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Thyroid cancer brain metastasis: survival and genomic characteristics of a large tertiary care cohort

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Abstract

Purpose: Brain metastasis (BM) in patients with differentiated thyroid cancer (DTC) are rare but associated with poor prognosis. We examined risk factors for overall survival (OS) in this population and explored the pattern of genomic alterations.

Materials and Methods: Single institution, retrospective review of all patients with DTC from January 2000–November 2016, identified 79 patients for analysis. Multiple prognostic factors, including age, gender, distal metastasis (DM), diagnosis time, DM sites, BM diagnosis time, BM number and size, genomic sequencing data, craniectomy, external beam radiation (EBRT), and kinase inhibitor therapies were evaluated. Univariate and multivariate analyses were performed.

Results: Median survival after BM was 18 months. One- and three-year survival was 63% and 33% respectively. Univariate analysis identified four covariates correlated with prolonged survival: time between DTC diagnosis and BM < 3 years ($p = 0.01$), time from initial DM diagnosis to BM 22 months ($p = 0.03$), 3 BM sites ($p = 0.002$), and craniectomy ($p = 0.05$). Multivariate model revealed three variables associated with OS: DTC diagnosis to BM time < 3 years ($p = 0.04$),

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craniectomy ($p = 0.06$), and patients with < 3 BM sites ($p = 0.06$). The majority of patients with BM had a telomerase reverse transcriptase (TERT) promoter-mutation. However, mutational status was not an independent predictor of survival.

Conclusions: For BM from DTC, time interval between DTC diagnosis and BM, number of BM sites, and craniectomy were independently associated with OS. Further studies are needed to define the role of genomic mutations in advanced cancer.

Keywords

DTC; thyroid; brain metastasis; craniectomy; TERT; BRAF

Introduction

Patients with differentiated thyroid cancer (DTC) and distal metastasis (DM) have poorer overall survival than those without metastasis. Brain metastases (BM) account for 0.1 to 5% of DM and are associated with even poorer survival with the range of mean overall survival (OS) from 7.1–33 months [1, 2]. This constitutes a pressing need for earlier diagnosis and presents challenges in treatment decision-making. Choi et al. performed survival analysis on 37 patients by looking at prognostic factors including age, brain metastatic numbers, cognitive function, and presence of extracranial metastasis prior to BM [2]. Saito et al. published similar findings in their study with 25 patients [3]. Figueiredo et al. demonstrated improved survival by describing the importance of BM intervention with radiation therapy and/or neurosurgery in their 21-patient cohort [4].

The main limitation of these prior studies is their small sample sizes, which weaken the statistical power and reliability of their results. Our study aims to report univariate and multivariate analyses of multiple prognostic and survival factors in a larger cohort of patients with DTC and BM. To our knowledge, our study is currently the largest cohort of DTC patients with BM. Furthermore, no study has explored genetic profiles in similar patients. Ultimately, we retrospectively analyzed 79 patients with DTC and BM. Twenty of these patients had genetic profiling with IMPACT screening. While this patient demographic has previously been annotated with standard clinicopathologic information, imaging, and kinase inhibitor and/or radioactive iodine (RAI) therapy, we hypothesized that genomic information may introduce another clinically relevant independent variable [5].

Materials and Methods

Patient selection

Our institution's patient records from January 2000 to November 2016 were retrospectively searched for thyroid cancer diagnosis according to the hospital billing code in line with the international classification of diseases. The search resulted in 14,411 patients, which was further filtered to 241 patients due to the inclusion of the BM diagnostic code. Additional exclusion of patients with anaplastic or medullary thyroid cancer or the presences of a synchronous neoplasm was performed (Fig. 1). 79 patients diagnosed with DTC and BM met inclusion into our study.

Tumor histology

Primary thyroid tumors were classified according to the most recent World Health Organization criteria with the exception of tall cell variant (TCV-PTC) and poorly differentiated thyroid cancer [6]. Tumors were classified as TCV-PTC if they contained 50% tall cells. The latter cell type was defined as having a height at least twice its width with an oncocyctic cytoplasm [7]. Poorly differentiated thyroid cancer was defined by proliferative grading features: 5 mitoses/10 high-power fields and/or tumor necrosis regardless of architectural pattern. This definition differs from the most recent Turin proposal, which requires the presence of a solid/trabecular/insular growth pattern in addition to proliferative grading [8]. However, in a recent study, both classifications were found to be comparable in predicting intermediate prognosis of thyroid cancer [9].

Imaging and BM criteria

Brain metastases were confirmed by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). An example is shown in Figure 2. The number of BMs were counted on diagnostic brain MRI. The size of a metastasis was measured on MRI using the longest diameter in the axial view regardless of lesion location or morphology.

The approach to treatment for the BM was left to the discretion of the treating physician. Treatment options included surgical resection, RAI therapy, external beam radiation therapy (EBRT), or a combination of these therapies. While most patients received EBRT, some had craniectomies. A breakdown of the number of patients receiving EBRT, RAI, craniectomy, or combination therapy can be found in Table 1.

Genetic analysis

At our institution many tumor biopsy samples were sent for targeted genomic analysis referred to as IMPACT, a test designed with custom DNA probes for exons and selected introns of 341 oncogenes, tumor suppressor genes, and members of pathways deemed actionable by targeted therapies [10, 11]. Twenty out of 79 patients received IMPACT genetic testing with samples from thyroidectomy, neck dissection, craniectomy, or biopsy. As expected, the genomically annotated specimens are biased toward extracranial sites, given the difficulty in accessing an intracranial lesion. In the end, 3 samples were obtained from BM, with the remaining 17 from extracranial sites.

Statistical analysis

Survival analysis was performed using the Kaplan-Meier method. Survival time was defined as time from the date of BM diagnosis to the date of death, or to the date of last follow-up for censored patients. The log-rank test was used in univariate analysis to identify covariates associated with survival. Continuous covariates were categorized into groups for the log-rank test, and those that were significantly associated with survival in univariate models were included in a multivariate Cox proportional hazards model. P values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 (Cary, NC).

Results

Clinicopathologic characteristics and treatment

Details for the 79 patients are presented in Table 1. Well-differentiated papillary cancer represented 54% of the total sample. Other histological groups included 37% poorly differentiated, 5% follicular cell, and 4% Hurthle cell. Stage I, II, and IV patients comprised similar percentages (around 30% each), with only 8% stage III patients. All but one patient (n = 78) underwent a thyroidectomy. For this one patient MRI showed multiple BMs, so the patient only underwent palliative treatment with whole brain radiation. Twenty-seven patients (34%) had DMs at the time of diagnosis. Of note, lung metastases were by far the most common type (70%), followed by bone metastases (24%).

The average time to development of BM was approximately 6.6 years. The average time between DM diagnosis and BM was approximately 22 months. The median age at the time of BM diagnosis was 61 years old (range: 24–89 years old). Among them, 37 were male (46%) and 44 were female (54%). Thirty-five percent of patients received a craniectomy, 65% received kinase treatment, and 82% received EBRT. Only 14% (11 patients) received RAI after BM diagnosis, and 5% (4 patients) received both RAI and craniectomy.

Imaging characteristics of BM

Approximately 84% of patients (66/79) had three or fewer brain lesions. Among them, 46 patients had one brain lesion, 14 had two lesions, and 6 had three lesions. Thirteen patients, or about 16%, had more than three lesions. Seventy-one percent of brain lesions were 1 cm in maximum size. The mean size of the BM was 1.8 cm. Only 5 of the 11 (45%) RAI-treated patients exhibited radioiodine avidity in the BM. Of note, due to the high background of the brain FDG uptake, no FDG avidity of the BM was studied. Instead, the FDG avidity of other DMs was seen in 71 patients (96%) as reported in Table 1.

IMPACT genetic analysis

As shown in Table 2, 16 of 20 (80%) patients were TERT promoter mutation-positive, and 11 patients (55%) were BRAF-V600E-positive. Concurrent TERT promoter and BRAF-V600E mutations were noted in 10 patients (50%). Overall, TERT and/or BRAF-V600E mutations were positive in 17 patients (85%). Four TP53 mutations (20%) were seen, with only two double mutations (10%) of TP53 and TERT. One NRAS mutation patient (5%) and one TERT + NRAS double-positive patient (5%) were also identified. Within the 16 TERT-positive patients, 7 had papillary cancer, 7 had poorly differentiated cancer, and 2 had Hurthle cell cancer. The TERT subtypes were primarily C228T (81%) and C250T (13%). Among the 11 BRAF-V600E-positive patients, 4 had poorly differentiated cancer and 7 had papillary cancer. The IMPACT tissue samples came mostly from metastatic disease, primarily from the lymph nodes and lung. Only 3 of the 20 patients had samples from their cranial lesions, and only 2 out of 20 patients had thyroid tissue for the genetic sampling.

Survival

Of 79 total patients with BM, 55 died (70%; Fig. 3). Causes of death included thyroid cancer (n = 51) and lung infection (n = 4). Median survival time after BM was 18 months (range:

0–72). Survival was 63% (95% confidence interval, or CI: 51–73) at 1 year and 33% (95% CI: 21–45) at 3 years (Fig. 3). The median follow-up time for survivors was 20 months (range: 1 month–14 years).

Four covariates were significantly associated with survival in the univariate analysis (Table 3, Fig. 4). Patients with a time interval between TC diagnosis and BM diagnosis of < 3 years had a better survival outcome (median survival time: 25 months) than patients with a time interval of > 3 years (median: 14 months; $p = 0.01$). Median time from initial DM to time of BM was 22 months; patients below the median had significantly better survival than patients above the median (30 months vs. 17; $p = 0.03$). Patients with ≤ 3 BM sites had a better survival outcome (median survival time: 22 months) than those with > 3 sites (median: 11 months; $p = 0.002$). Finally, patients who underwent craniectomy after BM had a better survival outcome (median survival time: 30 months) than patients with no craniectomy (median: 14 months; $p = 0.05$). No statistically significant effects of age, sex, histology, maximum BM tumor size, initial DM at time of TC diagnosis, site of initial DM, external beam radiotherapy, or kinase inhibitor therapy after BM were detected.

Time interval between TC diagnosis and BM diagnosis, time from initial DM to time of BM, number of BM sites, and craniectomy after BM were included in a multivariate analysis (Table 3). Time from initial DM to BM was not included in the multivariable model due to high collinearity with time from diagnosis of TC to BM (Spearman correlation coefficient $\rho = 0.69$). In the multivariate model, the three variables were significantly or borderline significantly associated with survival. There was a two-fold increase in hazard for patients with a longer time interval between TC diagnosis and BM diagnosis (HR: 1.95; 95% CI: 1.05–3.6; $p = 0.04$). Patients who underwent a craniectomy had a 42% decrease in hazard, compared to those who did not undergo the procedure (HR: 0.58; 95% CI: 0.32–1.0; $p = 0.06$), and patients with > 3 BM sites had a two-fold increase in hazard compared to those with ≤ 3 sites (HR: 1.94; 95% CI: 0.97–3.9; $p = 0.06$).

Discussion

The prognosis, characteristics, and survival of DTC with BM have been difficult to study due to its overall low prevalence in the population. In this study, we report the largest cohort of such patients with a subset annotated with genomic analysis. In keeping with previous publications, increased survival was seen in patients with craniectomy. The mean survival of these patients was 30 months, significantly longer than the non-craniectomy group (14 months). These results reiterate the importance of surgical intervention for patients with incurable DTC with central nervous system involvement, as recommended in the 2009 American Thyroid Association guidelines [12].

Meanwhile, our results demonstrated some important findings that were different from previous studies. We found that patients with BM within 3 years of diagnosis of thyroid cancer (< 3 year group) have a better prognosis than those beyond 3 years of diagnosis (> 3 year group), in direct contrast to the Choi et al. 2016 study (2). This result can be explained by the pivotal role of time in BM evolution. For example, the number of BMs depended on the time between BM and thyroid cancer diagnosis (seen in the multivariate analysis). The

univariate analysis showed that the time between BM and DM is a significant prognostic factor, but not in the multivariate analysis, since it actually linearly correlates with the time between BM and thyroid cancer diagnosis. Also, as indicated above, whether or not a patient underwent a craniectomy was a significant prognostic factor. Craniectomy is usually indicated in patients with few but not multiple BMs. Accordingly, patients with a relatively early course of BM, who were possibly treated more aggressively earlier in their disease, underwent the procedure. Overall survival was worse when BM was discovered beyond 3 years (3 year group) post-diagnosis, likely because the overall disease burden was greater and progression had occurred at multiple non-brain sites. Also, there is known referral bias, as patients tend to come to our tertiary care institution with advanced stages of disease. These patients may have had fewer targeted treatment options with multifocal metastatic disease. In our series, the median time from diagnosis of thyroid cancer to BM is 22 months, or 1.8 years. This finding likely validates referral bias, since the prior series had a greater latency (3–12 years) [2–4, 13].

Additionally, 34% of patients had initial DM at the time of diagnosis, which is also higher than the previous studies.

The number of brain metastases has previously been shown to be a significant prognostic factor [2, 3]. In keeping with their methods, 66 out of 79 patients (84%) had 3 lesions, in contrast to 21 out of 37 patients (57%) in Choi [2], and 13 out of 22 (59%) patients in Saito [3]. We again demonstrated in the univariate and multivariate analyses that patients with 3 BM had increased survival than those with > 3 BM (univariate $p = 0.002$; multivariate $p = 0.06$). Although our multivariate analysis lays just adjacent to the typically defined level of 0.05, this is still evidence that the number of BM lesions is independently associated with survival outcome.

It is logical to consider the likelihood of transformation or dedifferentiation of the DM from the original cancer. This was only observed in two cases: one patient with original well-differentiated thyroid cancer developed biopsy-proven poorly differentiated BM 16 years later, and another patient with poorly differentiated thyroid cancer evolved into anaplastic BM within 10 months. In the other 25 patients who received craniectomy and had either BM biopsy or surgical pathological result, the majority of metastases were similar to the original cancer morphologically.

No previous data was available regarding genetic factors that predispose patients to BM. Our genetic test results demonstrate that the TERT mutation is most frequently encountered. In the 20patient subset that received IMPACT testing, 16 (80%) were found to be TERT-positive. TERT has been proven to be an important gene associated with many advanced and aggressive cancers. TERT mutation has been linked to the poor survival and higher prevalence of DM [14, 15], and refractory radioactive iodine in DTC [16]. The histological groups in the TERT-positive patients were not very different from the overall group (total: 79), with 44% papillary thyroid cancer and 44% poorly differentiated cancer (54% and 37% in overall groups, respectively). Our results are consistent with the findings of Xing et al. [16]. The BRAF-V600E mutation, a well-known oncogene, was the second most common in 11 out of 20 patients (55%). Interestingly, 10 out of these 11 BRAF-V600E-positive cases

featured TERT mutations. According to the literature, there is a synergistic effect between TERT and BRAF-V600E mutations [17]. The TERT + BRAF V600E-positive mutations greatly reduced survival time in comparison to the BRAF-V600E-alone group [18, 19].

Lastly, 20% (4 patients) had positive TP53 mutations, and 2 out of 4 were TERT + TP53-positive. The TP53 was found in 3 poorly differentiated and 1 Hurthle cell cancer. TP53, a tumor suppressor gene mutation, has been reported to be associated with anaplastic thyroid cancer and has recently been found to be one of the major genetic factors affecting the dedifferentiation of thyroid cancer [5, 20].

Only one patient was NRAS-positive and another one was TERT + NRAS-positive, of which the histology was poorly differentiated cancer. NRAS belongs to the RAS family, a group of well-known oncogenes, including KRAS and HRAS. RAS is frequently seen in follicular cell variant or follicular cell cancer [5]. A recent publication indicated that RAS alone is associated with a relatively benign prognosis [21]. However, when it co-exists with a TERT mutation, the cancer becomes more aggressive.

Conclusion

This retrospective study provides some statistical evidence that a small number of clinical features including time interval between DTC diagnosis and BM, time interval from initial DM to BM, number of BM sites, and craniectomy were independently associated with survival outcomes. No gender, age, genetic factors, or EBRT/kinase inhibitor treatment significantly affected prognosis or survival. High incidence of TERT gene mutations was observed as one might expect in advanced stage metastatic thyroid cancer, even if the initial lesion was well-differentiated. As genomic testing becomes a more integrated component of treatment algorithms, these data may be used to personalize treatment.

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Figure 1.
Inclusion criteria for addition in our retrospective review of the medical record.

Figure 2.

Patient with thyroid cancer and metastasis to the brain. (A) Metastasis to the brain was suspected after whole body ^{131}I scan, where increased uptake in the right cranium was noted (white arrow). Non-contrast CT of the head (B) and ^{18}F -FDG positron emission tomography (PET)/CT identifies a hyperintense mass with increased tracer uptake (C). (D and E) Flair and Contrast enhanced MRI of the brain identify the metastatic mass in the right frontal region (white arrow).

Figure 3.
Kaplan-Meier graph evaluating overall survival during follow-up in our patient population.

Figure 4.

Kaplan-Meier graph of overall survival after the diagnosis of brain metastasis for a number of associated factors. (A) Time from thyroid cancer diagnosis to brain metastasis; (B) Time from any metastasis to brain metastasis; (C) Number of brain metastasis; (D) Craniectomy procedure.

Table 1.

Clinical Characteristics of Patients with Brain Metastases from Thyroid Cancer (n=79)

Characteristic	No. (range or %)
Age at diagnosis of BM (years) – median (range)	61.5 (24–89)
Time from diagnosis of TC to BM (years) – median (range)	6.6 (0–41)
Sex (Male)	35 (44.3)
Histology [*]	
Papillary	42 (53.9)
Poorly differentiated	29 (37.2)
Follicular	4 (5.1)
Hurthle cell	3 (3.8)
TC stage at diagnosis [†]	
I	25 (32.9)
II	22 (29.0)
III	6 (7.9)
IV	23 (30.2)
Extrathyroidal extension [‡]	
None	16 (23.5)
Minimal	36 (53.0)
Gross	16 (23.5)
Vascular invasion present [§]	43 (69.4)
Number of BM sites (>3)	13 (16.5)
Max size of BM tumor (≥ 1 cm)	56 (70.9)
Received chemotherapy	61 (77.2)
EBRT after BM	63 (81.8)
Radioactive iodide therapy after BM	11 (13.9)
Craniectomy after BM [¶]	27 (34.6)
Radioactive iodide therapy and craniectomy after BM	4 (5.1)
Kinase inhibitor given ^{**}	51 (65.4)
RAI avidity ^{††}	5 (45.5)
FDG PET avidity ^{‡‡}	71 (96.0)
Initial DM at time of TC diagnosis	27 (34.2)
Time from initial DM to BM (months) – median (range)	22 (0–170)
Site of initial distant metastasis	
Lung	55 (69.6)
Bone	19 (24.1)
Brain	15 (19.0)
Other	6 (7.6)

Abbreviations: BM, brain metastasis; TC, thyroid cancer; EBRT, external beam radiation therapy; DM, distal metastasis.

Values reported as frequency (percent), unless otherwise noted. Values from two-level variables are presented for only one level.

* Unknown for 1 patient

[†] Unknown for 3 patients

[‡] Unknown for 11 patients

[§] Unknown for 17 patients

^{||} Unknown for 2 patients

[¶] Unknown for 1 patient

^{**} Unknown for 1 patient

^{††} Reported for 11 patients who had RAI after brain metastasis

^{‡‡} Unknown for 5 patients

Table 2.

Univariate Analysis of Predictors Associated with Survival in Patients with Brain Metastasis from Thyroid Cancer with IMPACT

Univariate			
Variable	n	Median survival months (95% CI)	P
TERT			
No	4	25 (13–25)	0.94
Yes	16	63 (8–63)	
TERT or BRAF			
No	3	25 (13–25)	0.74
Yes	17	63 (8–63)	

Table 3.

Univariate Analysis of Predictors Associated with Survival in Patients with Brain Metastasis from Thyroid Cancer

		Univariate		Multivariate	
Variable	n	Median survival months (95% CI)	P	HR (95% CI)	P
Age					
< 55 years	23	27 (12–72)	0.09		
≥ 55 years	56	17 (11–23)			
Sex					
Male	35	18 (8–22)	0.07		
Female	44	26 (11–42)			
Time from diagnosis of TC to BM					
< 3 years	31	25 (14–63)	0.01	Ref.	0.04
≥ 3 years	48	14 (10–23)		1.95 (1.05–3.6)	
Histology					
Papillary	29	19 (11–30)	0.46		
Other	36	17 (11–41)			
Initial DM at time of TC diagnosis					
No	52	18 (13–27)	0.41		
Yes	27	22 (7–46)			
Time from initial DM to BM					
< 22 months	37	30 (11–52)	0.03	*	
≥ 22 months	42	17 (11–23)			
Initial DM in brain					
No	64	17 (11–25)	0.15		
Yes	15	46 (7–63)			
Initial DM in lung					
No	24	38 (11–52)	0.19		
Yes	55	17 (10–26)			
Initial DM in bone					
No	60	18 (12–25)	0.36		
Yes	19	38 (7–50)			
Number of BM sites					
3	66	22 (14–38)	0.002	Ref.	0.06
> 3	13	11 (1–19)		1.94 (0.97–3.9)	
Maximum size of BM tumor					
< 1 cm	23	22 (8–63)	0.23		
≥ 1 cm	56	18 (11–26)			
EBRT after BM					
No	14	11 (1–46)	0.48		
Yes	63	19 (13–30)			
Craniectomy after BM					

Variable	n	Univariate		Multivariate	
		Median survival months (95% CI)	P	HR (95% CI)	P
No	51	14 (8–23)	0.05	Ref.	0.06
Yes	27	30 (14–50)		0.58 (0.32–1.0)	
Kinase inhibitor after BM					
No	27	14 (5–18)	0.38		
Yes	51	25 (13–7)			

Abbreviations: TC, thyroid cancer; DM, distal metastasis; BM, brain metastasis; EBRT, external beam radiation therapy.

* Time from initial DM to BM not included in multivariable model due to high colinearity with time from diagnosis of TC to BM (Spearman correlation coefficient $\rho = 0.69$).