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Gamma Knife Radiosurgery for Brain Metastasis from Primary Thyroid Cancer

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ABSTRACT

AIM: To analyze the efficacy and safety of Gamma Knife radiosurgery (GKRS) in the management of thyroid cancer brain metastases (TCBM).

MATERIAL and METHODS: This retrospective study analyzed patients who underwent GKRS for TCBM at two centers between September 2005 and February 2025. Patients' clinical and radiological outcomes, including local tumor control and overall follow-up, were investigated.

RESULTS: Among the 3,834 patients who underwent GKRS for brain metastases at two centers, only 0.26% had primary thyroid cancer. A total of 10 patients with 40 TCBM were treated by GKRS, with a median of two metastases per patient. The most common metastasis site was the frontal lobe (47.5%), and 60% of patients had multiple metastases. Papillary carcinoma was the most frequent histological subtype (57.1%). The median latency from thyroid cancer diagnosis to the development of brain metastases was 22 months. The median GKRS dose was 23 Gy, and local failure occurred in 5% of treated metastases. Radiation-induced necrosis was observed in one case and resolved without clinical impact. Intracranial distant metastases developed in two patients. The median follow-up was 8 months, and 80% of patients died during follow-up, with one death attributed to brain metastasis.

CONCLUSION: The limited number of patients and the short follow-up period, partly reflecting the aggressive nature of TCBM, may have influenced the study results. Nevertheless, despite the short follow-up, GKRS provided favorable local control without significant adverse effects, suggesting that it may be an effective treatment option for TCBM.

KEYWORDS: Thyroid neoplasms, Brain neoplasms, Radiosurgery, Treatment outcome

ABBREVIATIONS: GKRS: Gamma knife radiosurgery, **TCBM:** Thyroid cancer brain metastasis, **SRS:** Stereotactic radiosurgery, **WBRT:** Whole brain radiotherapy, **RT:** Radiotherapy

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INTRODUCTION

The presence of brain metastases represents a significant neurological challenge for patients with cancer. While lung cancer accounts for the majority of brain metastases (≥50%), the incidence of thyroid cancer is relatively rare, with a reported incidence ranging from 0.15% to 1.3% (2,11). Although brain metastases are uncommon in thyroid cancer, their presence is associated with a poor prognosis and reflects a more aggressive disease course (8,18).

Since TCBM is a rare condition, there is still no consensus on the optimal treatment approach. Several treatment approaches, including surgical resection, external beam radiotherapy, radioiodine therapy, stereotactic radiosurgery (SRS), tyrosine kinase inhibitors, and whole brain radiotherapy (WBRT), are available. Resection of one or more foci of brain metastases has been reported to significantly improve survival (9). The disease-specific median survival following the diagnosis of brain metastases is significantly longer in patients who undergo local resection of one or more metastatic lesions (16.7 months) than in those who do not receive surgical intervention (3.4 months) (7). In patients with brain metastases from thyroid cancer who are not candidates for surgical resection, or as a first-line treatment, SRS offers a safe and effective therapeutic option (5,21).

SRS delivers focused high-dose radiation to intracranial tumors in single or multiple sessions, offering a precise and minimally invasive therapeutic option. In most cases, it has become a standard treatment modality for brain metastases originating from various primary cancers, used either as a first-line therapy or as an adjunct to other treatments, such as surgical resection and/or WBRT (1,14,20,24). Notably, SRS has been shown to provide superior preservation of cognitive function compared with WBRT (4,6). Despite these treatment approaches, the management of TCBM remains challenging because of the limited clinical experience with this rare condition. In this study, we aimed to evaluate the efficacy of GKRS on brain metastases in the management of TCBM.

MATERIAL and METHODS

Eligibility and Demographic Data

The data of patients who underwent GKRS treatment for TCBM at two centers between September 2005 and February 2025 were analyzed.

The study inclusion criteria were as follows: (a) age ≥18 years, (b) histologically verified thyroid malignancy, (c) radiologically confirmed brain metastases, and (d) patients who received GKRS for brain metastases. Patients with inadequate follow-up information (< 2 months) were excluded. All data were retrieved from the patient charts and neuroimaging databases. Available histological findings and targeted systemic therapies were collected for each patient.

Radiosurgical Technique

Gamma Knife radiosurgery was performed using the Leksell Gamma Knife® Model 4C, Perfexion, and Icon (Elekta Instrument AB, Stockholm, Sweden). Target delineation was based on T1-contrast weighted MRI, and the gross tumor volume was considered equivalent to the clinical and planning target volumes. Shots with 4, 8, and 16 mm collimators were placed within the target and adjusted to simultaneously achieve high target coverage, high selectivity, gradient index < 3, and reasonable treatment times using the best-fit isodose method until a clinically acceptable plan was formulated by a team of neurosurgeons, medical physicists, and radiation oncologists. The organs at risk were contoured, and the treatment planning objective was to minimize radiation exposure to the normal brain as much as possible.

Follow-up and Outcome Parameters

After GKRS, patients underwent routine clinical neurological assessment and brain diagnostic imaging every 2–4 months, depending on imaging results and clinical features. All pretreatment and posttreatment radiological examinations were evaluated by a team comprising a radiation oncologist, neurosurgeon, and neuroradiologist. Radiological response was evaluated according to the Response Assessment in Neuro-Oncology Brain Metastases criteria (13). Partial response was defined as ≥30% reduction in the longest diameter of target lesions, and complete response as the disappearance of all target lesions. Both partial and complete responses were considered local controls. Progression was defined as a ≥20% increase in the smallest recorded target lesion diameters on the study, with an absolute increase of ≥ 5 mm. Local failure was defined as progression within the previously treated lesion, whereas distant failure referred to new or progressive lesions outside the treated field. In equivocal cases, advanced imaging (e.g., perfusion MRI, MRS) or histopathology was used for clarification. LC was assessed throughout the study until local failure or death. All patients were classified using the recursive partitioning analysis and graded prognostic assessment classification systems of the Radiation Therapy Oncology Group (RTOG) (10,25).

Statistical Analysis

All analyses were conducted using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize patient and tumor characteristics. Continuous variables were presented as median [minimum–maximum], whereas categorical variables were expressed as frequencies and percentages. The median was selected as the measure of central tendency because of the positively skewed distribution of the data. Local control and clinical outcomes were assessed on both a per patient and per-tumor basis. Radiological and clinical follow-up data were analyzed using descriptive methods.

RESULTS

Ten patients received GKRS treatment for a total of 40 metastases. Of these, six patients were male (60%), and the median age at the diagnosis of brain metastases was 67 years [range, 23–84]. Each patient had a median of 2 [range, 1–18] brain metastases, and 60% of patients had > 1 metastatic brain tumor. The most common location of metastases was the frontal lobe (47.5%). Histological data were unavailable for three patients. Among those with known thyroid cancer histol-

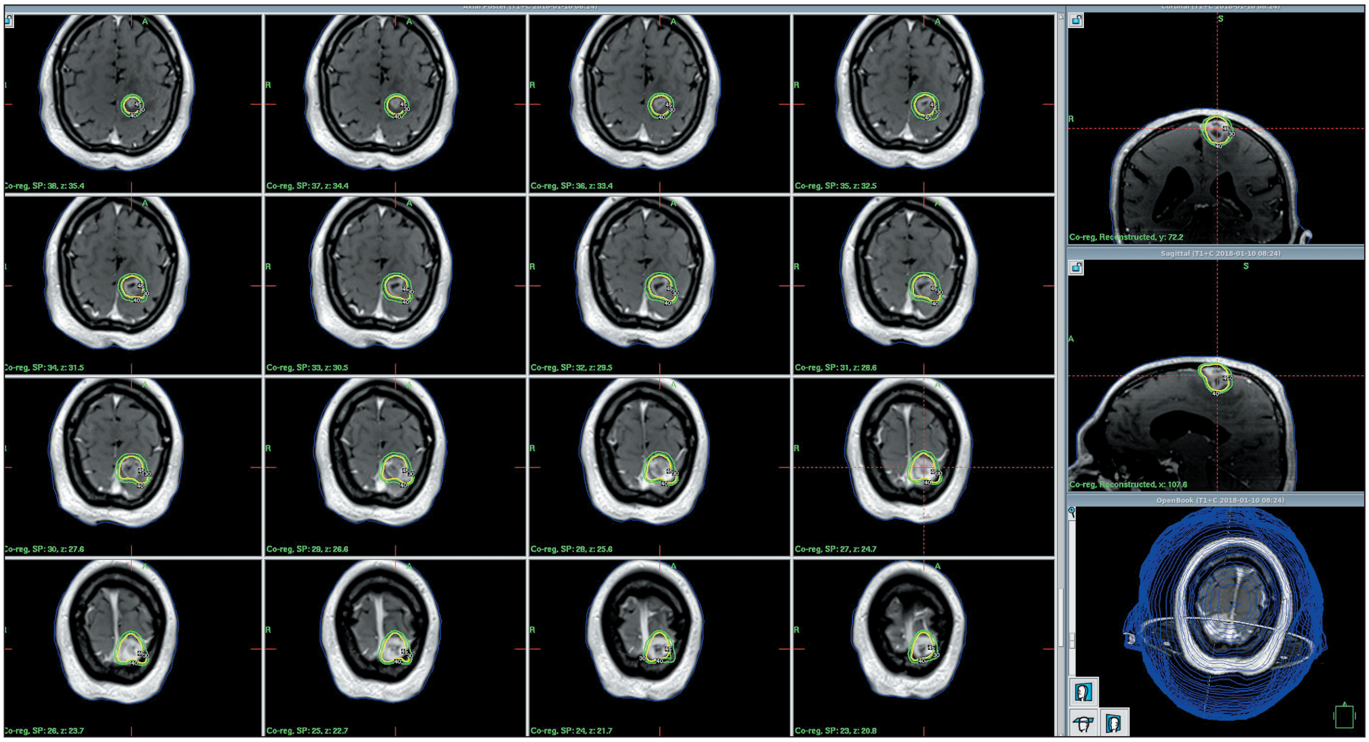

Figure 1: Gamma Knife treatment plan for a brain metastasis from thyroid carcinoma. Axial, coronal, and sagittal post-contrast T1-weighted MRIs show a single parenchymal brain metastasis originating from thyroid carcinoma. The lesion is delineated by the yellow contour line, representing the gross tumor volume. The green isodose lines indicate the radiosurgical dose distribution, which conforms tightly to the tumor borders. High conformality and a steep dose fall-off are achieved to minimize radiation exposure to the surrounding normal brain tissue.

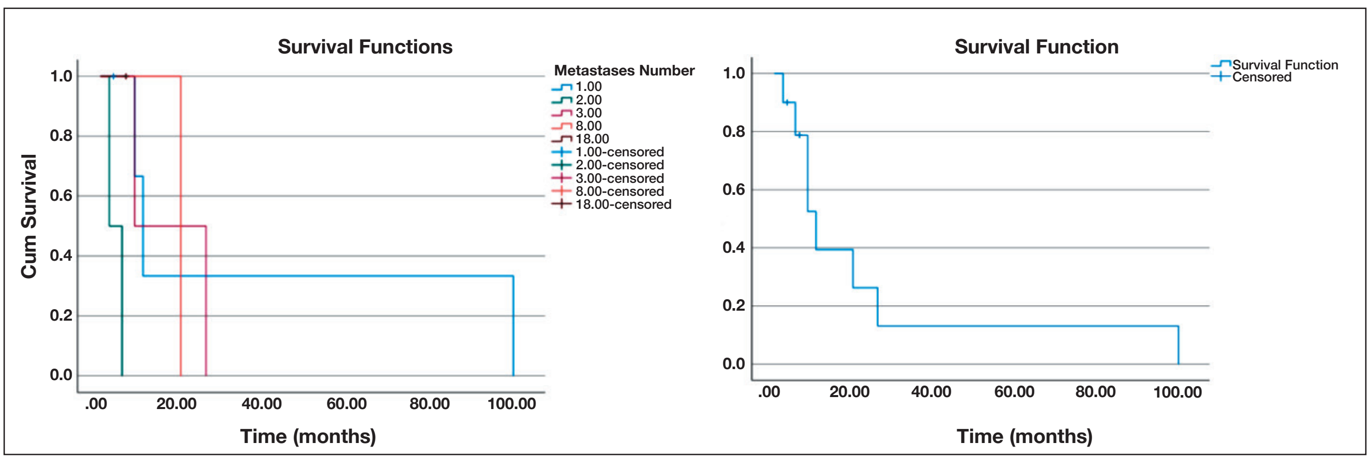

Figure 2: Kaplan–Meier survival curves showing (left) overall survival according to the number of brain metastases and (right) overall survival following Gamma Knife radiosurgery.

ogy, the most common type was papillary carcinoma (57.1%), followed by follicular carcinoma (28.5%) and anaplastic carcinoma (14.2%). 50% of patients had distant metastases (lung, bone, spine, and adrenal gland). One patient presented with brain metastasis at diagnosis; all other patients had undergone prior thyroidectomy (90%). Most patients had favorable clinical status at the time of GKRS, with a median KPS score of 90 [range 70–90]. Detailed patient characteristics are presented in Table I.

Histopathological examination of the previous thyroidectomy specimen showed a BRAF V600E mutation in one patient, a TERT mutation in one patient, and both mutations in one patient. Nuclear atypia was detected in 30% of patients, and all patients had multiple (≥2) brain metastases.

Before GKRS treatment, 40% of patients had undergone prior surgery for TCBM. The median duration from thyroid cancer diagnosis to the detection of brain metastasis was 22 months

Table I: Patient Characteristics

Patient No.	Age at diagnosis of BM / Gender	Pathology	Mutation-Atypia	KPS before GKRS	RPA / GPA	Distant organ metastasis	Metastasis Number / Location	Symptom	Interval from thyroid cancer to BM diagnosis / BM to GKRS (months)	Follow-up (months) / Status / Cause of death	Additional treatments
1	45 / Male	Anaplastic	TERT, Nuclear atypia	90	I / 4	-	3 / Frontal, temporal, cerebellum	Headache	5 / 0	8 / Dead / Progression of brain metastases	Pre-GKRS: thyroidectomy
2	72 / Male	Papillary	BRAF V600E, TERT, Nuclear atypia	90	II / 3	-	2 / Cerebellum, parietal	Headache	37 / 2	5 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, RAI
3	74 / Female	Papillary	-	90	II / 3	-	1 / Frontal	Dysphasia	0 / 0	10 / Dead / Sepsis	-
4	67 / Female	Follicular	Nuclear atypia	70	II / 1	Lung, bone	2 / Cerebellum, frontal	Headache	47 / 3	2 / Dead / Pneumonia	Pre-GKRS: thyroidectomy, craniotomy, WBRT, RAI
5	67 / Male	Papillary	-	90	II / 3	-	1 / Frontal	Amnesia	0 / 24	98 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, craniotomy, RAI
6	60 / Male	Papillary	BRAF V600E	70	II / 1	Lung	1 / Frontal	Hemiparesis	168 / 1	8 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, WBRT, RAI
7	84 / Male	Follicular	-	90	II / 1	Lung, bone, spine, adrenal gland	8 / Frontal (2), parietal (1), occipital (2), cerebellum (2), temporal (1)	Amnesia	53 / 0	19 / Dead / Multisystem failure	Pre-GKRS: thyroidectomy, craniotomy, RAI. After-GKRS: LINAC and CyberKnife treatment for distant metastases
8	69 / Female	N/A	Data not available	90	II / 2	Lung, bone, spine	1 / Temporal	Headache	7 / 0	2 / Unknown	Pre-GKRS: thyroidectomy, RAI, RT for spine metastasis
9	23 / Female	N/A	Data not available	80	II / 1	Lung, bone	18 / Frontal (10), parietal (4), occipital (3), cerebellum (1)	(Incidental)	2 / 0	6 / Unknown	Pre-GKRS: thyroidectomy, RAI, RT for lung metastasis
10	50 / Male	N/A	Data not available	90	I / 4	-	3 / Frontal (2), temporal (1)	Headache	48 / 3	25 / Dead / Progression of extracranial metastases	Pre-GKRS: thyroidectomy, RAI

BM: *Brain metastasis,* ***GPA:*** *Graded prognostic assessment,* ***RPA:*** *Recursive partitioning analysis,* ***GKRS:*** *Gamma Knife radiosurgery,* ***RAI:*** *Radioactive iodine,* ***RT:*** *Radiotherapy*

Table II: Gamma Knife radiosurgery treatment characteristics

	Median [range]	Mean – std. deviation
Treatment volume (cm^3)	0.108 [0.01-17.4]	1.476±1.57
Margin dose (Gy)	23 [15-24]	21.7±1.77
Maximal dose (Gy)	44 [20-50]	42.48±6.02

[range, 0–168 months]. The median latency period between the diagnosis of brain metastasis and SRS was 0.5 months [range, 0–27]. At the time of diagnosis, the most common symptom was headache (50%). Two patients had amnesia, one had dysphasia, one had hemiparesis, and one was diagnosed incidentally.

The median treatment volume was 0.108 cm^3 [range, 0.01–17.4]. The median marginal dose was 23 Gy [range, 15–24 Gy] (Table II). Local failure was detected in 2 (5%) metastases treated with GKRS. One case of radiation-induced necrosis was identified on radiological follow-up; however, this radiological finding regressed on subsequent imaging and did not result in additional clinical symptoms. This patient had eight metastases, six of which developed radiation-induced necrosis after GKRS treatment. These six lesions received a dose of 24 Gy at a median isodose line of 67.5% [range: 50–85%], with a median lesion volume of 0.122 cm^3 [range: 0.014–0.372 cm^3]. Intracranial distant metastases were detected in two patients during radiological follow-up. One patient received additional radiological treatment for intracranial distant metastases. Before GKRS, two patients had received WBRT, and eight patients (80%) had received radioactive iodine treatment.

The median follow-up period was 8 months [range 2–98 months]. Long-term follow-up data were unavailable for two patients (3 and 6 months). Eighty percent of patients died during follow-up; one death was due to brain metastasis, whereas the others were attributed to oncological comorbidities.

DISCUSSION

Morbidity and mortality in patients with primary thyroid cancer are higher among those with distant metastases. Individual prognosis depends on factors, such as the histology of the primary tumor, its distribution, and the number of metastatic sites (19). According to the literature, the most common site of distant metastasis in thyroid cancer is the lungs, followed by the brain (12,27). Although numerous studies have evaluated treatment outcomes for brain metastases from lung or breast cancer, there is a dearth of research on treatment outcomes for TCBM because of its rarity; the incidence of brain metastasis from thyroid cancer is less than 1% (11). Although patients with primary thyroid cancer generally have better survival outcomes than those with other cancers, such as lung or gastrointestinal cancers, the prognosis for patients with TCBM is significantly poorer (16,29). In our study, long-term follow-up data were unavailable for two patients. Eight patients died during the follow-up period: one due to the progression of brain metastases, one due to the progression of extracranial metastases, and six due to systemic complications, such as sepsis, pneumonia, and multisystem failure.

TCBMs are predominantly located in the supratentorial region (9). These metastases are often asymptomatic; however, a subset of patients may present with clinical symptoms, most commonly with headache and visual disturbances (28). In our series, the most frequent metastasis location was the frontal lobe (47.5%), and the most common presenting complaint was headache.

The BRAF V600E and TERT promoter mutations are frequently associated with thyroid carcinomas characterized by a more aggressive prognosis (22,28). Osborne et al. reported that these mutations can occur simultaneously, and their synergistic effect significantly reduces overall survival rates (19). In our series, although the mean survival time after GKRS was 21.87 months, one patient had BRAFV600E/TERT mutations and survived for only 5 months after GKRS.

Current guidelines recommend complete surgical resection of TCBM as the first-line treatment for patients whose performance status permits craniotomy (12). Several studies have demonstrated that total surgical resection is associated with improved survival outcomes, particularly in cases of single brain metastasis (7,15). According to the American Thyroid Association guidelines, stereotactic radiotherapy is considered equally effective as surgical intervention for patients with a limited number of brain metastases (<3) and can be re-administered if new intracranial lesions develop (12). WBRT or SRS is recommended as the primary treatment for patients with multiple (>3) metastatic lesions (9). The CNS guideline for metastatic brain tumors states that SRS alone can be considered equivalent to surgery plus WBRT based on level III evidence (17). Vlachos et al. conducted a meta-analysis comparing postoperative SRS with WBRT in 248 patients (128 WBRT, 120 SRS) who underwent resection of solitary brain metastases. Their findings demonstrated no statistically significant difference in local recurrence rates between the two treatment modalities (RR = 0.92, 95% CI 0.51–1.66, p = 0.78). Importantly, the study demonstrated that SRS was associated with equivalent or superior neurocognitive outcomes and quality of life measures compared to WBRT, while maintaining comparable efficacy in local tumor control (26).

Although WBRT provides effective control of both local and distant diseases, it does not improve overall survival. Moreover, it has significant negative impacts on patients' quality of life, causing symptoms, such as fatigue, headaches, cognitive decline, and behavioral changes (3). These adverse effects can significantly impair patients' daily functioning and overall well-being. RAI therapy is not commonly used for treating brain metastases, as limited data support its effectiveness (27).

SRS offers a more favorable toxicity profile compared to WBRT, with significantly reduced short- and long-term adverse effects, including fatigue, headaches, cognitive impairment, and behavioral changes. Notably, SRS has demonstrated effectiveness in patients with multiple brain metastases (30). SRS, alone or in combination with WBRT, has demonstrated impressive local control rates for brain metastases (7). Furthermore, studies have shown that SRS provides outcomes comparable to surgical resection in terms of both local and distant control (23). In a series of 42 patients, Bunevicius et al. reported that during a mean imaging follow-up period of 25.2 months after SRS, local failure—defined as tumor progression and/or radiation necrosis—occurred in only 4% of the treated brain metastases. These failures were observed at a mean of 7.2 months following SRS (5). In this study, we observed a similarly favorable local control rate of 95% with no significant treatment-related complications.

The scarcity of robust clinical data necessitates a highly individualized treatment approach, taking into consideration factors, such as the number, size, and location of metastatic lesions, as well as the patient's overall clinical status and prognosis.

CONCLUSION

The small number of patients and the short follow-up period due to the aggressive course of TCBM limit the study's findings. Nevertheless, during this follow-up period, GKRS achieved favorable local control without any significant adverse effects.

Declarations

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Availability of data and materials: The datasets are available from the corresponding author upon reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

Ethics approval and consent to participate: This retrospective study, based on prospectively managed data, was approved by the Institutional Review Board of Koç University (2022.022.IRB1.017, date: 19.12.2025) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

AUTHORSHIP CONTRIBUTION

Study conception and design: SP, AG
Data collection: MAT, EV, VK, MOA
Analysis and interpretation of results: MAT, SP, AG
Draft manuscript preparation: MAT, DCY,
Critical revision of the article: SP, AG
Other (study supervision, fundings, materials, etc...): SP, AG
All authors (MAT, DCY, AHD, MOA, EV, VK, AG, SP) reviewed the results and approved the final version of the manuscript.

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