Brain Metastases From Differentiated Thyroid Carcinoma: Prevalence, Current Therapies, and Outcomes

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Background and Objective: The brain is an unusual site for distant metastases of differentiated thyroid carcinoma (DTC). The aim of this study was to document the prevalence of brain metastases from DTC at our institutions and to analyze the current therapies and the outcomes of these patients.

Methods: We performed a retrospective chart review of patients with DTC and secondary neoplasia of the brain.

Results: From 2002 to 2016, 9514 cases of thyroid cancer were evaluated across our institutions and 24 patients met our inclusion criteria, corresponding to a prevalence of 0.3% of patients with DTC. Fourteen (58.3%) were female and 10 (41.7%) were male. Fifteen patients had papillary thyroid cancer (PTC) (62.5%). Brain metastases were diagnosed 0 to 37 years (mean $\pm$ SD, 10.6 $\pm$ 10.4 years) after the initial diagnosis of thyroid cancer. Patients undergoing surgery had a median survival time longer than those that did not undergo surgery (27.3 months vs 6.8 months; P = 0.15). Patients who underwent stereotactic radiosurgery (SRS) had a median survival time longer than those that did not receive SRS (52.5 months vs 6.7 months; P = 0.11). Twelve patients (50%) were treated with tyrosine kinase inhibitors (TKIs), and they had a better survival than those who have not used a TKI (median survival time, 27.2 months vs 4.7 months; P < 0.05).

Conclusion: The prevalence of brain metastases of DTC in our institutions was 0.3% over 15 years. The median survival time after diagnosis of brain metastases was 19 months. In our study population, the use of TKI improved the survival rates.

Freeform/Key Words: thyroid cancer, DTC, brain metastases, prevalence, therapies

Brain metastases are more common than primary tumors of the central nervous system. The primary cancers that most frequently develop brain metastasis are lung (19.9%), melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers [1]. For differentiated thyroid cancer (DTC), the brain is an unusual site for distant metastases, occurring in about 0.15% to 1.3% of the cases [2]. Studies conducted in tertiary referral centers reported a prevalence of brain metastases from DTC of 1.2% [3] and 1.4% [4].

Historically, brain metastases from any primary tumor are associated with poor prognosis, but recent operative advances and new modalities of treatment have substantially increased survival [5]. Several retrospective studies have attempted to determine the possible impact of therapies on the prognosis of patients with brain metastases from DTC [3, 4, 6, 7]. The 2015 American Thyroid Association guidelines on differentiated thyroid cancer, in recommendation 94, state that surgical resection and stereotactic radiosurgery are the mainstays of therapy for brain metastases from DTC. Iodine-131 (^{131}I) can be used if the lesions concentrate radioactive iodine. Yet this is a weak recommendation, based on low-quality evidence [8].

The goal of our study was to document the prevalence of brain metastases from DTC at MedStar Health institutions over 15 years and to analyze current therapies and the outcomes of affected patients.

1. Methods

We searched MedStar Health institutions' pooled patient electronic health records database, corresponding to 10 hospitals in Maryland and Washington, DC. We used the Explore application on the Explorys platform (IBM, Armonk, NY) to obtain deidentified patient data from 2002 to 2016. This technology uses a server behind the firewall of participating MedStar Health institutions to capture information from patients in a privacy-protected and Health Insurance Portability and Accountability Act–compliant framework [9]. Medical charts containing the diagnosis of thyroid cancer [International Classification of Diseases, Ninth Revision (ICD-9) 193 or 10th Revision (ICD-10) C73] and secondary neoplasia of the brain (ICD-9 198.3 or ICD-10 C79.3) were initially retrieved, for a total of 51 charts. Local electronic medical records were used to perform the chart reviews. Patients with medullary and anaplastic thyroid cancer were excluded, as were those with other active primary malignancies except squamous cell or basal cell skin carcinoma. The MedStar Health Research Institutional Review Board approved the study. Because this was an electronic medical records-based study, the need for informed consent was waived.

2. Statistical Analysis

All data extracted from electronic medical records were summarized by using descriptive statistics, such as means, SDs, and range, for continuous variables and frequencies and percentages for categorical variables. The Kaplan-Meier method was implemented to calculate survival time from initial diagnosis of thyroid cancer and from the diagnosis of brain metastases, including median survival time and the survival rate at 3 months, 6 months, 1 year, 2 years, and 5 years. Survival curves were compared across treatment and demographic strata with log-rank tests and bivariate Cox regressions. Statistical significance was determined with a P value threshold of 0.05. Analyses were performed with R software, version 3.3 [10], using the survival, ggplot2, and R2wd packages [11–14].

3. Results

Between 2002 and 2016, a total of 9514 patients with a diagnosis of thyroid cancer were evaluated across all MedStar hospitals. Ninety-three percent of these cases were estimated to be DTC based on epidemiological data [15], which corresponds to 8848 cases. Of these patients, we identified 51 with DTC and secondary brain malignancy (Fig. 1). Patients with
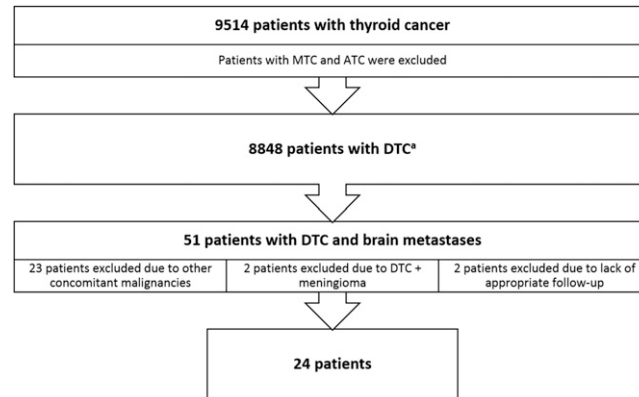
Figure 1. Study design. [a]Estimated number of DTC based on epidemiological data (93%). Abbreviations: ATC, anaplastic thyroid cancer; MTC, medullary thyroid cancer.

other primary malignancies or without appropriate follow-up data were excluded. Among the 24 patients who met our inclusion criteria, 14 (58.3%) were female and 10 (41.7%) were male. The mean age at diagnosis of DTC was 46.3 ± 15.2 years (range, 4 to 73 years). The baseline characteristics of patients are described in Table 1.

Table 1. Baseline Characteristics

Patient No.	Sex	Age at Diagnosis of Thyroid Cancer (y)	Histology (Thyroid)	Size of Thyroid Tumor (cm)	TNM Classification[a]	Time From Diagnosis to BM (y)	ECOG Performance Status at Diagnosis of BM	Survival After Diagnosis of BM (mo)
1	M	51	FVPTC + PDTC	7.6	T3N1bM1	1.4	1	18
2	F	61	FVPTC + PDTC	2.5	T2N0M0	0.6	2	27
3	M	43	FVPTC + TC	1	T1aN1aM0	13.1	1	5
4	F	43	FVPTC	0.9	T1aN0M1	0	1	119
5	F	54	FVPTC	—[b]	—	0	4	26
6	M	4	PTC	—	—	28.3	1	2
7	M	39	PTC	5	T3N0M0	13.4	2	21
8	F	29	PTC	—	—	13.8	—	No follow-up
9	M	42	PTC	1.1	T3N1bM0	2.6	2	62
10	M	48	PTC	3	T3N1bM1	5.2	1	108[c]
11	M	28	PTC	—	—	37.2	1	51
12	M	35	PTC	—	—	30.1	3	6
13	F	50	PTC	2.2	T2NxM1	8.8	1	36[c]
14	F	69	PDTC	2.5	T3N0M1	1.1	4	1
15	F	66	HTC	—	—	10.2	2	15
16	M	57	HTC+PDTC	6.5[b]	T4aNxM1	0.5	1	1
17	F	54	FTC+PDTC	1.7	T1bN0M0	3.3	4	0
18	F	73	FTC	—	—	10.5	3	No follow-up
19	F	47	FTC	—	—	18.7	2	4
20	F	57	FTC	4	T4bNxM1	0.1	2	6
21	F	34	FTC	3	T2NxM0	12.1	3	26
22	F	30	FTC	—	—	15.3	4	2
23	F	45	FTC	4.2	T3N0M0	14.3	4	0
24	M	51	—	—	—	14.2	1	68
Mean ± SD		46.3 ± 15.2		3.23 ± 2.04		10.6 ± 10.4		19[d]

Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; F, female; FVPTC, follicular variant of papillary thyroid cancer; HTC, Hürthle cell thyroid cancer; M, male; PDTC, poorly differentiated thyroid cancer; TC, tall cell.

[a]For patients whose original biopsy specimen was available.

[b]No surgery done.

[c]Alive at study completion.

[d]Median survival time.

A. Pathology of the Thyroid Tumor and Extracranial Metastases

Fifteen patients had papillary thyroid cancer (PTC) (62.5%). Of these, 10 patients had classical variant and 5 had follicular variant of PTC, either pure (2 patients) or with areas of poor differentiation (2 patients) or tall cell features (1 patient). Seven patients had follicular thyroid cancer (FTC) (29.2%), of whom 2 had areas of poor differentiation and 2 patients had Hürthle cell features. One patient had poorly differentiated thyroid cancer, and 1 patient had no report from the original tumor but had confirmed brain metastases from differentiated thyroid cancer. In patients with brain metastases, individuals with PTC had a median survival time of 27.3 months compared with 4.7 months for patients with FTC and 1.06 months for the patient with poorly differentiated thyroid cancer. This difference was statistically significant ($P < 0.05$).

For patients in whom the original thyroidectomy pathology report was available, the mean size of the tumors was 3.2 ± 2.0 cm. We could not classify the initial stage (TNM classification) of all patients because nine patients (37.5%) had thyroid surgery and initial follow-up of thyroid cancer at other institutions, and the histology of the original tumor was not available. TNM classification of patients whose original pathology report was available is presented in Table 1.

Two patients did not have thyroidectomy. One patient presented with an inoperable tumor whose biopsy sample was compatible with poorly differentiated carcinoma with Hürthle cell features. The other patient had a diagnosis of thyroid nodules but was lost to follow-up; this patient returned several years later with a brain tumor that was compatible with metastatic thyroid carcinoma suggestive of the follicular variant of PTC based on biopsy (surgical specimen).

All but one patient had extracranial metastatic disease, notably in the lungs (21 patients) and bones (18 patients). The only patient who had no report of other metastatic sites had an irregular follow-up.

B. Eastern Cooperative Oncology Group Performance Status of the Patients

Patients were classified according to the Eastern Cooperative Oncology Group (ECOG) performance status [16] at the time of diagnosis of brain metastases: grade 1 (nine patients), grade 2 (six patients), grade 3 (three patients), and grade 4 (five patients). For one patient the performance status could not be characterized.

C. Radioiodine Scanning and Treatment

The mean number of ^{131}I treatments was 2.8 ± 1.6 (range, 0 to 6). The mean cumulative activity of ^{131}I was 635.9 ± 415.9 mCi (23.5 ± 15.4 GBq). Only 1 of 24 patients (4.1%) had ^{131}I uptake on diagnostic scans corresponding to the brain metastases. Two patients (8.3%) had ^{131}I uptake on posttherapy scans (Fig. 2). All the patients who had thyroidectomy (91.6%) have received ^{131}I therapy according to the staging of their tumors, not as a specific treatment
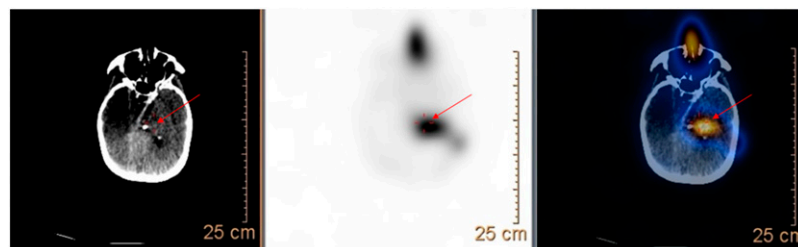

Figure 2. A 6-mm lesion on the left parietal lobe on single-photon emission CT-CT (transverse view). Images of posttherapy radioiodine scan demonstrate focal intense radioiodine activity in the left cerebral cortex localized to the left parietal lobe with help of the low-dose CT (red arrows).

of the brain lesions. Most of them had a high cumulative dose, suggesting persistent advanced metastatic disease.

D. Diagnosis of Brain Metastases

Brain metastases were diagnosed 0 to 37 years after the initial diagnosis of thyroid cancer, with a mean ± SD of 10.6 ± 10.4 years. The mean age at diagnosis of brain metastases was 57.4 ± 11.2 years. The lesions were diagnosed by MRI for 12 patients, by CT for 6 patients, and by positron emission tomography-CT for 4 patients. For 2 patients no radiologic report was available, but the oncologist communicated the diagnosis of brain metastasis.

E. Features of Brain Lesions

Of the 24 patients, 14 had a single brain lesion, 4 had two to three lesions, and 5 patients had four or more lesions; for one patient there was no report of the number of lesions (Table 2). Among the 14 patients (58.3%) who had symptoms related to the presence of brain lesions, 7 (50%) presented with headache. The mean size of the brain lesions was 2.7 ± 2.0 cm (range, 0.4 to 10.0 cm). Molecular data for the tumors with brain metastasis were available for only one patient (patient 13).

Table 2. Brain Metastases and Treatment Modalities

Patient No.	Localization of BM	Number of BM	Size of BM (cm)	Surgery	WBRT	SRS	TKI	Survival After BM (mo)
1	Right occipital lobe, central sulcus, and dura mater	Multiple	1	N	N	N	Y	18
2	Cerebellum	1	0.7	N	N	Y	N	27
3	Parietal lobe, thalamus, cerebellum	Multiple	2.8	Y	Y	Y	Y	5
4	Biparietal region; infratemporal fossa	Multiple	3.5	Y	Y	N	Y	119
5	Frontal lobe	1	10.0	Y	N	N	N	26
6	Frontal lobe	1	0.4	N	N	N	Y	2
7	Intraventricular	1	2	N	Y	Y	Y	21
8	Right frontal lobe	1	4.2	Y	N	Y	N	N/A
9	Left frontal lobe	1	0.7	N	N	Y	Y	62
10	Occipital lobe, temporal lobe, cerebellum	3	3.6	Y	Y	N	Y	108[a]
11	Temporal, occipital and parietal lobes	Multiple	1.9	N	N	Y	Y	51
12	NA	—	—	N	Y	N	N	6
13	Parasagittal occipital falcine	1	2.8	Y	Y	N	Y	36[a]
14	No results on chart	3	—	N	Y	N	N	1
15	Suboccipital region	1	3.8	Y	N	Y	N	15
16	Right and left frontal lobe	2	3.2	N	N	N	N	1
17	Parietal-occipital region	1	2.5	N	N	N	N	0
18	Lateral ventricle	1	—	N	N	N	N	NA
19	Right frontoparietal region and left frontal region	Multiple	3.2	Y	Y	N	N	4
20	Cerebellum	1	1.8	N	Y	N	Y	6
21	Interhemispheric fissure	1	1	N	N	N	Y	26
22	Pituitary	1	0.8	Y	N	N	N	2
23	Parietal lobe	1	3.6	N	N	N	N	0
24	Frontal parietal region, temporal region and cerebellum	3	3.2	Y	Y	Y	Y	68

"Multiple" refers to more than three lesions.
Abbreviations: BM, brain metastases; N, no; NA, not available; Y, yes.
[a]Alive at study completion.

F. Modalities of Treatment of Brain Metastases

Patients were treated with combinations of surgery, stereotactic radiosurgery (SRS) and/or whole-brain radiotherapy (WBRT). Of 24 patients, 10 (41.7%) had surgery, 8 (33.3%) had SRS, and 10 (41.7%) had WBRT (Table 2). Patients undergoing surgery had a median survival time of 27.3 months, compared with 6.8 months for those who did not undergo surgery. This difference was not statistically significant ($P = 0.15$) (Fig. 3a). Patients who received SRS had a median survival time of 52.5 months in comparison with 6.7 months for those who did not receive SRS. Again, the difference was not statistically significant ($P = 0.11$) (Fig. 3b). For WBRT, no difference was noted in the survival of patients receiving or not receiving this therapy (21.3 months vs 19.1 months, respectively; $P = 0.50$) (Fig. 3c).

Twelve patients (50%) were treated with a tyrosine kinase inhibitor (TKI). Of these patients, 8 were treated with a single agent and 4 patients received two or three agents in sequence (Table 3). Patients who were treated with TKIs had a median survival time of 27.2 months in comparison with 4.7 months for those who were not treated with a TKI. This difference was statistically
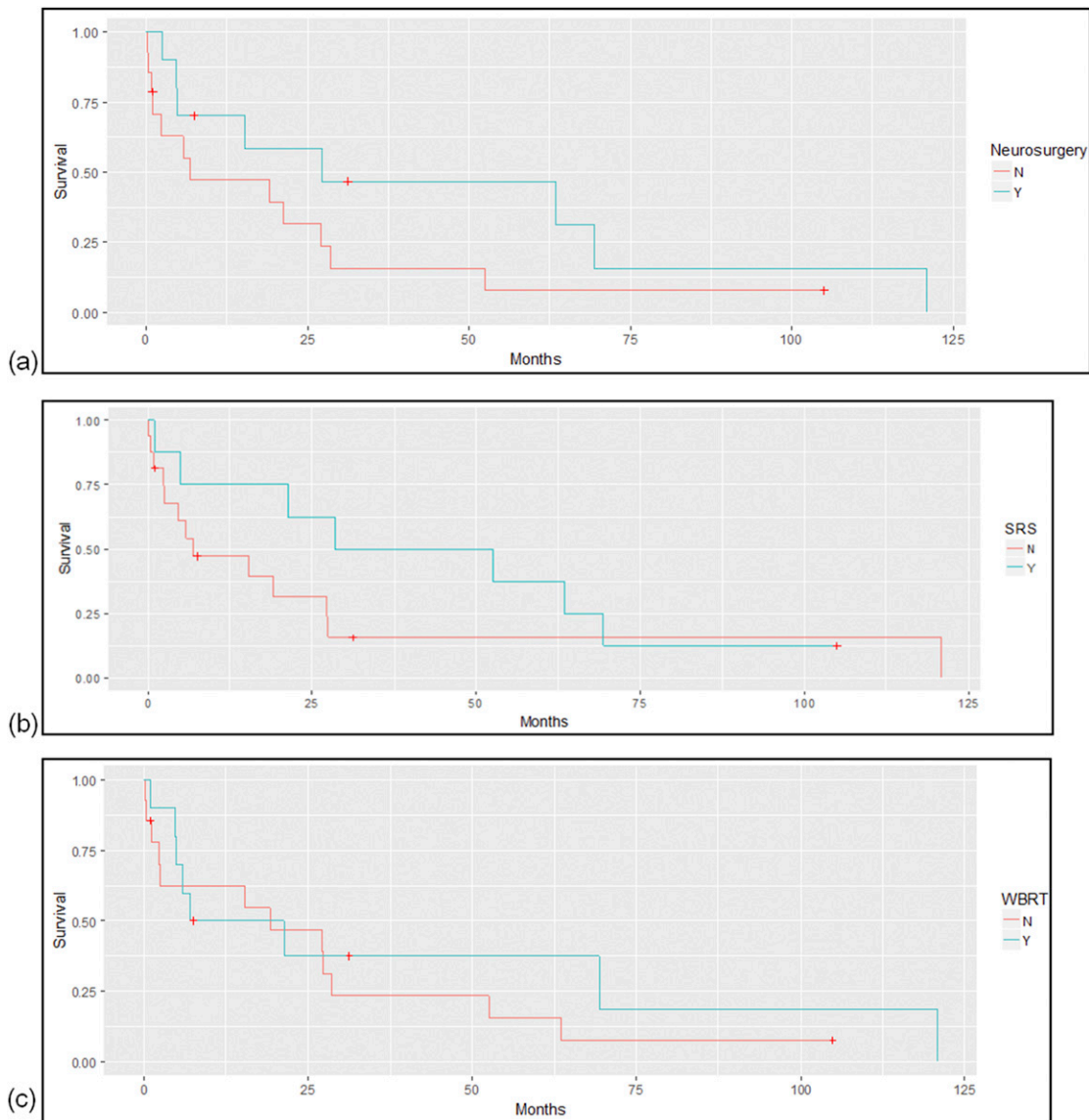

Figure 3. Kaplan-Meier curves of death from date of brain metastases by neurosurgery (a), SRS (b), and WBRT (c).

Table 3. Therapy With TKIs

Patient No.	TKI	Use Before BM Diagnosis	Survival After Diagnosis of BM (mo)
1	Sunitinib	Yes	18
3	Sunitinib	No	4.8
4	Sorafenib	No	118.8
6	Sunitinib	Yes	2.4
7	Sorafenib	No	21
9	Sorafenib,[a] lenvatinib	No	62.4
10	Sorafenib, lenvatinib	No	108[b]
11	Sunitinib, sorafenib, lenvatinib	No	51.6
13	Sorafenib, entrectinib, crizotinib	No	36[b]
20	Lenvatinib	No	6
21	Lenvatinib	No	26.4
24	Sunitinib	No	68.4

Abbreviation: BM, brain metastases.

[a]Previous use of vemurafenib.

[b]Alive at study completion.

significant ($P < 0.05$) (Fig. 4). The use of TKIs reduced the odds of death by approximately 73%. The log-rank test confirmed that the Kaplan-Meier curves were statistically different.

G. Overall Survival

The median survival time of the entire group after diagnosis of DTC was 174 months or 14.3 years (Fig. 5). The median survival time after diagnosis of brain metastases was 19 months (Fig. 6). Overall survival rates at 12, 24, and 60 months were 92.7%, 87.5%, and 70.8%, respectively. Two patients were alive at 9 years (108 months) and 3 years (36 months) after their diagnosis of thyroid cancer.

4. Discussion

This is a retrospective study examining patients with brain metastases from DTC in all MedStar Health Institutions, the largest healthcare provider in Maryland and Washington, DC. In this population, we found 24 cases of confirmed brain metastases from DTC, corresponding to an estimated prevalence of 0.3%.

There are few reports of the prevalence of brain metastases of DTC in the literature [3, 4]. In 1997, Chiu *et al.* [3] reported a 1.2% prevalence of brain metastases in a subgroup of DTC in a tertiary referral oncology center during a period of 51 years. Another retrospective study
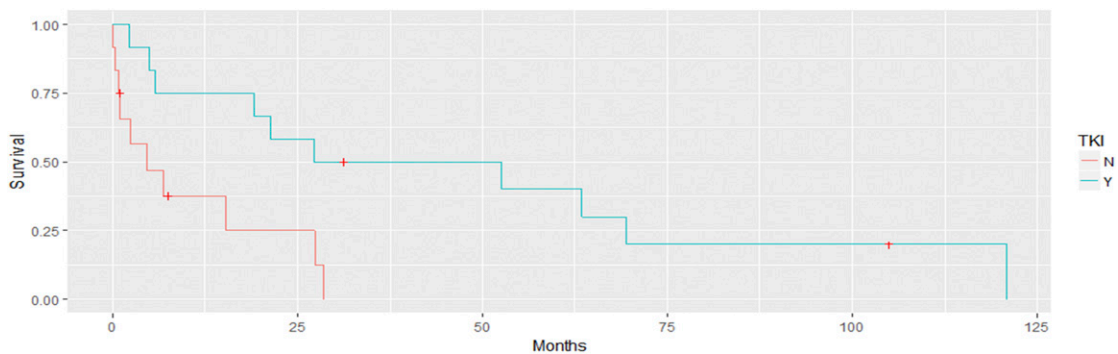

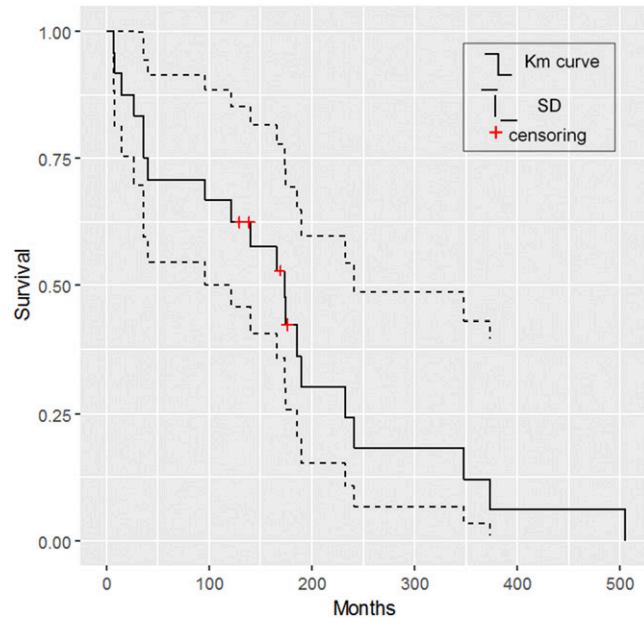**Figure 4.** Kaplan-Meier curves of death from date of brain metastases by use of TKI.

Figure 5. Kaplan-Meier (Km) curve of time of death from date of thyroid cancer diagnosis.

reported a 1.4% prevalence of brain metastases of DTC in a large tertiary referral center over 23 years [4]. In our population, during a period of 15 years, the prevalence of brain metastases from DTC was 0.3%. This number is considerably lower than that observed in previous studies, possibly because it includes heterogeneous hospitals across our organization, composed of seven regional hospitals, one rehabilitation hospital, one university hospital (MedStar Georgetown University Hospital), and one tertiary hospital (MedStar Washington Hospital Center). An alternative explanation for the low prevalence of brain metastases in our study is the exclusion of 23 patients with other concomitant malignancies. We applied this exclusion criterion when it was not possible to determine which cancer was responsible for the patient's brain metastases.
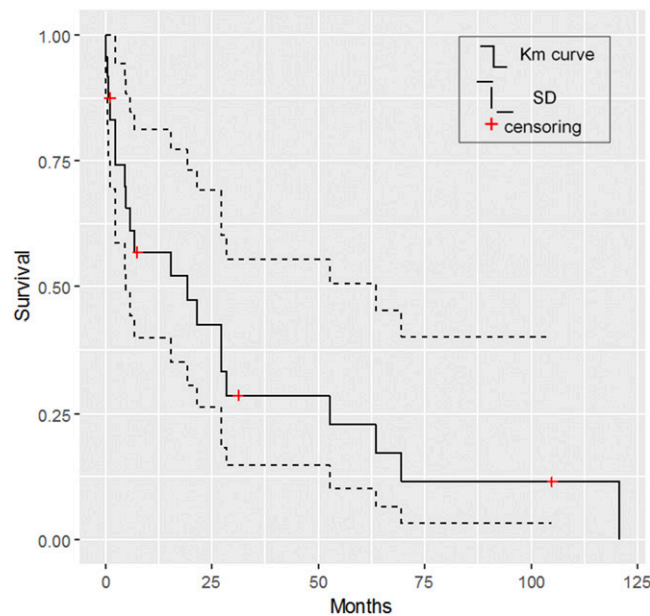

Figure 6. Kaplan-Meier (Km) curve of time of death from date of brain metastases diagnosis.

Given the rarity of brain metastases in DTC, there are no large retrospective studies about the prognosis of brain metastases, but in various studies >150 cases have been reported [17]. Chiu *et al.* [3] reported a median survival time of 12.4 months for the subgroup of 32 patients with DTC. In 2003, McWilliams *et al.* [6] described 16 cases with brain metastases of thyroid cancer over 25 years, including 14 patients with DTC. The median survival time after the diagnosis was 17.4 months, and 85% of the patients died of their extracranial disease. In another study [4], the median survival time was 7.1 months, but patients treated with surgery and/or SRS had a better outcome, with a median survival time of 11.9 months. The most important prognostic factor to select patients for more aggressive treatments was a performance status ≤2. This finding was corroborated by a recent survival analysis of patients with brain metastases from thyroid cancer [18]. In that study 37 patients with DTC diagnosed with brain metastases were divided into three prognostic groups. The authors characterized four good prognostic factors (age ≤ 60 years, performance status ≤ 2, ≤3 brain metastases sites, and no extracranial metastases before brain metastases). The median survival after brain metastases was 8.8 months for the entire group. For the subgroup with age ≤60 years and more than two good prognostic factors, the median survival time was 32.8 months. Compared with those studies, the median survival time in our study was higher (19 months), which can be attributed to the use of TKIs combined with local treatment of the metastatic lesions. In this study, 15 patients (62.5%) had a performance status ≤2.

With regard to histopathology, among retrospective studies [3, 4, 6, 7, 18], small series [19–24], and case reports [25–28], there is a predominance of brain metastases from PTC. This is in accordance with its higher prevalence but also highlights the fact that PTC is not universally an indolent malignancy. Our study corroborates these data, as 13 of 24 patients (54%) had PTC, 8 of them the classical variant of PTC.

[131]I can be considered for the treatment of brain metastases from DTC if the lesions concentrate radioactive iodine [8]. Few data address the efficacy of ^{131}I, and this treatment has been associated with important adverse effects, such as sudden hemorrhage into the brain lesion [29] and cerebral edema [30]. Therefore, ^{131}I therapy for brain metastases should be considered in the context of the appropriateness of surgical resection and stereotactic radiosurgery, and when the brain metastases have appropriate ^{131}I uptake [17]. Ideally, the maximum prescribed activity of ^{131}I should be dosimetrically determined. Patients can be prepared for ^{131}I therapy with thyroid hormone withdrawal or recombinant human TSH. The shorter exposure of the brain metastases to elevated TSH stimulation from recombinant human TSH injections potentially minimizes the possibility of growth of the tumor and the possibility of cerebral edema. Nevertheless, the use of steroids (and less frequently glycerol and/or mannitol) immediately before ^{131}I therapy has been recommended to minimize cerebral edema; treatment should be continued for a substantial period of time after administration of the therapeutic prescribed activity of [131]I [17]. In our cohort, only two patients (8.3%) had ^{131}I uptake corresponding to the brain metastases. We believe that brain lesions usually do not demonstrate substantial ^{131}I uptake, and the use of RAI for both diagnostic and therapeutic reasons may be less effective. In the presence of other previous or synchronous distant metastases, as documented here and in other studies [3, 4, 18], diagnostic imaging of the brain is warranted, regardless of the presence of neurologic symptoms. In our study, almost 60% of the patients had symptoms related to the brain lesions, suggesting advanced disease, although brain metastases may be asymptomatic. The fact that high-risk patients are not routinely screened for brain metastases may also be responsible for the low prevalence observed in our study. Unless otherwise contraindicated, contrast-enhanced MRI is the screening modality of choice to exclude the presence of brain parenchymal metastatic disease [31]. In our study, the brain lesions were detected by MRI in 50% of the patients, followed by CT in 25%. Given the normal glucose uptake of the brain, positron emission tomography-CT may underdiagnose some brain lesions, so other cross-sectional imaging studies, such as MRI and CT, may better characterize these lesions.

The decision-making for selecting the type of treatment is driven both by patient factors, such as age and systemic disease burden, and by tumor factors, such as number and location

of lesions and, more recently, the biology of the tumor based on molecular testing. The standard of care is the neurosurgical resection of individual symptomatic brain metastases. In our patients, the use of image-guided neuronavigation systems may have contributed to more effective procedures, especially in the last decade.

Radiotherapy modalities include WBRT, SRS, and focused external-beam radiotherapy [5]. WBRT has been widely used to treat various patients with multiple brain metastases, mainly for palliative purposes [32]. Radiation-induced dementia is a serious complication that may occur 6 to 12 months after radiation, and this potential adverse effect should be considered for patients who are more likely to live longer [33]. In our study, one patient declined WBRT specifically because of concern for his cognitive deterioration. Stereotactic radiosurgery, either Gamma Knife® (Elekta, Stockholm, Sweden) or CyberKnife® (Accuray, Sunnyvale, CA), has been associated with high local control rates, but factors such as functional status of the patient, systemic disease control, size and location of the lesions, and tumor histology directly affect the response rate. Clinical judgment and patient preference must help guide treatment decisions between surgical resection and stereotactic radio-surgery [33]. There are few data regarding the outcomes of SRS for brain metastases of thyroid cancer. Bernad *et al.* [34], in a retrospective multi-institutional study that included 23 patients with thyroid cancer, found that patients who received SRS had a median survival time of 37.4 months in comparison with 12.3 months for those not treated with this technique ($P = 0.29$). Likewise, in our cohort, we found that patients receiving SRS had longer survival than those who did not receive this therapy (52.5 months vs 6.7 months, respectively), without statistical significance ($P = 0.11$). In our study, this trend was not observed for patients that received WBRT.

Systemic control of the disease clearly affects the overall survival of patients with brain metastases from DTC as of any other malignancy. In accordance with previous studies [3, 4, 18], we observed that patients with DTC usually present with extracranial metastases at the diagnosis of brain metastases. The use of TKIs for patients with radioiodine-refractory DTC has significantly improved progression-free survival [35–37]. In the current study, 12 patients (50%) were treated with different types of TKIs because of the widespread nature of radioiodine refractory disease. No intracranial hemorrhage was reported. The use of TKIs was the only treatment statistically significant for survival after development of brain metastases. Nevertheless, this finding must be interpreted with caution because of a possible selection bias: TKIs are not usually prescribed for patients with a poor performance status. In addition, the issue of whether TKIs cross the blood-brain barrier is not completely understood.

Data are very limited about the effectiveness of TKIs in brain metastasis from DTC. Shen *et al.* [38] published a case report describing good clinical and radiological response of brain metastases of FTC to sorafenib. There are more data for other malignancies. Koutras *et al.* [39] found that sunitinib was effective and safe for a patient with brain metastases from renal cell carcinoma. Another study showed that lenvatinib was effective *in vitro* and *in vivo* for the treatment of glioblastoma, thus suggesting good penetration in the blood-brain barrier of mice [40]. Several prospective clinical trials have focused on malignancies that commonly metastasize to the brain, such as melanoma and lung and breast cancers. First-generation TKIs seem to have limited blood-brain barrier penetration; however, next-generation TKIs, such as osimertinib and ceritinib, may have better ability to cross the blood-brain barrier [32]. Entrectinib is a new TKI targeted at *NTRK*, *ROS1*, and *ALK* fusions that was developed to cross the blood-brain barrier. In one of our patients (patient 13), an *EZR* (exon10)/*ROS1* (exon14) fusion was identified in the brain specimen. This appeared to be the first description of an *EZR-ROS1* fusion in DTC. After 4 weeks of therapy with entrectinib, her brain metastasis and a rib lesion remained stable, and a periaortic nodule and a liver metastasis resolved; this corresponds to a partial response by RECIST1.1 [41]. Other drugs, such as the *RET* inhibitors LOXO-292 and BLU-667, are under investigation [42, 43] and may be more relevant because *RET/PTC* are the most commonly observed fusions in DTC.

Our study has several limitations inherent to its retrospective nature and number of patients. However, considering the rarity of brain metastases from DTC, it is unlikely that a

prospective study could be conducted. The number of brain metastases from DTC may be underestimated in our population because of the number of patients excluded as a result of other concomitant primary malignancies. Moreover, the use of clinical databases supposes the correct use of diagnostic codes for accurate patient identification. Another limitation of our study is the lack of molecular data from the brain lesions for most patients. Yet this study has the strength of bringing real-world data from patients who are being followed at a referral center and community hospitals. Furthermore, it gives important insight into the impact of novel therapies, including modern surgical techniques, SRS and TKIs.

5. Conclusion

The prevalence of brain metastases of DTC in MedStar Health institutions was 0.3% over 15 years. This diagnosis is associated with high mortality, but advances in surgical techniques and radiation therapy may change this scenario. In our selected population, the use of TKIs was the only therapy that improved the survival rates. Further studies in this area are warranted.

Acknowledgments

References and Notes

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