases in order to minimize clinical deterioration. The considerable proportion (30%) of asymptomatic brain lesions in the present study justifies the use of brain imaging in all patients with disseminated disease.

Serum thyroglobulin levels were high ($1,496 \pm 874$ ng/ml) in all patients with brain metastases who were negative for anti-thyroglobulin antibodies, confirming the differentiated nature of the thyroid cancer. Practically, however, a high thyroglobulin level is a problematic indicator to suspect brain metastases given that all the patients in the present study had

distant metastases in other sites. For the same reason, high serum thyroglobulin levels cannot serve as an indicator of response to therapy.

The median survival time of 15 months in the present cohort is longer compared with those reported in other studies, namely 7.1 months (13), 9.4 months (25) and 12.4 months (24). This difference in survival time may be attributable to the relatively young age of the patients in the present study (median, 53.5 years) compared with those in previous studies (with median ages of 59 and 63 years) (13,17,24,26), the exclusion of patients with anaplastic-type cancer from the present study, and the aggressive treatment approach employed in the present study. For example, patient no. 7 underwent five neurosurgeries in addition to EBRT and RAI. The use of stereotactic radiotherapy in patients with a limited number of brain foci has been increasing, because it allows for the delivery of a large dose to the target mass while minimizing damage to normal brain tissue (17). Treatment with SRS alone or in addition to whole-body radiation therapy has been demonstrated to achieve a local control rate of 96% without any procedure-associated complications (18). In the present study cohort, the patients who were treated for brain metastases with surgery and/or radiation achieved a longer survival time compared with untreated patients (patient nos. 4 and 9), similar to previous studies (13,17,18). In a recent study by Choi *et al* (26), the median overall survival time following diagnosis of brain metastases was 16.7 months in treated patients compared with 2.6 months in untreated patients.

The results of the present study should be interpreted with caution due to the retrospective design of the study and the inclusion of only a small sample of patients from a single institution. However, due to the rarity of NMTC with brain metastases and the lack of data from prospective studies, management decisions currently rely on case reports and retrospective studies (23). The present study is of interest due to the improved outcome achieved in the aggressively treated patients, the high association observed between brain metastases and lung metastases in NMTC and the high incidence of incidentally diagnosed brain metastases.

In conclusion, the present study demonstrates that a higher-than-expected proportion of patients with lung and bone metastases from NMTC also exhibit brain metastases. Therefore, systemic screening should be considered for all patients with disseminated NMTC. Surgical resection of all operable metastatic lesions with multidisciplinary adjuvant treatment is critical to improve patient survival.

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