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Associated factors of brain metastases and diagnostic yield of staging brain magnetic resonance imaging in anaplastic thyroid cancer

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Background: This study aimed to identify the associated factors for brain metastasis (BM) in patients with anaplastic thyroid cancer (ATC) and estimate the diagnostic yield of staging brain magnetic resonance imaging (MRI) during the initial evaluation of ATC.

Methods: This retrospective, single-center study included patients newly diagnosed with ATC who underwent brain MRI, from May 2008 to July 2024. The patients were stratified into two groups (BM vs. non-BM). The clinical characteristics of ATC were compared between the two groups using the chi-squared test and multivariable logistic regression analysis. The diagnostic yield of initial staging brain MRI from 2010 to 2024 was calculated.

Results: A total of 77 patients (61.52±13.19 years old, 37 men) were included. BM was observed in 19 patients (24.7%). The occurrence of BM was significantly associated with extracranial metastasis (p=0.004), especially lung metastasis (p=0.017), and neurologic symptoms (p=0.001). On multivariable logistic regression analysis, after adjusting for age, sex, and primary thyroid tumor size, the presence of extracranial metastases (odds ratio [OR]: 16.09 [2.39–360.70], p=0.019) and neurologic symptoms (OR: 5.95 [1.73–24.08], p=0.007) were independently associated with BM. The diagnostic yield of staging brain MRI during the initial evaluation of ATC was 6.1% (3/49). The diagnostic rate of BM was 26.5% (18/68) in patients with extracranial metastases and 38.9% (14/36) in those with neurological symptoms.

Conclusion: Routine staging or surveillance brain MRI in patients with extracranial metastasis is likely to offer significant benefits.

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Key Words: brain metastases; anaplastic thyroid cancer; magnetic resonance imaging; neoplasm metastasis

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INTRODUCTION

Although anaplastic thyroid cancer (ATC) is a rare malignancy, representing only 2% of thyroid cancers, it is notorious for its aggressive behavior and dismal prognosis, with a median overall survival time of 3–5 months.[1,2] ATC often manifests suddenly and progresses rapidly; approximately 50% of patients present with distant metastasis at diagnosis,[2] highlighting the critical need for timely diagnosis and immediate treatment initiation. Moreover, ATC frequently metastasizes to the brain, with reported incidence rates ranging from 3% to 11%.[2,3] Brain metastasis (BM) often leads to neurological deficits, significantly diminishing the quality of life. In addition, thyroid cancer BMs exhibit a bleeding tendency, leading to serious neurologic deterioration.[4] Therefore, identifying associated factors for BM in patients with ATC is essential for early detection, which could substantially improve both the quality of life and overall prognosis.

The 2021 American Thyroid Association guidelines

recommend brain magnetic resonance imaging (MRI) at the time of initial staging in patients being considered for therapy.[5] Although this recommendation is classified as strong, the guideline rates the quality of supporting evidence as low.[5] Brain MRI is also advised when clinically indicated, typically in the presence of symptoms suggestive of brain metastases, such as neurologic deficits or headache.[5] However, guidance remains limited regarding the use of brain MRI in clinical scenarios beyond initial staging and the presence of neurological symptoms.

The associated factors for BM in patients with ATC remain undetermined due to the rarity of this disease. Therefore, the purpose of our study was twofold: first, to identify the factors associated with the occurrence of BM, and second, to assess the diagnostic yield of brain MRI conducted either during the initial evaluation of ATC or in patients with associated factors, as identified in our study.

SUBJECTS AND METHODS

1. Participants

This retrospective, observational, single-institution study was approved by the Institutional Review Board of our institution, which waived the requirement for informed consent. We conducted a retrospective search of electronic medical records from May 2008 to July 2024 and identified 187 patients with pathologically confirmed ATC via surgical resection or biopsy. Of these, 101 patients were excluded because they had not undergone brain MRI for the evaluation of BM, and an additional nine were excluded because of concurrent primary malignancies other than thyroid cancer. Finally, 77 patients were included in this study (Fig. 1). A total of 152 BMs were observed in 77 patients. A total of 104 brain MRI scans were obtained for the following reasons: initial staging, apparent neurological symptoms, and progression of distant metastasis.

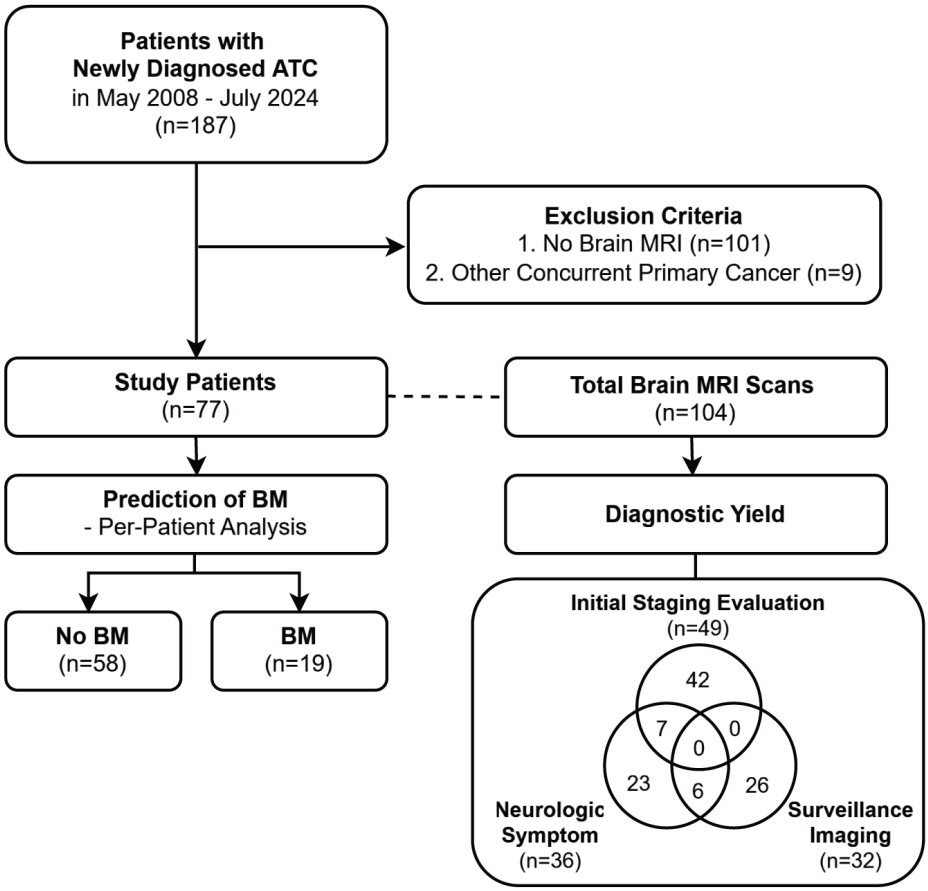

Fig. 1. Flow chart of the patient enrollment process. ATC, anaplastic thyroid cancer; BM, brain metastasis; MRI, magnetic resonance imaging.

2. Baseline characteristics

Initial stages were determined according to the Eighth Edition of the American Joint Committee on Cancer guidelines. The presence or absence of extracranial metastases and neurological symptoms, including headache, dizziness, nausea, focal neurological deficits, seizures, cognitive impairment, syncope, and altered mental status, was evaluated at the time of brain MRI surveillance. Data on sex and age were retrieved from electronic medical records. Primary tumor size was measured based on the largest diameter observed on neck computed tomography or ultrasound scans. In addition, *BRAF*, *TERT* promoter, *RAS,* and *PIK3CA* mutations, as well as the Ki-67 labeling index, were assessed whenever feasible. Peptide nucleic acid-mediated clamping polymerase chain reaction was utilized to detect *BRAF* mutations.[6] *TERT* promoter mutations were identified through pyrosequencing,[7] and *RAS* and *PIK3CA* mutations were investigated using next-generation sequencing.[8]

3. Diagnostic yield of brain MRI with different BM associated factors

The diagnostic yield of brain MRI, defined as the proportion of patients with true-positive BMs among those with certain BM-associated factors, served as the secondary outcome of this study. Specifically, the yield was calculated by dividing the number of true-positive results by the total number of patients presenting with each BM-associated factor. We calculated the diagnostic yield of brain MRI performed during initial staging and assessed the yield of brain MRI specifically in patients with extracranial metastasis, neurological symptoms, or extracranial progression. Extracranial progression was defined as tumor progression outside the brain based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria (i.e., progressive disease), which led to a change in the treatment regimen.

4. MRI acquisition

Routine MRIs to evaluate BMs were performed using a Siemens 3T Vida scanner (Siemens Healthineers; Erlangen, Germany) or a GE 3T Discovery MR750 scanner (GE Healthcare; Milwaukee, WI, USA). The BM MRI protocol included T1-weighted imaging (T1WI), T2-weighted imaging, fluid-attenuated inversion recovery, SWI, and contrast-enhanced T1WI. Contrast-enhanced images were acquired after administration of gadobutrol (0.2 mmol/kg, Gadovist; Bayer Schering Pharma, Berlin, Germany). The detailed parameters are provided in Supplementary Table 1.

5. Statistical analysis

The baseline characteristics were compared between patients with and without BM. Continuous variables were compared using Student's *t*-test, whereas categorical variables were compared using the χ^2 or Fisher's exact test. To identify the associated factors for the occurrence of BM in ATC, multivariable logistic regression analysis was performed using independent factors, including age at initial cancer diagnosis, sex, primary tumor size, presence or absence of extracranial metastasis, and neurological symptoms. Statistical analyses were performed using R software (version 4.3.2). Statistical significance was set at $p<0.05$.

6. Ethics statement

This retrospective, observational, single-institution study was approved by Gangnam Severance hospital Institutional Review Board (3-2024-0206), which waived the requirement for informed consent.

RESULTS

1. Patient characteristics

The study included 77 patients, with a nearly equal distribution of males (37, 48.05%) and females (40, 51.95%), and a mean age of 61.52±13.19 years. Among the patients, 19 exhibited BMs, whereas 58 did not. A comparison of the initial tumor stages between the two groups revealed a significant difference ($p=0.006$). In addition, extracranial metastases at the time of brain MRI surveillance were more frequently observed in patients with BMs than in those without BMs (94.74% vs. 58.62%, $p=0.004$). Specifically, lung metastasis was more common in patients with BMs (84.21% vs. 53.45%, $p=0.017$). In addition, neurological symptoms were more prevalent in

patients with BMs than in those without BMs (73.68% vs. 31.03%, p=0.001). No significant differences were noted in sex, age at ATC diagnosis, thyroid tumor size, or *BRAF/TERT* promoter/*RAS/PIK3CA* gene mutations between the two groups (Table 1).

2. Associated factors for BM occurrence

The multivariable logistic regression analysis revealed that the occurrence of BM was independently associated with the presence of extracranial metastasis (odds ratio [OR]=16.09, 95% confidence interval [CI]: 2.39–360.7, p=0.019) and neurologic symptoms (OR=5.95, 95% CI: 1.73–24.08, p=0.007) at the time of surveillance brain MRI. The other analyzed factors were not statistically significant (Table 2).

3. Diagnostic yield of brain MRI with different BM associated factors

The diagnostic yields of brain MRI for different BM associated factors are summarized in Table 3. Of the 49 brain MRI scans conducted for initial staging, three revealed BMs, resulting in a diagnostic yield of 6.12% (3/49). Among the 68 brain MRI scans of patients with extracranial metastases, 18 were reported to show BMs, yielding a diagnostic rate of 26.47% (18/68). Of the 36 brain MRI scans from patients presenting with neurological symptoms, 14 confirmed the presence of BM, with a diagnostic yield of 38.89% (14/36). We evaluated the diagnostic yield of BM in patients who underwent brain MRI due to extracranial progression. Of the 29 brain MRI scans, 13 revealed BMs, with a diagnostic rate of 44.83% (13/29).

DISCUSSION

This retrospective study aimed to identify the associated factors for the occurrence of BMs in patients with ATC. Our findings indicate that BM occurrence is significantly associated with the presence of extracranial metastasis at the time of brain surveillance, and the presence of neurological symptoms. Multiple logistic regression analysis confirmed that extracranial metastasis and neurological symptoms were independent predictors of BMs in patients with ATC. Furthermore, the diagnostic yield of surveillance brain MRI was 26.47% in patients with extracranial metastasis and 38.89% in those with neurological symptoms. These findings suggest that brain MRI may be clinically useful in ATC patients with extracranial metastasis or neurological symptoms.

In the present study, extracranial metastasis was a significant predictor of BM in patients with ATC. This finding aligns with the well-established notion that BMs frequently arise in settings of extensive metastasis.[9,10] Previous research has demonstrated that 58.8% of patients with BMs also concurrently presented with extracranial metastases.[9] In addition, several studies utilizing genome-wide molecular techniques have proposed two modes of disease progression: one suggests a monoclonal origin, where metastases descend from a common “metastatic precursor”; and the other posits that multiple metastatic lesions are seeded by different clones present within the primary tumor.[11] Furthermore, evidence indicates that metastasis-to-metastasis seeding occurs more frequently than metastases originating directly from the primary tumor.[12-14] Another noteworthy finding from our study is that patients with lung metastases were more likely to develop BMs compared with those without lung metastases (Fig. 2). Previous studies also reported the co-existence of other organ metastases and BMs in patients with thyroid cancer.[3,15] The most frequent coexisting metastatic sites were the lungs (85%).[15] Although the specific mechanisms underlying this phenomenon are unknown, one plausible explanation involves the route of metastasis. As the central nervous system lacks a lymphatic system, cancer cells can only reach the brain through the bloodstream. Lung cancer frequently metastasizes to the brain via this pathway.[16] Similarly, lung metastases may have a predisposition to spread to the brain. Nonetheless, further research is required to draw definitive conclusions.

Current guidelines recommend brain MRI at the time of initial staging in ATC patients being considered for therapy, although the quality of evidence supporting this recommendation is rated as low.[5] Notably, the diagnostic yield of brain MRI in patients with stage II non-small cell lung cancer (NSCLC)—for whom routine screening is recommended by National Comprehensive Cancer Network (NCCN) guidelines—has been reported as 4.68%.[17,18] In our study, the yield during the initial staging was 6.12%, indicating a potentially higher prevalence of brain metas-

Table 1. Clinical characteristics of patients with or without brain metastasis

Characteristic	Non-BM (n=58)	BM (n=19)	Total (n=77)	*p*-value
Sex				0.945
Female	30 (51.72)	10 (52.63)	40 (51.95)	
Male	28 (48.28)	9 (47.37)	37 (48.05)	
Age	61.74±14.54	60.84±8.02	61.52±13.19	0.798
Primary tumor size (cm)	4.84±2.34	4.58±1.91	4.78±2.23	0.661
T stage				0.441
T1	2 (3.45)	1 (5.26)	3 (3.90)	
T2	6 (10.34)	2 (10.53)	8 (10.39)	
T3a	4 (6.90)	2 (10.53)	6 (7.79)	
T3b	5 (8.62)	4 (21.05)	9 (11.69)	
T4	41 (70.69)	10 (52.63)	51 (66.23)	
N stage				1
N0	11 (18.97)	3 (15.79)	14 (18.18)	
N1	47 (81.03)	16 (84.21)	63 (81.82)	
M stage				0.003*
M0	32 (55.17)	3 (15.79)	35 (45.45)	
M1	26 (44.83)	16 (84.21)	42 (54.55)	
Stage group				0.006*
IVA	1 (1.72)	0 (0.0)	1 (1.30)	
IVB	31 (53.45)	3 (15.79)	34 (44.16)	
IVC	26 (44.83)	16 (84.21)	42 (54.55)	
Extracranial metastasis at surveillance brain MRI				0.004*
Absent	24 (41.38)	1 (5.26)	25 (32.47)	
Present	34 (58.62)	18 (94.74)	52 (67.53)	
Lung metastasis				0.017*
Absent	27 (46.55)	3 (15.79)	30 (38.96)	
Present	31 (53.45)	16 (84.21)	47 (61.04)	
Bone metastasis				0.064
Absent	47 (81.03)	11 (57.89)	58 (75.32)	
Present	11 (18.97)	8 (42.11)	19 (24.68)	
Neurologic symptoms				0.001*
Asymptomatic	40 (68.97)	5 (26.32)	45 (58.44)	
Symptomatic	18 (31.03)	14 (73.68)	32 (41.56)	
BRAF				1
Wild	28 (62.22)	6 (66.67)	34 (62.96)	
Mutated	17 (37.78)	3 (33.33)	20 (37.04)	
TERT promoter				0.066
Wild	17 (47.22)	0 (0.0)	17 (40.48)	
Mutated	19 (52.78)	6 (100.00)	25 (59.52)	

Table 1. Continued

Characteristic	Non-BM (n=58)	BM (n=19)	Total (n=77)	*p*-value
RAS				0.381
Wild	20 (58.82)	2 (33.33)	22 (55.00)	
Mutated	14 (41.18)	4 (66.67)	18 (45.00)	
BRAF and *TERT* promoters				1
Not both mutated	30 (83.33)	5 (83.33)	35 (83.33)	
Both mutated	6 (16.67)	1 (16.67)	7 (16.67)	
PIK3CA and *TERT* promoters				1
Wild	31 (91.18)	6 (100.00)	37 (92.50)	
Mutated	3 (8.82)	0 (0.0)	3 (7.50)	
Ki67 labeling index (%)	45.52±24.70	53.00±23.35	46.43±24.38	0.527
Ki67 labeling index (%)				0.567
<20	7 (19.44)	0 (0.0)	7 (17.07)	
≥20	29 (80.56)	5 (100.00)	34 (82.93)	

Values are presented as number (%) or mean±standard deviation.
BM, brain metastasis; MRI, magnetic resonance imaging.
Asterisk (*) indicates a *p*-value<0.05.

Table 2. Multiple logistic regression analysis of brain metastasis occurrence in patients with anaplastic thyroid cancer

Variable	OR (95% CI)	*p*-value
Age	0.97 (0.91–1.03)	0.327
Sex	0.59 (0.16–2.05)	0.407
Primary tumor size	1 (0.71–1.39)	0.988
Extracranial metastasis (Presence vs. absence)	16.09 (2.39–360.7)	0.019*
Neurologic symptoms (Presence vs. absence)	5.95 (1.73–24.08)	0.007*

OR, odds ratio; CI, confidence interval.
Asterisk (*) indicates a *p*-value<0.05.

tases in ATC compared to stage II NSCLC. These findings provide further support for routine screening brain MRI in ATC patients, consistent with current recommendations.

Recent studies have explored the ATC mutational landscape and enhanced our understanding of the molecular pathogenesis of thyroid cancer. The *BRAF-V600E* mutation, occurring in 10-50% of ATCs, activates the mitogen-activated protein kinase pathway leading to uncontrolled cell proliferation, is correlated with poor prognosis in ATC patients and is strongly related to extra-thyroidal invasion and cervical lymph node metastasis in papillary thyroid cancer.[19,20] A study on a mouse model revealed that *BRAF-V600E* mutation coexisting with a mutation of *PIK3CA,* which is one of the catalytic subunits of the phosphatidylinositol-3 kinase enzyme complex, can lead to the development of ATC.[21] Telomerase reverse transcriptase (*TERT*) promoter mutation, which is associated with cellular immortality and tumorigenesis by maintaining telomere length at the ends of chromosomes, is linked to aggressive, metastatic, and thyroid stem cell phenotypes.[22] Furthermore, concomitant *BRAF/PIK3CA* and *TERT* promoter mutations are linked to poor prognosis in patients with ATC.[23,24] In our study, neither *BRAF-V600E* mutation nor concomitant *BRAF/PIK3CA* and *TERT* promoter mutation were associated with the development of BM. These findings suggest that the process of BM is influenced by a complex interplay of different biological factors beyond the inherent aggressiveness of the primary tumor.

This study has certain limitations. First, as this was a single-institution retrospective analysis, our findings may not be generalizable. For example, not all patients with extracranial progression underwent brain MRI, our calculated diagnostic yield in this population may differ from that of real-world data. Second, ATC is very rare; although

Table 3. Diagnostic yield of brain magnetic resonance imaging with different brain metastasis associated factors

Clinical condition	Number of total brain MRI	Number of brain MRI with BM	Diagnostic yield
Initial staging brain MRI	49	3	6.12%
Presence of extracranial metastasis at brain surveillance	68	18	26.47%
Presence of neurological symptoms	36	14	38.89%
Presence of extracranial progression	29	13	44.83%

BM, brain metastasis; MRI, magnetic resonance imaging.

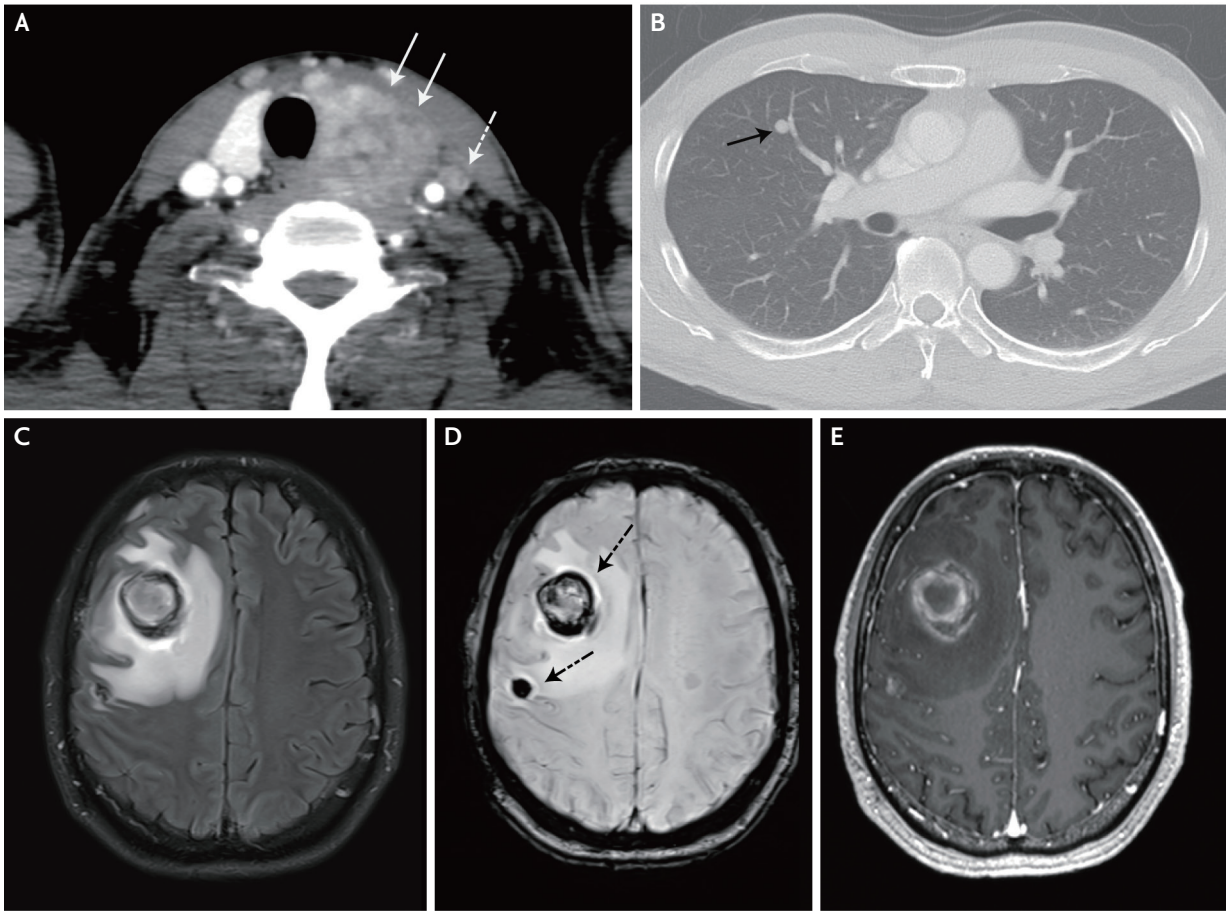

Fig. 2. Representative case of a 54-year-old male patient with anaplastic thyroid cancer and brain metastasis. (A) Neck computed tomography (CT) demonstrates a large mass replacing the left thyroid gland with extrathyroidal extension (white arrow) and a nodal metastasis (white dotted arrow) in the left level III. (B) Chest CT reveals a lung metastasis (black arrow) in the right middle lobe. (C) Fluid attenuated inversion recovery displays multiple brain metastases with peri-regional edema in the right frontal lobe. Brain metastases show hemorrhage (black dotted arrow) on susceptibility-weighted image (D) and enhancement on contrasted enhanced T1-weighted image (E).

the number of patients was the largest compared with that of previous studies, it was not large enough to draw a robust conclusion. Therefore, multicenter studies with larger sample sizes are required to validate our findings and explore the underlying biological mechanisms. Lastly, genetic analyses were not available for some patients, which may have influenced the results.

In conclusion, our results provide support to the current recommendations to perform brain MRI at initial staging and in the presence of neurological symptoms in ATC pa-

tients. Beyond these established indications, we identified extracranial metastasis as an independent and significant factor associated with BM. These findings suggest that brain imaging should also be considered in asymptomatic patients with extracranial metastasis, which may help guide more comprehensive surveillance strategies in ATC management.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.31728/jnn.2025.00170.

Ethics Statement

This study was approved with a waiver of informed consent by the Gangnam Severance Hospital, Yonsei University Health System Institutional Review Board (3-2024-0206), ensuring adherence to ethical guidelines and the protection of participants' rights and welfare.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Ahn SJ. Data curation: Park M, Joo B. Formal analysis: Yi J. Investigation: Yi J, Kim SM. Methodology: Yi J, Ahn SJ. Validation: Park M, Joo B. Visualization: Yi J. Writing - original draft: Yi J. Writing - review & editing: Kim SM, Ahn SJ.

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Conflicts of Interest

No potential conflicts of interest relevant to this article was reported.

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