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Survival and Recurrence in Thyroid Cancer Brain Metastases: Prognostic Factors and Treatment Implications

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Research Article

Keywords: Thyroid cancer, Brain metastases, Malignant tumor, Deep-learning

Posted Date: July 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9988983/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective

Brain metastases from thyroid cancer are uncommon, and factors associated with survival and recurrence remain poorly defined. We reviewed our single-center experience to identify clinical, radiological, and pathological features associated with outcome.

Method

Among 18,726 patients treated for brain metastases at our center between 2005 and 2024, 37 had thyroid cancer brain metastases. Clinical, radiological, treatment, and pathological data were reviewed retrospectively. Survival and recurrence were analyzed using Kaplan–Meier methods and Cox regression. Tumor microenvironment features were additionally quantified using a deep learning–based analysis of pathological slides.

Results

Among patients with differentiated thyroid cancer, longer brain metastasis–free interval, a solitary intracranial lesion, and Ki-67 > 10% were associated with survival on univariate analysis, and Ki-67 remained significant on multivariate analysis. Recurrence was more frequent in patients with multiple intracranial lesions, extracranial metastases, and Ki-67 > 10%, whereas extracranial metastases remained independently associated with recurrence. Patients with isolated skull metastases had longer survival than other metastatic subgroups, and patients who underwent retreatment after recurrence survived longer than those who did not. Radiological appearances were heterogeneous and often misleading before surgery. On pathological analysis, higher stromal proportion and lower immune cell proportion were associated with worse outcome.

Conclusion

In this cohort, Ki-67 was associated with both survival and recurrence in differentiated thyroid cancer brain metastases. Active treatment after recurrence may still be worthwhile in selected patients, and extracranial disease burden should be considered in treatment planning. Quantitative microenvironmental features may provide additional prognostic information.

1. Introduction

Thyroid cancer is the most common endocrine malignancy, but distant metastases are relatively uncommon.[1] When distant spread occurs, the lungs and bones are the most frequent sites.[2–4]

Treatment options for metastatic thyroid cancer include radioactive iodine therapy, surgery, radiotherapy, and targeted therapy, although their roles vary by tumor subtype and site of disease.[5]

Brain metastases from thyroid cancer are rare, with reported incidences of 0.3%–1.5% in differentiated thyroid cancer and even lower rates in other subtypes.[6,7] Despite their rarity, they are usually associated with poor prognosis and difficult management decisions. Radioactive iodine therapy has limited value in intracranial disease, and both surgery and radiotherapy must be tailored to lesion number, location, and overall disease burden.[8–10] Most published data come from small retrospective series, and the factors associated with outcome are still not fully established.

In daily practice, these patients raise several questions that remain difficult to answer. Which patients are most likely to benefit from aggressive local treatment? Does recurrence after initial treatment justify further intervention? How often are these lesions recognized before surgery? To address these questions, we reviewed our experience with thyroid cancer brain metastases at a high-volume neurosurgical center and examined factors associated with survival, recurrence, and radiological presentation. We also explored whether quantitative microenvironmental features on pathological specimens were related to outcome.

2. Materials and Methods

2.1. Study Design

We reviewed the medical records of patients who underwent craniotomy at our center between 2005 and 2024. A total of 45 patients were pathologically confirmed to have thyroid cancer metastases involving the cranium or intracranial compartment. Eight patients were excluded because of loss to follow-up. The final cohort consisted of 37 patients. The study flowchart is shown in Fig. 1.

2.2. Comprehensive Tumor Assessment

Clinical variables were collected from the medical records, including age, sex, pathological subtype, presenting symptoms, time from diagnosis of the primary tumor to development of brain metastases, number of intracranial lesions, lesion size, lesion location, extracranial metastatic disease, treatment history, and recurrence status.

2.3. Definition of Clinical Status

A Karnofsky Performance Status (KPS) score of 70 or lower was defined as poor functional status. For analysis, intracranial disease was categorized as a solitary lesion or multiple lesions, and lesion size was categorized as 2 cm or smaller versus larger than 2 cm.

Local recurrence was defined as radiographic progression of a previously treated lesion, indicated by a 20% or greater increase in the contrast-enhancing diameter on follow-up CT or MRI. Time to recurrence

was calculated from the date of surgery or stereotactic radiosurgery to the date of radiographic recurrence.

2.4. Quantitative Pathological Analysis

Whole-slide pathological images from surgically treated cases were analyzed to quantify tumor microenvironment features. A deep learning–based pipeline was used to identify tumor, stromal, and immune cells on hematoxylin and eosin–stained sections. Based on these data, we calculated the tumor–stroma ratio (TSR) and immune cell proportion for each case. To support visualization of spatial immune cell distribution, immune cell density maps were generated from the classified nuclei. These analyses were used to explore associations between pathological features and clinical outcomes. Additional technical details are provided in the Supplementary Methods.

2.5. Statistical Analyses

Statistical analyses were performed using SPSS version 23.0, and figures were presented with GraphPad Prism version 10.0. Survival and recurrence were analyzed using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression was used to identify variables associated with survival and recurrence. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

The cohort included 37 patients with thyroid cancer metastases involving the brain or skull. Of these, 32 patients (86.5%) had differentiated thyroid carcinoma (DTC), including 27 with papillary thyroid carcinoma and 5 with follicular thyroid carcinoma. The remaining 5 patients had medullary thyroid carcinoma or anaplastic thyroid carcinoma.

Among the 32 patients with DTC, 19 developed recurrence after treatment, whereas 13 remained alive without recurrence at last follow-up. Because medullary and anaplastic thyroid carcinomas are biologically distinct and were represented by only a small number of cases, these patients were analyzed separately. Compared with the non-DTC group, patients with DTC had a lower recurrence rate ($p = 0.02$), a lower Ki-67 index ($p = 0.014$), and longer median survival ($p < 0.0001$)(Table 1).

Table 1
Patient characteristics (N = 37)

Characteristic	All patients	DTC	ATC/MTC	p Value*
No. of patients	37 (100.0)	32 (86.5)	5 (13.5)	
Gender				
female	26 (70.3)	24 (75.0)	2 (40.0)	0.144
male	11 (29.7)	8(25.0)	3 (60.0)	
Age at diagnosis of cranial metastases				
≥ 55yrs	24 (64.9)	20 (62.5)	4 (80.0)	0.638
< 55yrs	13 (35.1)	12 (37.5)	1 (20.0)	
Diameter of the largest cranial lesion				
< 20mm	9 (24.3)	8 (25.0)	1 (20.0)	0.648
≥ 20mm	28 (75.7)	24 (75.0)	4 (80.0)	
Single or multiple cranial lesions				
Single	20 (54.1)	19 (59.4)	1 (20.0)	0.123
Multiple	17 (45.9)	13 (40.6)	4 (80.0)	
Co-existing extracranial metastases				
None	10 (27.0)	9 (28.1)	1 (20.0)	0.588
One or more organ	27 (73.0)	23 (71.8)	4 (80.0)	
Treatment for cranial metastases				
Surgery	30 (81.1)	27 (84.4)	3 (60.0)	0.233
No surgery (SRS/ TT)	7 (18.9)	5 (15.6)	2 (40.0)	
Recurrence				
Yes	18 (48.6)	13 (40.6)	5 (100.0)	**0.020**
No	19 (51.4)	19 (59.4)	0 (0.0)	
Symptomatic				

Abbreviations: DTC, differential thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer, SRS, stereotactic radiotherapy, TT, targeted therapy.

* DTC versus ATC/MTC.

Characteristic	All patients	DTC	ATC/MTC	p Value*
Yes	25 (67.6)	20 (62.5)	5 (100.0)	0.122
No	12 (32.4)	12 (37.5)	0 (0.0)	
Ki67 index				
≤ 10%	20 (54.1)	20 (62.5)	0 (0.0)	**0.014**
> 10%	17 (45.9)	12 (37.5)	5 (100.0)	
Recurrence				
Yes	24 (64.9)	19 (59.4)	5 (100.0)	0.098
No	13 (35.1)	13 (40.6)	0 (0.0)	
Survival				
Median survival time	35	48	12	**< 0.0001**

Abbreviations: DTC, differential thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer, SRS, stereotactic radiotherapy, TT, targeted therapy.

* DTC versus ATC/MTC.

3.2. Survival in Patients With Differentiated Thyroid Cancer

Survival analysis was performed in 32 patients with DTC brain metastases (Table 2). On univariate analysis, longer brain metastasis–free interval ($p = 0.041$), a solitary intracranial lesion ($p < 0.001$), and Ki-67 > 10% ($p < 0.0001$) were associated with survival. On multivariate analysis, Ki-67 remained significantly associated with survival ($p = 0.044$). Survival curves are shown in Fig. 2.

Table 2
Kaplan-Meier and Cox regression analysis of predictive factors for survival rate in DTC patients (N = 32)

Factor		Average survival time,	P-value	
	N	months	Kaplan-Meier log-rank test	Cox regression
Gender				
Male	8	34.3 ± 32.3	0.395	/
Female	24	41.8 ± 36.7		
Age at diagnosis of cranial lesions				
> 55 years	20	42.1 ± 39.7	0.575	/
≤ 55 years	12	36.3 ± 27.7		
Symptom				
Yes	20	39 ± 30.8	0.356	/
No	12	41.3 ± 43.3		
Histological type				
PTC	27	32.7 ± 25.1	0.074	/
FTC	5	78.8 ± 57.8		
Interval to cranial lesions				
< 5 years	14	21.7 ± 17	**0.041**	0.054
≥ 5 years	18	54 ± 39.6		
Single or multiple cranial lesions				
Single	19	44.8 ± 40	**< 0.001**	0.770
Multiple	13	32.6 ± 26.8		
Co-existing extracranial metastases				
No	9	69.9 ± 47.3	0.216	/
Yes	23	28.1 ± 20.8		
Tumor size				
> 2cm	24	33.6 ± 27.1	0.165	/

Factor		Average survival time,	P-value	
	N	months	Kaplan-Meier log-rank test	Cox regression
Gender				
≤ 2cm	8	58.6 ± 50.7		
Metastatic site				
Brain	23	34.2 ± 23	0.935	/
Skull	9	56.9 ± 57.8		
Ki67 index				
≤ 10%	20	52.7 ± 38.9	**< 0.0001**	0.044
> 10%	12	18.6 ± 10.2		

3.3. Recurrence in Patients With Differentiated Thyroid Cancer

Recurrence occurred in 13 patients, with a median time to recurrence of 48 months. Multiple intracranial lesions ($p < 0.001$), extracranial metastases ($p = 0.043$), and Ki-67 > 10% ($p < 0.0001$) were associated with recurrence on univariate analysis. On multivariate analysis, extracranial metastases remained an independent predictor of recurrence ($p = 0.038$) (Table 3). Recurrence curves are shown in Fig. 3..

Table 3
Kaplan-Meier and Cox regression analysis of predictive factors for recurrence rate in 32 DTC patients (N = 32)

Factor		Average recurrence time,	P-value	
	N	months	Kaplan-Meier log-rank test	Cox regression
Gender				
Male	8	25.6 ± 20.5	0.803	/
Female	24	36.9 ± 34.9		
Age at diagnosis of cranial lesions				
> 55 years	20	36.4 ± 37.2	0.741	/
≤ 55 years	12	30.3 ± 21.8		
Symptom				
Yes	20	30.9 ± 22.7	0.229	/
No	12	39.5 ± 44.1		
Histological type				
PTC	27	27.7 ± 20.7	0.088	/
FTC	5	68.8 ± 58		
Interval to cranial lesions				
< 5 years	14	20.1 ± 18.2	0.236	/
≥ 5 years	18	45 ± 36.4		
Single or multiple cranial lesions				
Single	19	41.3 ± 37.6	**< 0.001**	0.24
Multiple	13	23.6 ± 17.9		
Co-existing extracranial metastases				
No	9	62.3 ± 46.5	**0.043**	**0.038**
Yes	23	23 ± 14.3		
Tumor size				

Factor		Average recurrence time,	P-value	
	N	months	Kaplan-Meier log-rank test	Cox regression
Gender				
> 2cm	24	28.5 ± 23	0.155	/
≤ 2cm	8	50.9 ± 48.5		
Metastatic site				
Brain	23	29.6 ± 19	0.861	/
Skull	9	47.6 ± 55.4		
Ki67 index				
≤ 10%	20	45.7 ± 35.2	**< 0.0001**	0.229
> 10%	12	14.8 ± 9.4		

3.4. Survival in the Skull Metastases Subgroup

Because skull metastases raise different clinical and surgical considerations from brain parenchymal metastases, we examined this subgroup separately. Although no significant survival difference was observed when skull metastases were grouped together and compared with brain parenchymal metastases, subgroup analysis showed that patients with isolated skull metastases had longer survival than those with non-isolated skull metastases or brain parenchymal metastases (Supplementary Table 3 and Supplementary Fig. 1).

3.5 Survival After Retreatment for Recurrent Disease

Among the 13 patients with recurrent DTC, 8 underwent additional treatment after recurrence. Treatment details are summarized in Supplementary Table 1. Patients who received retreatment had longer survival than those who did not (Supplementary Fig. 2). At last follow-up, patients treated with surgery combined with radiosurgery or targeted therapy also appeared to have lower recurrence rates than those treated with surgery alone or radiosurgery alone (Supplementary Fig. 3).

3.6 Clinical Features of Medullary and Anaplastic Thyroid Carcinoma

Because only 5 patients had medullary thyroid carcinoma or anaplastic thyroid carcinoma, these cases were summarized descriptively (Supplementary Table 2). The mean age was 69 years (range 54–81 years). Survival from diagnosis of brain metastasis ranged from 3 to 20 months. All lesions were located in the brain parenchyma, most commonly in the temporal lobe. Three patients had lung metastases before intracranial disease developed. Overall outcomes were poor despite treatment.

3.7 Radiological Features of Thyroid Cancer Intracranial Metastases

Radiological presentation was heterogeneous, and preoperative diagnosis was often difficult. Imaging findings are summarized in Supplementary Table 4, and five representative cases are shown in Fig. 4.

One patient with bilateral lower-extremity weakness had a cystic left frontal lesion with a markedly elevated Cho/NAA ratio on magnetic resonance spectroscopy; pathology confirmed metastatic papillary thyroid carcinoma with positive BRAF V600E staining (Fig. 4A). Another patient with left visual decline was initially diagnosed with meningioma, but pathology showed metastatic papillary thyroid carcinoma (Fig. 4B). A third patient presenting with headache had a right frontal hyperdense lesion on CT that was initially interpreted as cavernous malformation; pathology later confirmed metastatic papillary thyroid carcinoma, also positive for BRAF V600E (Fig. 4C). In a fourth patient with headache, dizziness, and limb incoordination, a fourth ventricular lesion was suspected to be hemangioblastoma before pathology established metastatic follicular thyroid carcinoma (Fig. 4D). The fifth patient had an asymptomatic right frontal skull lesion with marked bony destruction on CT, which was confirmed pathologically as metastatic papillary thyroid carcinoma (Fig. 4E)..

3.8 Quantitative Analysis of the Tumor Microenvironment

Pathological slides from surgically treated cases were analyzed to quantify tumor, stromal, and immune cell components. Based on these measurements, we calculated the tumor–stroma ratio and immune cell proportion for each case (Fig. 5A).

Cases with a higher stromal proportion tended to have worse survival (Fig. 5B), and cases with a lower immune cell proportion also tended to have less favorable outcomes (Fig. 5C). In addition, recurrent tumors and tumors with multiple intracranial lesions showed differences in microenvironmental composition, including higher immune cell proportion and lower tumor–stroma ratio in some subgroups (Fig. 5D and E). These findings should be interpreted as exploratory..

4. Discussion

In this cohort, outcome in thyroid cancer brain metastases was related to both tumor biology and overall disease burden. Among patients with differentiated thyroid cancer, a longer brain metastasis–free interval, a solitary intracranial lesion, and a lower Ki-67 index were associated with better survival, whereas extracranial metastases were associated with recurrence after treatment. These findings suggest that prognosis cannot be judged from the intracranial lesion alone.

Ki-67 was associated with both survival and recurrence in this cohort. Patients with a higher Ki-67 index tended to have shorter survival and were more likely to relapse after treatment. This is consistent with the view that proliferative activity reflects a more aggressive disease course.[11–13] In practice, Ki-67 may

be useful when estimating risk after local treatment and deciding how closely these patients should be followed.

Extracranial disease also remained important after treatment of the intracranial lesion. Patients with extracranial metastases were more likely to recur, suggesting that local control does not necessarily translate into durable disease control. This may be particularly relevant in patients with active lung or nodal disease, in whom treatment of the intracranial lesion should be considered together with the overall systemic burden.[14,15]

Another clinically relevant finding was the association between retreatment after recurrence and longer survival. This does not mean that every patient with recurrent disease should undergo further intervention, but it does suggest that recurrence should not automatically lead to a purely palliative approach. In selected patients, repeat surgery, radiosurgery, or systemic therapy may still be reasonable, depending on lesion burden, symptoms, and overall disease status.

The subgroup analysis of skull metastases is also worth noting.[16–18] Skull metastases and brain parenchymal metastases are not equivalent from either a biological or a surgical perspective and should not automatically be grouped together.[19,20] Although no survival difference was seen when all skull metastases were analyzed together, patients with isolated skull metastases appeared to survive longer than those with non-isolated skull metastases or brain parenchymal metastases. One possible explanation is that selected patients with isolated skull metastases had less extensive intracranial disease.[21]

Radiological presentation was highly variable in this cohort. Several lesions were initially interpreted as glioma, meningioma, cavernous malformation, or hemangioblastoma before pathological confirmation. For neurosurgeons, this matters because the presumed diagnosis may influence operative planning, counseling, and perioperative expectations.[22] Thyroid cancer metastasis should therefore remain in the differential diagnosis when a patient with a history of thyroid malignancy presents with an atypical intracranial lesion, especially when the imaging pattern does not fit well with a more common primary lesion.

We also examined whether pathological features might help explain some of the heterogeneity in clinical course.[23–25] Cases with a higher stromal proportion tended to have worse survival, whereas cases with a lower immune cell proportion also appeared to fare less well. These findings are preliminary, but they suggest that variation in the tumor microenvironment may contribute to differences in behavior across patients. In this study, the pathological analysis was included to complement the clinical findings rather than serve as a separate endpoint.

Several aspects of this study may be useful in practice. In addition to overall survival, we examined recurrence and found that extracranial metastases were associated with recurrence after intracranial treatment. Some patients also appeared to live longer after retreatment for recurrent disease, which is

relevant when deciding whether further intervention is reasonable. We also found that isolated skull metastases did not behave in the same way as brain parenchymal metastases and that these lesions were often misclassified on preoperative imaging. In addition, quantitative pathological analysis suggested that stromal and immune cell composition may be related to clinical course.

This study has several limitations. It is retrospective, includes a limited number of patients, and reflects the experience of a single center. The study period was long, and treatment strategies changed over time. Subgroup comparisons were further limited by the small number of patients with medullary or anaplastic thyroid carcinoma. The pathological analysis was exploratory, and those findings should therefore be interpreted with caution.

Conclusions

In this cohort, Ki-67 and extracranial disease burden were associated with outcome in thyroid cancer brain metastases. Recurrence did not necessarily preclude further treatment, and selected patients appeared to benefit from continued intervention.

Abbreviations

DTC
differentiated thyroid carcinoma
MTC
Medullary and Anaplastic Thyroid Carcinoma
ATC
Anaplastic Thyroid Carcinoma
KPS
Karnofsky Performance Status
ECMet
Extracranial metastases

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the institutional ethics committee (IRB 2015-256, Huashan hospital, Institutional Review Board), and the requirement for written informed consent was waived because of the study design. All procedures performed in this study involving human participants were in accordance with the ethical standards. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patients.

Availability of data and materials

Not applicable.

Competing Interests

The authors declare no competing interests.

Funding

None declared.

Authors' contributions

TongLIn Pan and ZongZe Li write the manuscript, Hu Du conducts the pathological analysis, YingJun Liu and TongLin Pan make the statistical analysis, YiFei Cao and SiChen Li review the manuscript.

Acknowledgements

None declared.

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Figures

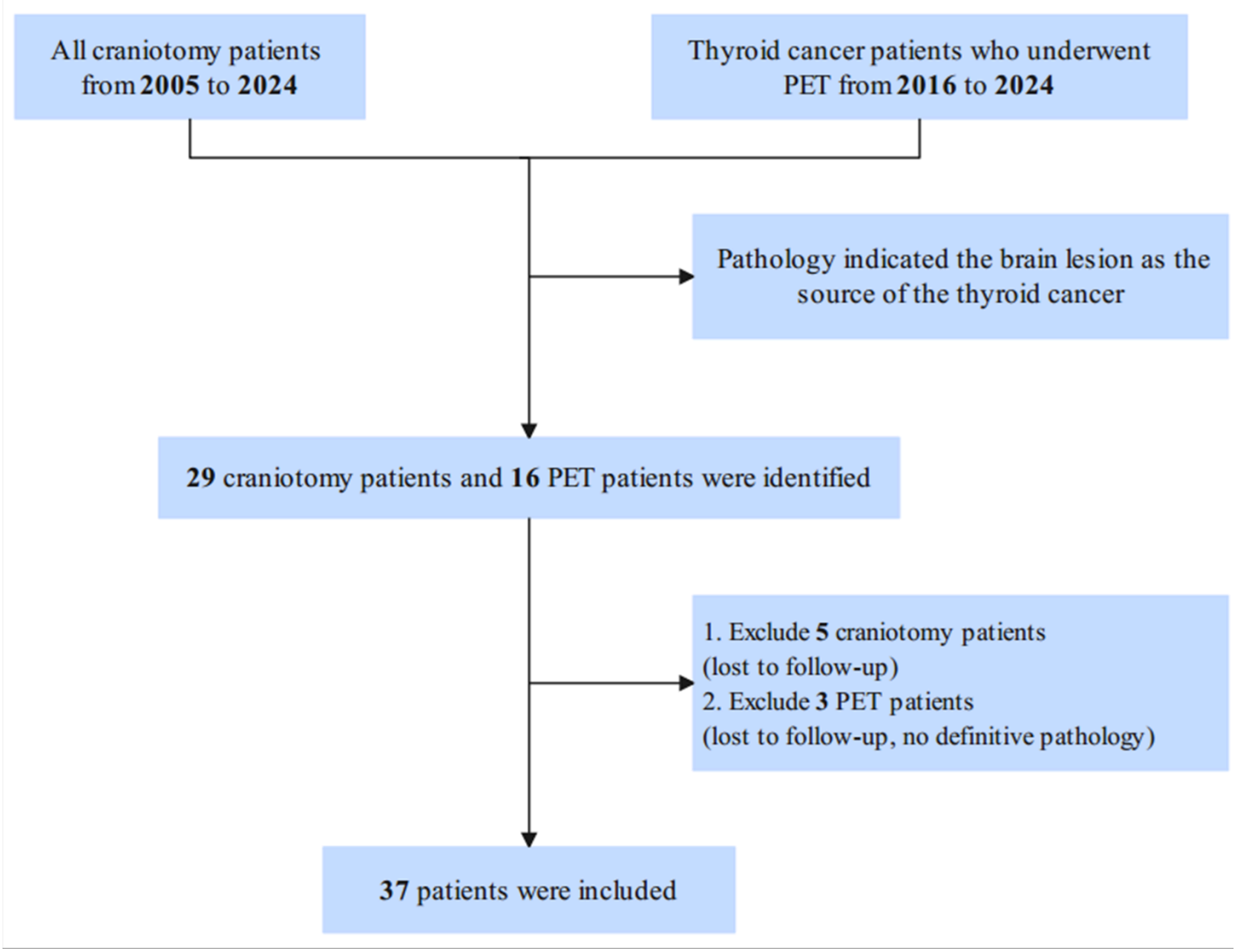


Figure 1

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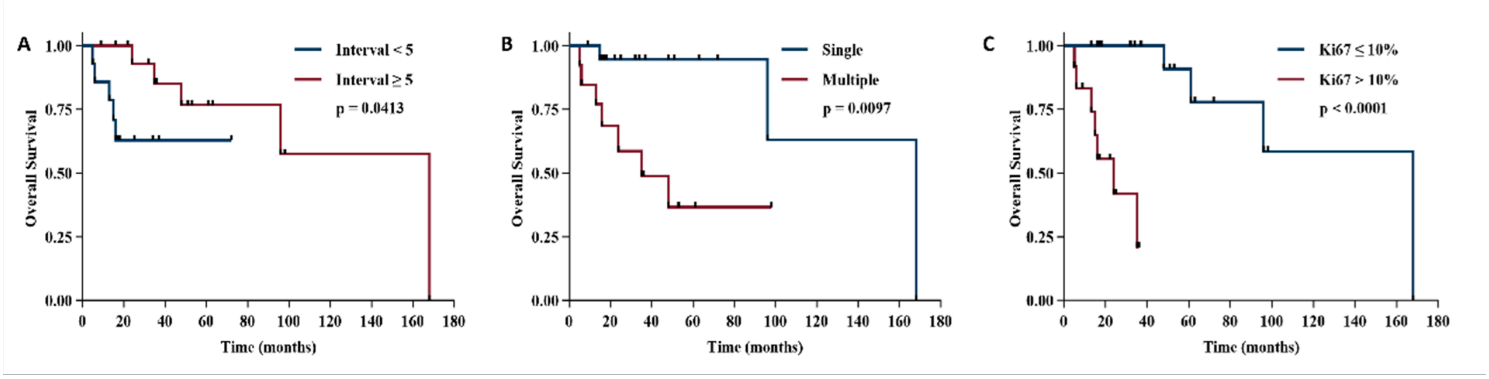


Figure 2

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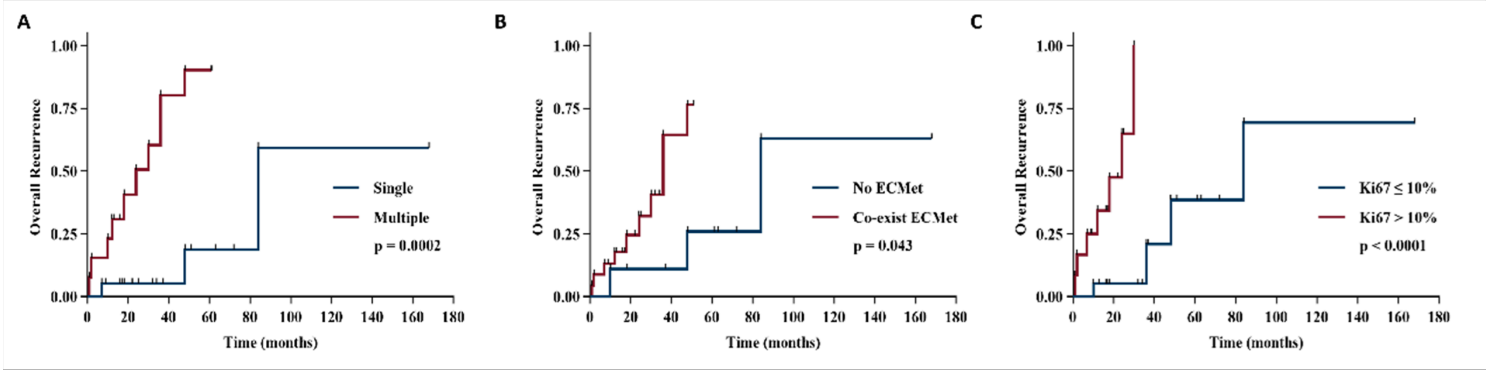


Figure 3

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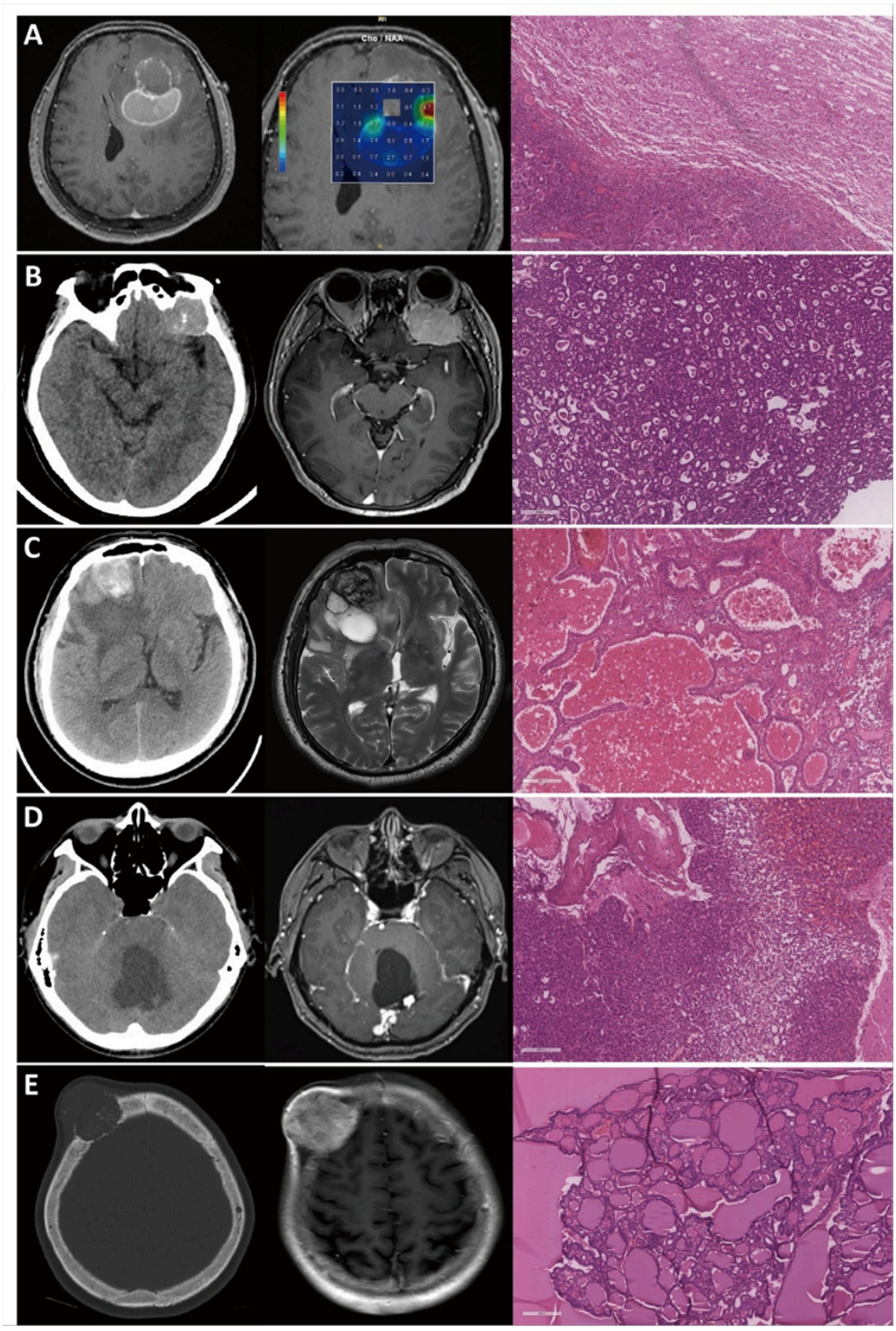


Figure 4

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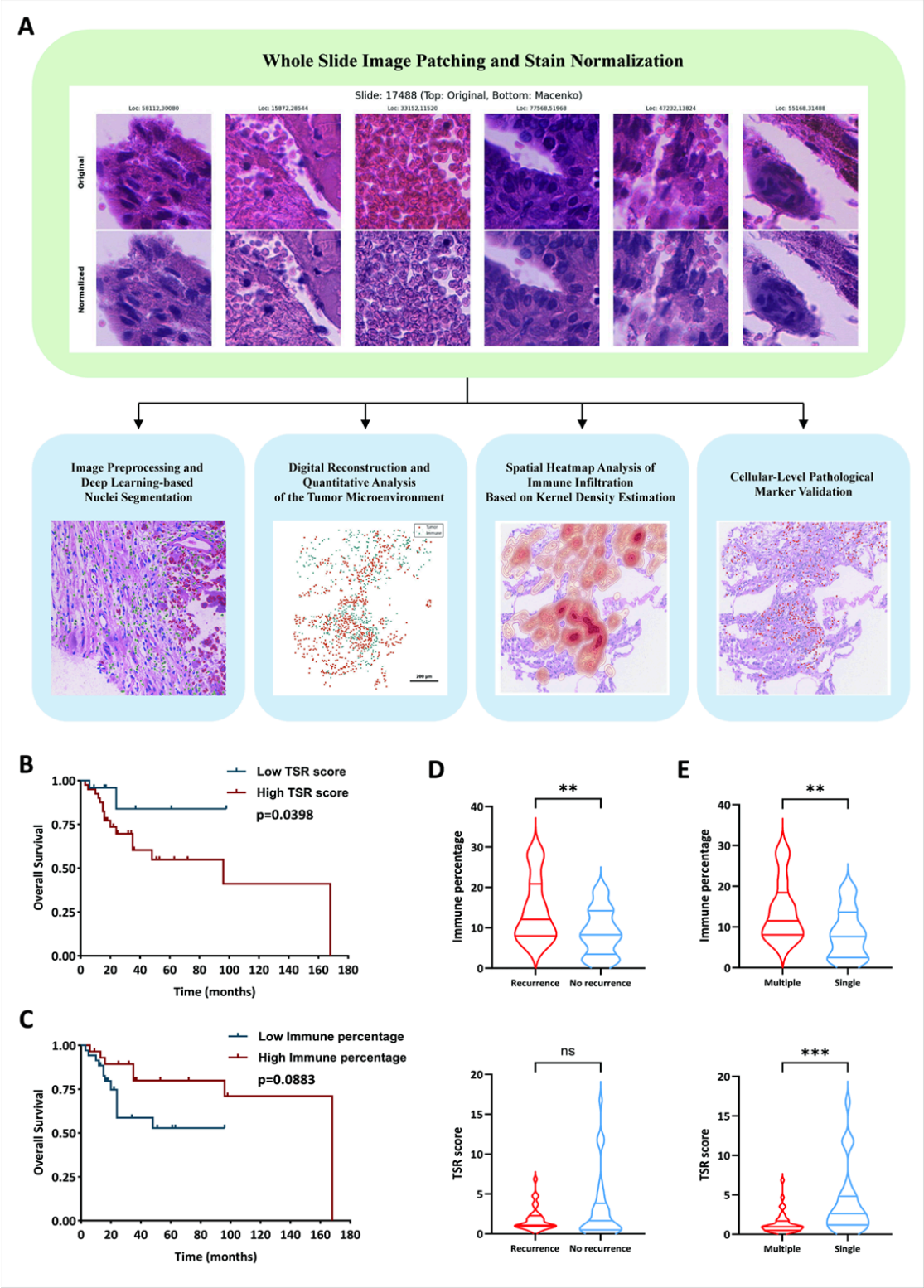


Figure 5

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