Hypodense Non-Enhancing Lesions: Histopathological Diagnosis Through Ct-Guided Stereotactic Brain Biopsy

Hipodens Kontrast Tutmayan lezyonlarda Bilgisayarlı Tomografi Eşliğinde Sterotaktik Beyin Biyopsisi Yoluyla Histopatolojik Tanı

SERRA SENCER, MURAT İMER, ALTAY SENCER,
SELHAN KARADERELER, ORHAN BARLAS

İstanbul School of Medicine, Department of Radiology (SS)
İstanbul School of Medicine, Department of Neurosurgery (Mİ, AS, SK, OB)

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Abstract: The histopathological diagnoses for a series of hypodense non-enhancing lesions were established through computed tomography (CT)-guided stereotactic brain biopsy. The aim was to retrospectively assess how well the imaging-based diagnoses correlated with the histological diagnoses in these cases.

Key words: CT-guided stereotactic brain biopsy, contrast enhancement

Özet: Hipodens-kontrast tutmayan lezyonlarda bilgisayarlı tomografi (BT)-eşliğinde stereotaktik beyin biyosisi yoluyla histopatolojik tanıya ilişkin deneyimimizin sunulması amaçlanmıştır. Görüntüleme esaslı ve histolojik tanının korelasyonu tartışılmıştır.

Anahtar Kelimeler: BT eşliğinde stereotaktik beyin biyopsisi, kontrast tutulumu

INTRODUCTION

The development of computed tomography (CT)-guided stereotactic brain biopsy has made it possible to histopathologically diagnose lesions in all intracranial locations with relatively low operative risk, thus avoiding open craniotomy. The technique is also considered minimally invasive, and has high diagnostic accuracy (2,4,11,12). Hypodense non-enhancing lesions are a large and intriguing group among the lesions that are detected on CT. They reflect a wide spectrum of pathologies, and many neoplasms (primary glial and metastatic) and lesions of biologically different nature (cerebritis and infarction, among others) can present with the same CT appearance. Although these other possibilities exist, a presumptive diagnosis of low-grade primary glial tumor is often made when a patient presents with the appropriate clinical picture (seizures and minimal neurologic deficit) and exhibits the "typical"

imaging features. These include low attenuation, minimal or no enhancement, lack of necrosis and hemorrhage, and absence of a significant mass effect (9,14).

Compared to CT studies of brain tumors, conventional anatomic magnetic resonance (MR) imaging offers better delineation of lesion boundaries (tumor and edema margins), a higher degree of contrast enhancement that helps determine tumor grade, and better tissue characterization (internal hemorrhage, necrotic and/or cystic changes). However, MR imaging does not always guarantee accurate histological diagnosis or identify tumor grade with certainty. Moreover, it can still be very difficult to distinguish between neoplastic and non-neoplastic tissue on these images (3,7,9,13). Although biologic and physiologic MR techniques, such as MR spectroscopy, yield important functional and metabolic information in pre- and especially postoperative brain imaging, non-invasive imaging still does not replace histopathological sampling in the preoperative/pretreatment evaluation of presumed brain tumors (13).

This study retrospectively investigated intra-axial brain lesions in 29 patients of wide age range who presented with seizures or minimal neurological deficit. In each case, the presumptive diagnosis on contrast-enhanced CT was low-grade primary glial tumor. The signs of low attenuation and lack of enhancement, hemorrhage, or significant mass effect led to the presumptive diagnoses. We reassessed all patients' CT findings as well as cranial MRI studies that were available for 11 of the cases, and compared the imaging results to histopathological diagnoses established by stereotactic biopsy. The aim was to determine how well the imaging-based diagnoses correlated with the definitive histopathological findings.

PATIENTS AND METHODS

A series of 412 consecutive patients who underwent CT-guided stereotactic brain biopsy for diagnostic purposes between 1991 and 1998 was evaluated retrospectively. The selected study group included only cases in which cranial CT imaging showed a hypodense non-enhancing lesion with no signs of internal calcification/hemorrhage and no significant mass effect.

The selected group included 8 females and 21 males of age range 10-56 years (mean age, 33 years). The clinical findings on admission were seizure in 17 patients and focal neurological deficit in 19 patients. Non-contrast-enhanced and contrast-enhanced (iohexol 300 mg/100 ml, Omnipaque, Nycomed, Ireland; dose 2 ml/kg body weight injected intravenously) cranial CT scans with 5 mm-thick continuous slices were performed in all cases. In 11 cases, T2-weighted (W), spin density, and T1-W spin-echo (SE) axial and coronal MR sequences, as well as enhanced (gadopentetic acid, Magnevist, Schering, Germany; dose 0.2 ml/kg body weight) axial and coronal T1-W SE series were captured using a 1 Tesla MR scanner. MR imaging was not performed in patients who were evaluated in our earlier experience due to financial reasons, and because the technique was not available to us at the time. No steroid treatment or any other medication that could alter contrast enhancement or lesion morphology was started prior to the imaging studies.

As mentioned, stereotactic biopsy was performed in all 29 cases, and this was done using Leksell's stereotactic biopsy system. In adults, the procedures were performed under local anesthesia, whereas general anesthesia was used for pediatric cases. After head immobilization and frame adjustment, a contrast-enhanced CT scan was done and the three-dimensional coordinates of the lesion were determined. Burr holes were drilled at the coronal suture for deep lesions, and immediately over the lesion for superficial ones. Biopsy samples 10 mm long and 1 mm thick were acquired using a Backlund's spiral needle. Slides were immediately prepared using the imprint smear technique. These were stained with hematoxylin and eosin, and were examined in the operating room by the neuropathologist. Additional samples were obtained when other staining methods were necessary to evaluate the biopsy. In order to assure adequate sampling, multiple biopsy specimens were acquired from different regions identified by CT, such as the periphery or center of the lesion, or tissue in the immediate vicinity of the lesion. Tissue was also obtained for full histological preparation and examination to establish the definitive diagnosis.

RESULTS

The anatomical distribution of the lesions is summarized in Table I. In 10 of the 11 patients who

underwent MR imaging, the lesions were hypointense on T1-W and hyperintense on T2-W sequences. One patient's lesion was hyperintense on T1-W images. In the gadolinium-injected series, eight patients showed no lesion enhancement and three showed a variable degree/pattern of enhancement. Table II lists the his topathological results from the CT-guided stereotactic biopsies, and Table III shows a comparative summary of the imaging-based and final histopathological diagnoses.

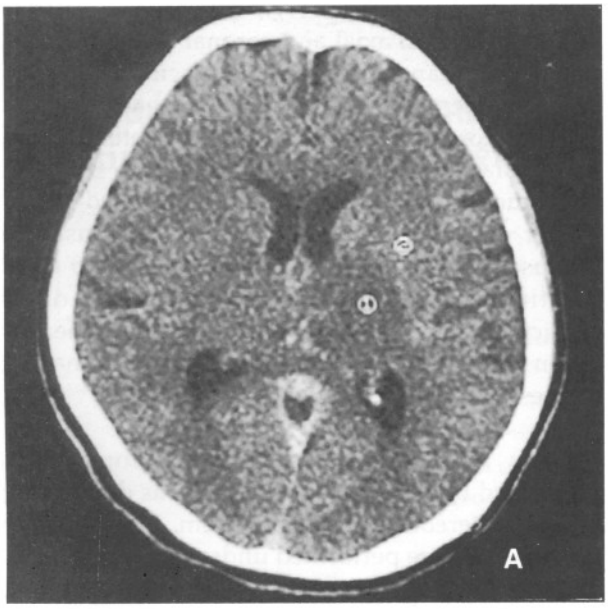

Figure 1a: A contrast-enhanced cranial CT scan of a 29 year-old female patient shows a relatively well-demarcated, low-attenuation, left thalamic lesion. There is no enhancement or mass effect.

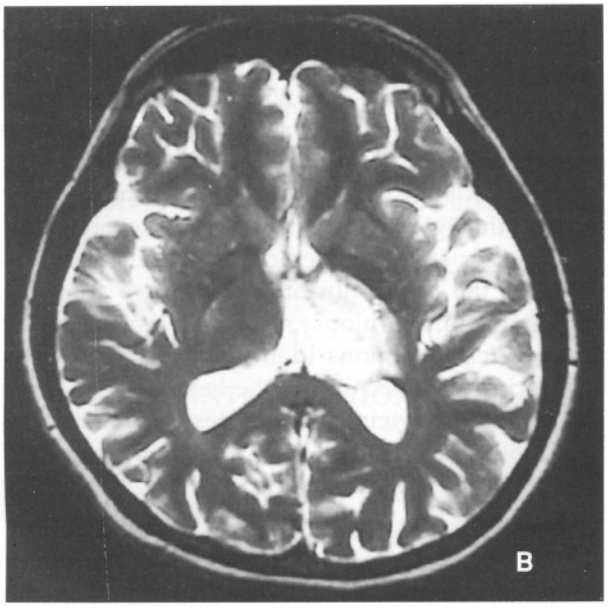

Figure 1b: The lesion was hyperintense on the axial T2-W MR scan.

In two solitary lesions, one of which was deep-seated with no mass effect and regular, well-demarcated margins, the diagnosis was gliosis. In these cases, the preliminary pathological diagnosis suggested that the lesions might have been peritumoral gliosis; however, no tumor cells were detected in the permanent sections, and it was speculated that these were cases of post-traumatic or post-infarction gliosis.

All three cases with the final pathological diagnosis of pilocytic astrocytoma were young adults who had lobar lesions in the cerebral hemispheres. Only one of these individuals underwent MR imaging, and this lesion showed low signal on T1- and high signal on T2-W sequences, with no significant enhancement.

Two patients with solitary lesions were diagnosed with metastasis. The MR scan done in one of these cases showed a high signal on T1-W images, which was in accord with the primary tumor, a melanocytic melanoma.

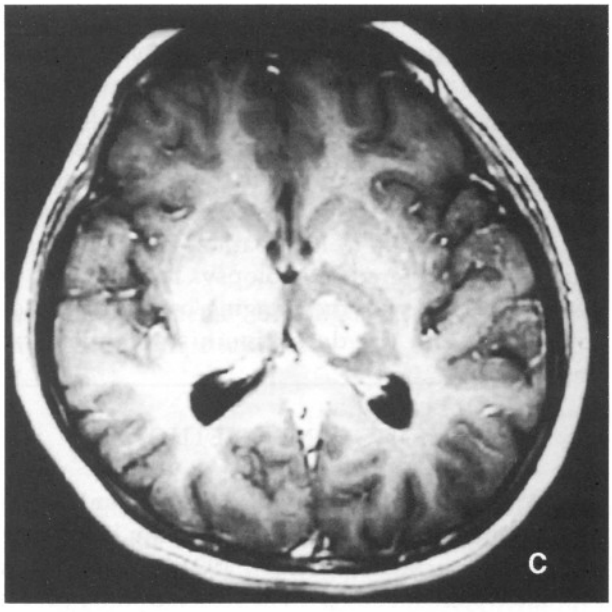

Figure 1c: There was significant central enhancement on the gadolinium-enhanced T1-W axial MR scan. The imaging diagnosis based on MR enhancement was anaplastic astrocytoma. Histologic examination revealed that the mass was actually a low-grade diffuse astrocytoma.

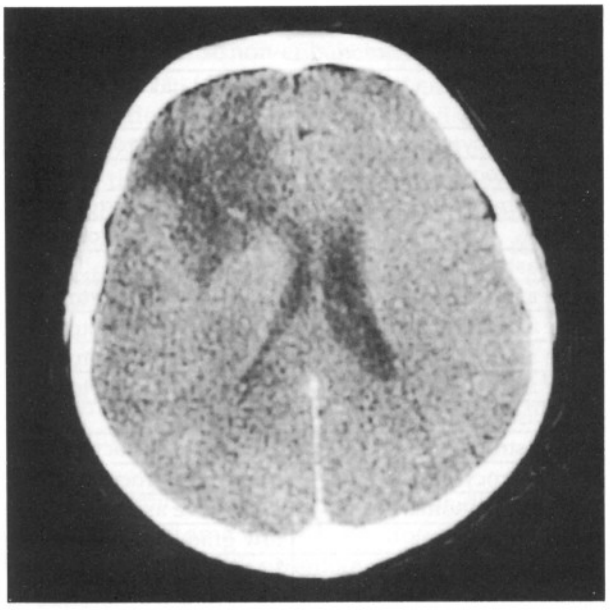

Figure 2: Post-contrast cranial CT of a 34-year-old male patient shows a low-attenuation right frontal lesion with no enhancement. The lesion borders are hazy and irregular. The diagnosis was low-grade diffuse astrocytoma on both imaging and histopathological examination.

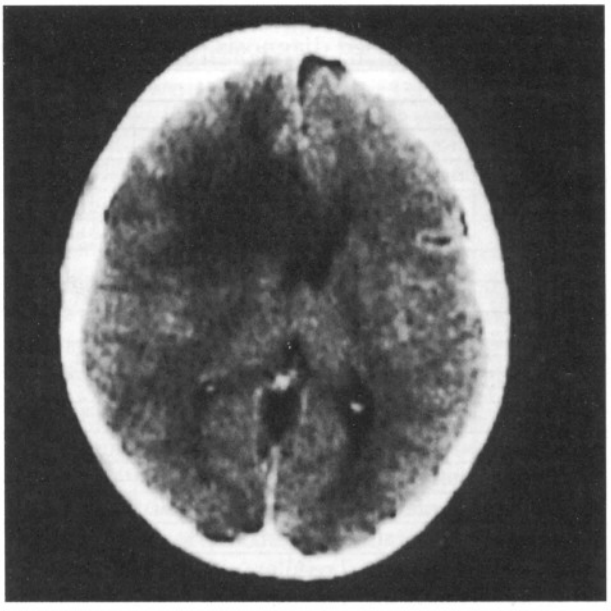

Figure 3: In another right frontal lesion in a 35-year-old female patient, the imaging findings were very similar to the case in Figure 2, but there was slightly greater mass effect. Examination of the stereotactic biopsy showed the lesion was an anaplastic astrocytoma.

Four individuals who had solitary hemispheric lesions with variable mass effect were diagnosed with anaplastic astrocytoma. Of these patients, only one underwent MR imaging. On this scan, the lesion showed high signal on the T2-W and low signal on the T1-W images, with mass effect and heterogeneous enhancement.

In the remaining cases, one patient's lesion generated low signal on T1-W and high signal on T2-W MR images, without any enhancement. This was finally diagnosed as a benign glial tumor, possibly an astrocytoma with oligodendroglial differentiation. Another patient's lesion was located in the basal ganglia. This lesion had regular and well-demarcated margins, with a cerebrospinal fluid-like signal. It was diagnosed as infarction, based on the detection of tissue necrosis with no evidence of neoplasia. In one individual with a solitary lesion in the basal ganglia, CT showed a relatively well-demarcated, hypodense, non-enhancing lesion with no mass effect. MR imaging was not done in this case, and the final histopathological diagnosis was vasculitis. In the case that received the final histopathologic diagnosis of cerebritis, CT showed multiple non-enhancing lesions with moderate mass effect. There was also no MR scan record for this case.

Table 1: Anatomic distribution and multiplicity of lesions (S: solitary lesion, M: multiple lesions).

Lesion location	Number of case
thalamic	2(S)
temporal	5(S)
frontal	9(S)
putamen	1(S)
parietal	4(S)
occipital and cerebellar vermis	1(M)
temporal and parietal	1(M)
temporal and frontal	1(M)
frontoparietal	2(S)
temporoparietal	2(S)
frontotemporal	1(S)

Table 2: Histopathological diagnoses of the lesions verified by CT-guided stereotactic brain biopsy.

Histopathological diagnosis	number and percentage of cases
low grade diffuse astrocytoma	14 (60.9 %9
pilocytic (circumscribed) astrocytoma	3 (13 %)
anaplastic astrocytoma	4 (17.4 %)
metastasi	2 (8.7 %)
nonneoplastic (gliosis, infarction, cerebritis)	6 (20.7 %)

Table 3: Comparison of imaging based and histopathological diagnoses. (CE: contrast enhancement, ID: imaging based diagnosis, HD: histopathological diagnosis)

Age, sex	CT		MRI			I. D	H. D
	mass effect	contours	T1	T2	CE		
29, F	none	regular	low	high	-	low grade astrocytoma	low grade astrocytoma
28, M	none	irregular				low grade astrocytoma	vasculitis
33, F	none	regular	low	high	-	low grade astrocytoma	pilocytic astrocytoma
30, F	none	regular	low	high	-	metastasis?	metastatic melanoma
27, M	none	irregular				low grade astrocytoma	gliosis
35, F	minimal	irregular	low	high	+	low grade astrocytoma	anaplastic astrocytoma
37, M	none	regular				low grade astrocytoma	low grade astrocytoma
56, M	none	regular	low	high	-	low grade astrocytoma	low grade astrocytoma
37, M	none	irregular				low grade astrocytoma	anaplastic astrocytoma
38, M	none	regular	low	high	-	low grade astrocytoma	infarction
34, M	minimal	irregular	low	high	-	low grade astrocytoma	low grade astrocytoma
28, F	none	irregular				low grade astrocytoma	pilocytic astrocytoma
52, M	moderate	irregular	low	high	+	anaplastic astrocytoma	low grade astrocytoma
28, F	moderate	irregular	low	high	+	anaplastic astrocytoma	low grade astrocytoma
33, F	moderate	regular	low	high	-	low grade astrocytoma	low grade astrocytoma
42, M	moderate	regular				metastasis	low grade astrocytoma
38, M	none	regular				infarction	gliosis
21, F	moderate	irregular	low	high	-	low grade astrocytoma	anaplastic astrocytoma
16, F	minimal	irregular				low grade astrocytoma	cerebritis
29, F	minimal	regular				low grade astrocytoma	low grade astrocytoma
38, M	none	regular				low grade astrocytoma	low grade astrocytoma
28, M	none	regular				low grade astrocytoma	anaplastic astrocytoma
35, M	none	irregular				low grade astrocytoma	pilocytic astrocytoma
30, M	none	regular				demyelination plaque	low grade astrocytoma
37, M	none	regular				low grade astrocytoma	low grade astrocytoma
10, M	none	irregular				low grade astrocytoma	nonneoplastic lesion
16, M	none	regular				metastasis/multicentric glioma	metastasis
37, M	none	regular				low grade astrocytoma	low grade astrocytoma
29, M	none	regular				low grade astrocytoma	anaplastic astrocytoma

A total of 13 cases were histologically diagnosed as low-grade astrocytoma of fibrillary histological subtype. The CT features of these lesions were variable in terms of mass effect, contour irregularity, and demarcation; however, all were hypodense and non-enhancing. In the five of these cases in which MR imaging was done, the lesion produced low signal on T1-W and high signal on T2-W series. Two of the five lesions showed enhancement. In only one case, the initial histopathological diagnosis was not clearly classified, but a frozen section preparation showed that the lesion was non-neoplastic. The final histopathological result for this case was unavailable.

DISCUSSION

Non-enhancing hypodense brain lesions are frequent findings on cranial CT studies in a wide spectrum of clinical settings. Traditionally, detection of a low-attenuation mass that does not enhance after contrast injection has been considered a reliable sign of low-grade or "well-differentiated" astrocytoma in an adult who presents with seizure, headache, or minor neurological deficit. Such cases may be treated conservatively until imaging shows tumor growth or enhancement, or until neurological deterioration occurs (9). However, the therapeutic approach is significantly different for higher-grade astrocytomas, for astrocytoma subtypes of different histology, or even for non-neoplastic lesions that may share the same imaging features. Thus, many studies have been conducted in attempt to define more reliable imaging criteria (3,6,9). Anatomical and, more recently, biological and physiological MR imaging techniques have enabled radiologists to better define and characterize these brain lesions, but despite the advances made in high-resolution CT and MR imaging, these techniques have not yet replaced histopathological evaluation.

In this series of 29 patients whose cranial CT scans showed hypodense non-enhancing intra-axial lesions, a total of 14 cases (48.3%) were histologically diagnosed as low-grade diffuse or circumscribed astrocytoma, and four (13.7%) were anaplastic astrocytomas. In their study of the correlation between MR imaging-based and histopathological diagnoses, Ginsberg and colleagues found low-grade astrocytomas in 60% and anaplastic astrocytomas in the remaining 40% of their patients with non-enhancing supratentorial brain tumors (7). Kondziolka and co-workers reported a higher percentage of anaplastic astrocytomas (9/20 cases) in their patients who had non-enhancing tumors on MR imaging (9).

The typical imaging findings for diffuse low-grade astrocytoma have been defined as a low-attenuation mass with no enhancement on CT, lack of contrast enhancement on CT, low signal intensity on T1-W and high signal intensity on T2-W MR images, and lack of paramagnetic contrast enhancement on MR imaging (5,10). However, our results and those of other studies in the literature show that lesions with the above imaging features may actually be astrocytomas of higher grade (7,9). The fact that some patients in our group had non-neoplastic and metastatic lesions may reflect the less stringent clinical inclusion criteria that we used for this study. For example, we did not focus on the onset of neurologic deficits or investigate for other neoplastic or systemic diseases.

Two patients (6.9%) in our series were diagnosed with metastasis. To our knowledge, none of the studies that have correlated imaging-based and histopathological diagnoses of hypodense non-enhancing lesions has reported finding this type of lesion. The lesions were intracerebral, solitary, and lobar in both cases. In the melanocytic melanoma case, the tumor produced high signal on T1-W images. The fact that a paramagnetic signal, which is highly suggestive of melanin pigment, was detected on MR indicates that brain biopsy was unnecessary in this patient.

Three cases (10.3%) in our series were diagnosed with pilocytic astrocytoma. All these lesions were in the cerebral hemispheres, and the patients were young adults. The classical imaging appearance of pilocytic astrocytoma is a cystic or solid mass that almost invariably shows nodular or internal enhancement on CT and MR imaging. With this type of tumor, imaging findings of a low-density non-enhancing mass are very unusual (14).

MR imaging performed in 11 (37.9%) of the cases revealed that the lesions were hypointense compared to normal white matter on T1-W images, and hyperintense on T2-W sequences. Also, the lesions generally appeared to be larger and more significant on the MR scans than they were on CT, and this has been reported previously (8). Three of the 11 lesions showed varying degrees of enhancement on MR imaging, although none of them enhanced on CT. This can be attributed to the better resolution achieved with MR, and the imaging parameters used. In general, contrast enhancement on CT and MR is considered to result from disruption of the blood-brain barrier by a neoplastic-inflammatory or demyelinating lesion, and is also related to technical parameters such as adequate perfusion and appropriate dosage of contrast medium, and contrast accumulation in the extracapillary interstitial compartment (1).

In summary, approximately 50% of the non-enhancing low-attenuation masses in this series did turn out to be low-grade astrocytomas; however, the rest of the patients received other diagnoses. Considering the possibility of higher-grade malignancy, these patients were lucky to have received rapid final diagnoses and appropriate medical care through a minimally invasive procedure. In the cases of non-neoplastic lesions, prompt diagnosis saved the patients from unnecessary intervention or prolonged follow-up.

CONCLUSION

In the preoperative diagnostic evaluation of a relatively common lesion, the low-attenuation non-enhancing mass, the results of our study and others in the literature suggest that histological examination remains the gold standard. Despite the advances that have been achieved in non-invasive imaging, histologic sampling is still essential to determine the correct histopathological cell type and tumor grading in brain lesions. Stereotactic biopsy is a safe way to collect the necessary tissue.

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Correspondence: Serra Sencer
Atakoy, 9.Kısım
A4-B, D: 81
34750 İstanbul, Turkey
Fax and Phone: 90 212 533 13 80
e-mail: altayser@superonline.com

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COMMENT

The authors have written an informative article discussing a series of 29 patients with hypodense non-enhancing cerebral lesions, who underwent stereotactic biopsy. Contrast enhancement is of value in the presence of a low density lesion, and this may be a sign of neoplastic changes. However, management of lesions without enhancement may be more difficult, and MRI scans may add no diagnostic information. Most cases is followed with suspicion of a low grade glioma without a definite diagnosis or undergo unnecessary aggressive surgery. In such a case, the differential diagnosis of a low glial tumor may include a cerebral infarct, cerebritis, demyelination, metastasis or high grade glioma as well. Naturally, completely different therapeutic approaches are indicated for each of these diseases. In the presented series, non-neoplastic lesions were diagnosed in six cases. These findings justify the importance of stereotactic biopsy in differential diagnosis and management of such cases.

In summary, cases with hypodense non-enhancing lesions present special difficulties in diagnosis and their management. Stereotactic biopsy should be a method of choice in most of these cases with advantages of being a less invasive surgical technique and of providing high rates of diagnostic accuracy in experienced neurosurgical centers,

Ali Savaş
Ankara