

Dysembryoplastic Neuroepithelial Tumor: A Benign but Complex Tumor of the Cerebral Cortex

Ji Hoon Phi^{1*} , Se Hoon Kim^{2*} 

¹Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Korea

²Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Received May 7, 2022

Revised June 5, 2022

Accepted June 15, 2022

Correspondence

Ji Hoon Phi

Division of Pediatric Neurosurgery,
Seoul National University
Children's Hospital,
Seoul National University
College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea

Tel: +82-2-2072-3639

Fax: +82-2-744-8459

E-mail: phijh@snu.ac.kr

Se Hoon Kim

Department of Pathology,
Severance Hospital,
Yonsei University
College of Medicine,
50-1 Yonsei-ro, Seodaemun-gu,
Seoul 03722, Korea

Tel: +82-2-2228-1769

Fax: +82-2-362-0860

E-mail: paxco@yuhs.ac

*Ji Hoon Phi and Se Hoon Kim
contributed equally to this work.

Dysembryoplastic neuroepithelial tumor (DNET) is a distinct type of low-grade glioneuronal tumor. Clinically, DNET is highly associated with intractable epilepsy in young children and adolescents. Therefore, the burden of the tumor comprises oncological concerns (recurrence), seizure control, and quality of life. The pathology of DNET is characterized by glioneuronal elements and floating neurons. Grossly, many DNETs harbor separate nodules on the medial side of the mass. Some of the satellite lesions are *bone fide* tumor nodules that grow during the follow-up. Therefore, removing all satellite lesions may be important to prevent tumor progression. Seizure control is highly dependent on the complete removal of tumors, and the presence of satellite lesions also exerts a negative impact on seizure outcomes.

Keywords Glioma; Recurrence; Seizure; Epilepsy; Children.

INTRODUCTION

Dysembryoplastic neuroepithelial tumors (DNETs) are a distinct type of low-grade glioma in terms of histology and clinical behavior. It belongs to the glioneuronal and neuronal tumor category in World Health Organization (WHO) classification of brain tumors. Slow-growing brain tumors arising

from the cerebral cortex, associated with chronic epilepsy in children have been described since the 19th century [1]. Many of the tumors are glioneuronal tumors such as gangliocytoma and ganglioglioma. In 1988, Daumas-Duport et al. [2] reported the presence of a particular type of glioneuronal tumor, distinguished from more common gangliogliomas and called the new entity a DNET. More than 30 years have passed since the publication of the original article, but a DNET, as a disease entity, has survived the test of time, during which 5 revised versions of the WHO classification of brain tumors have emerged [3,4]. In this review, we will introduce the general features of DNET and discuss some new findings in mo-

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2022 The Korean Brain Tumor Society, The Korean Society for Neuro-Oncology, and The Korean Society for Pediatric Neuro-Oncology

lecular biology and clinical practice on DNET.

CLINICAL FEATURES

DNET is a relatively uncommon type of brain tumor. The original study of Daumas-Duport et al. [2] comprised 39 patients from the epilepsy surgery registry of St. Anne Hospital and the brain tumor registry of Mayo Clinic; both were collected for decades. In fact, the patient numbers in many studies on DNET do not exceed a few dozen. In the Korean brain tumor registry, mixed glioneuronal tumors accounted for 7.0% of all gliomas diagnosed in 2013, but it was not specified how many DNETs were included [5]. Focusing on childhood tumors, DNET accounted for 1.5% of all brain tumors and approximately 30% of mixed glioneuronal tumors in the pediatric brain tumor registry of Seoul National University Children's Hospital [6].

DNET develops predominantly in children and adolescents. Young adults are occasionally diagnosed with DNETs, but most patients develop seizure attacks earlier than age 20. A strong association with chronic epilepsy is one of the defining features of DNET. Daumas-Duport et al. [2] emphasized that all of their patients presented with complex partial seizures except for 2 patients with headaches. In 2003, Luyken et al. [7] reported a large spectrum of brain tumors associated with chronic epilepsy. They coined the term long-term epilepsy-associated tumors (LEATs) to designate DNET, ganglioglioma, pleomorphic xanthoastrocytoma, and other rare glioneuronal tumors frequently found in patients with drug-resistant epilepsy. Although the concept of LEAT has been questioned primarily because of the heterogeneity of this clinical group, DNET is the representative tumor of LEATs with its strong epileptogenicity and benign nature [8]. DNETs occupied 5.9% of the European Epilepsy Brain Bank tissue registry, an extensive tissue cohort obtained from epilepsy surgery, and rank the fourth in the causes of epilepsy, next to hippocampal sclerosis, ganglioglioma, and focal cortical dysplasia (FCD) [9].

DNETs develop in the cerebral cortex, involving a whole gyrus or a wedge-shaped part of a cerebral lobe. The temporal lobe is the most common location, although any part of cerebral cortex can be involved [10]. Cortical location and predilection to the temporal lobe make patients with DNETs highly vulnerable to epileptic seizures. Another reason for its high epileptic potential is the dysplastic nature of DNET [2]. Typical DNETs comprise the tumor core surrounded by the rim of dysplastic cortex corresponding to FCD (a complex-type DNET) [11]. The dysplastic cortex around DNETs is regarded as highly epileptogenic [12]. Some DNETs lack a surrounding dysplastic cortex (a simple-type DNET) and epileptogenic

zone is co-localized with the tumor extent [13].

Focal seizures with or without impaired awareness are the most common symptoms of DNET. Secondary generalization is infrequent. Patients with DNETs usually progress into chronic drug-resistant epilepsy [11]. Headache is a rare complaint only for very large tumors. Focal neurologic deficits such as motor weakness are seldom observed in tumors near the primary motor cortex.

IMAGING FINDINGS AND SATELLITE LESIONS

CT shows a mass lesion of low attenuation involving cortex and subcortical area. MRI is the mainstay of diagnostic modality for DNET. DNETs typically have a bubble-like, or popcorn-like multinodular shape with low signal intensity in T1-weighted images and high signal intensity in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1). DNETs are poorly enhanced with gadolinium, but some tumors show patchy or partial enhancement. Gangliogliomas also involve cerebral cortex and subcortical white matter with a predilection to the temporal lobe. A small cystic or nodular architecture is characteristic for gangliogliomas, in contrast to the multicystic structure of DNETs. Strong gadolinium enhancement is more common (approximately 50%) in gangliogliomas [14]. However, it is difficult to distinguish non-enhancing gangliogliomas from DNETs and even from the FCD [14]. ^{11}C -methionine positron emission tomography (PET) is helpful because gangliogliomas show hypermetabolism whereas DNETs exhibit variably low metabolism [15].

There are many variants in the shape of DNETs. Chassoux et al. [16] classified the MRI morphology of DNETs into 3 categories: Type 1 polycystic, Type 2 nodular, and Type 3 diffuse (dysplastic). They correlated Type 1 with simple and complex histology and Type 2 and 3 with nonspecific histology, and the MRI types were highly associated with the extent of epileptogenic zone and surgical outcomes in terms of seizure control. However, the classification has not been widely used and the clinical correlation remains to be verified.

In the original study, Daumas-Duport et al. [2] reported the presence of nodular foci beneath the DNET mass. They showed that the nodular foci consisted of multiple cell types, i.e., neurons, astrocytes, and oligodendrocytes. Sometimes, glioma-like histology was observed in the nodular foci. Later, Urbach et al. [14] emphasized the multinodular architecture of DNET on MRI. They pointed out that sometimes single smaller cysts are observed in the vicinity of the tumor, from which they are clearly separated. We found that such small nodular foci are found in up to 50% of DNETs on high resolution MRI [17]. We called the foci 'satellite lesions' because they are clearly

separated from the tumor core by a thin white matter, documented on 3-planar MRI and intraoperative findings (Fig. 1). Removal of the satellite lesions may injure important functional tracts in the deep subcortical area and residual satellite lesions significantly impact tumor control and seizure control [17].

PATHOLOGICAL FEATURES

According to the WHO classification of brain tumors, DNET was described as below: the histopathological hall-

marks are the multinodular intracortical growth pattern (Fig. 2) and the pathognomonic specific glioneuronal element, i.e., the presence of columns oriented perpendicularly to the cortical surface, formed by bundles of axons lined by small oligodendroglia-like cells (OLCs) [18]. Between these columns, neurons with normal cytology appear to float in a mucoid matrix (floating neurons) (Fig. 3). Atypical features such as mitoses, high cellularity, necrosis, or eosinophilic granular bodies are absent or rare. To summarize, DNET has the following three characteristic findings: 1) multinodular intracortical pattern, 2) glioneuronal columns with OLCs, and 3) floating neurons

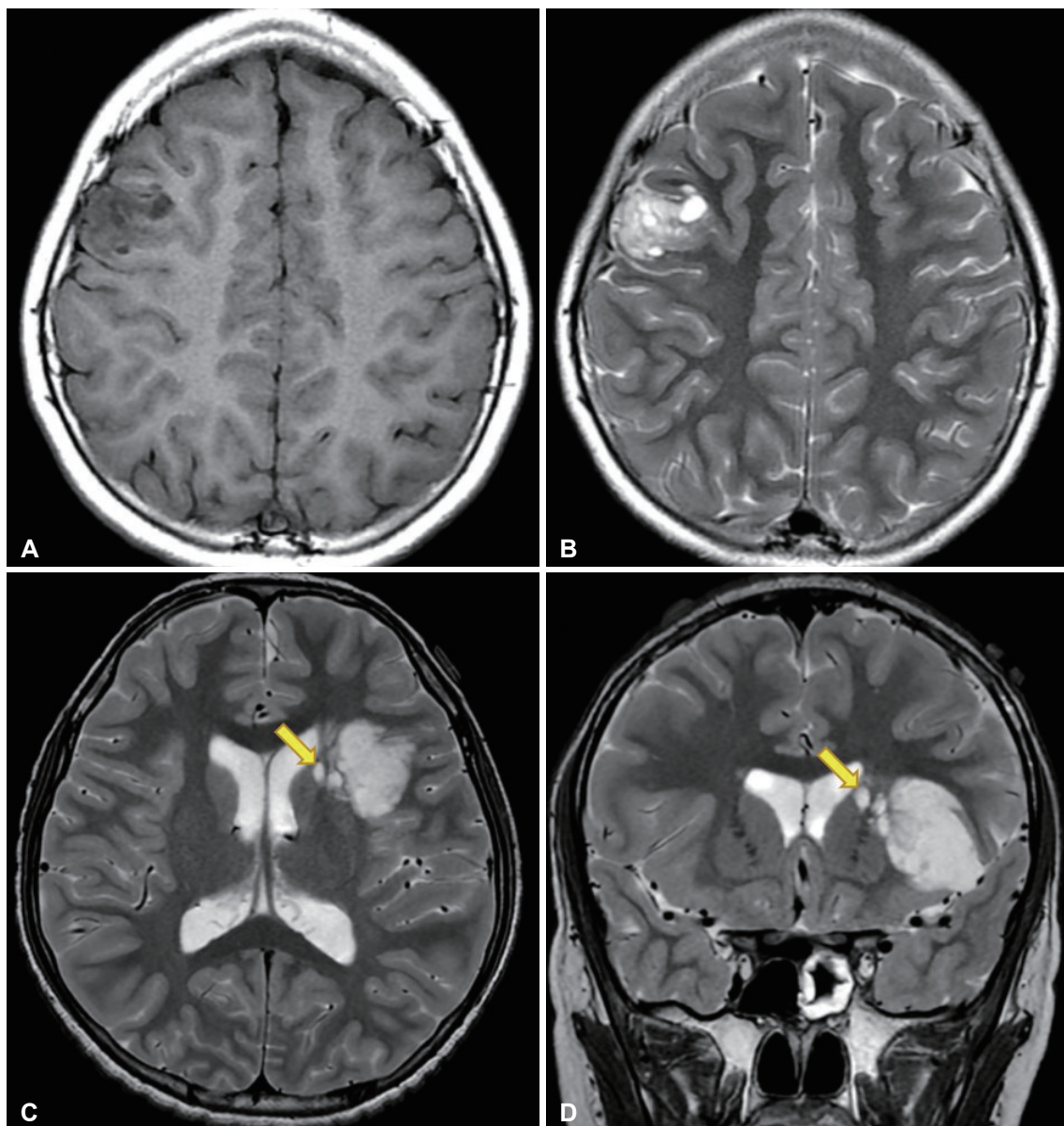


Fig. 1. Radiological features of dysembryoplastic neuroepithelial tumor. A and B: T1-weighted and T2-weighted magnetic resonance images of a 10-year-old girl who presented with recurrent focal seizures. A multinodular mass is located in the right middle frontal gyrus. C and D: T2-weighted axial and coronal images of a 12-year-old boy who came to the clinic for chronic epilepsy. A large tumor is situated in the insular and left inferior frontal lobes. There are several satellite lesions (yellow arrows) on the medial side of the mass, in the caudate nucleus and internal capsule.

in the mucoid matrix (mucin matrix) (Fig. 4).

DNET has several histological forms including simple, complex and diffuse/non-specific. Unlike the simple form with the typical histological features described above, the remaining forms have other histological attributes or lack the typical glioneuronal element. There are many controversies

between even experienced neuropathologists about the validity of the subtypes of DNET. In addition, DNETs share a lot of similar histological features with other tumors, especially gangliogliomas. These points are one of reasons for the introduction and upgrade of the term LEAT to 'low-grade, developmental, epilepsy-associated' brain tumors [8].

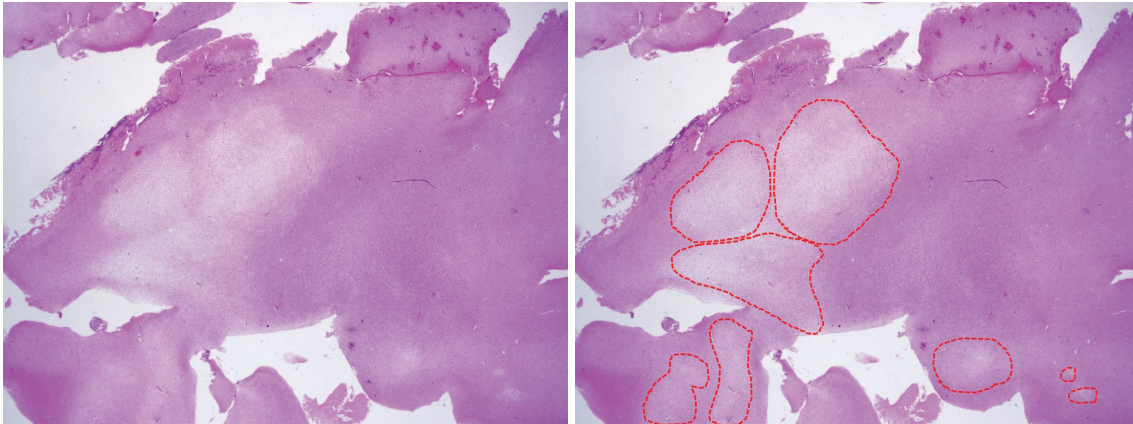


Fig. 2. Scan view of the dysembryoplastic neuroepithelial tumor (H&E staining; $\times 12.5$). The right side shows multinodular intracortical growth pattern (encircled by red dots).

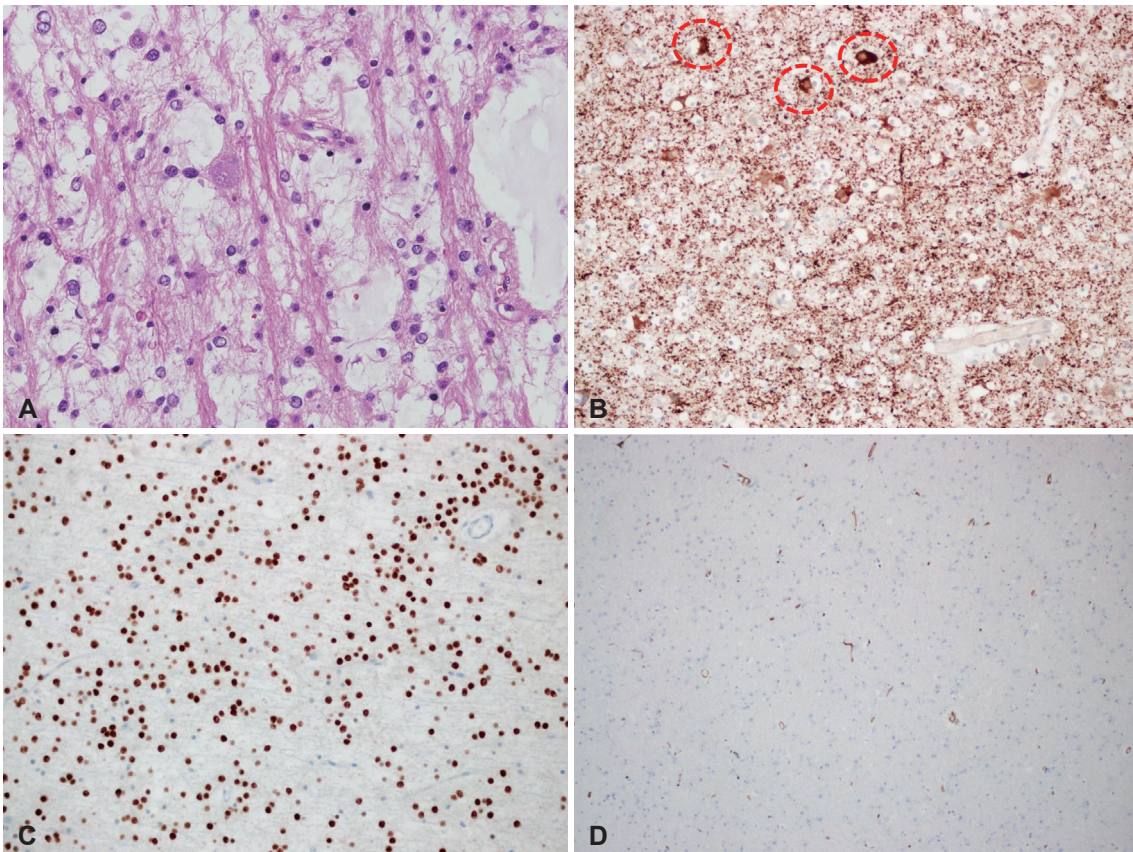


Fig. 3. Typical histological and immunohistochemical findings of dysembryoplastic neuroepithelial tumor. A: A high-power view (H&E staining; $\times 400$) shows glioneuronal elements (columns formed by bundles of axons lined by oligodendroglia-like cells [OLCs] and floating neurons in the multinodular growth pattern). B: Faint MAP2 expression in OLCs and marked expression in floating neurons (encircled by red dots) are noted (MAP2; $\times 200$). C: OLIG2 is expressed in the OLCs (OLIG2; $\times 200$). D: CD34 is negative in some cases. However, it can show variable expression (CD34; $\times 200$).

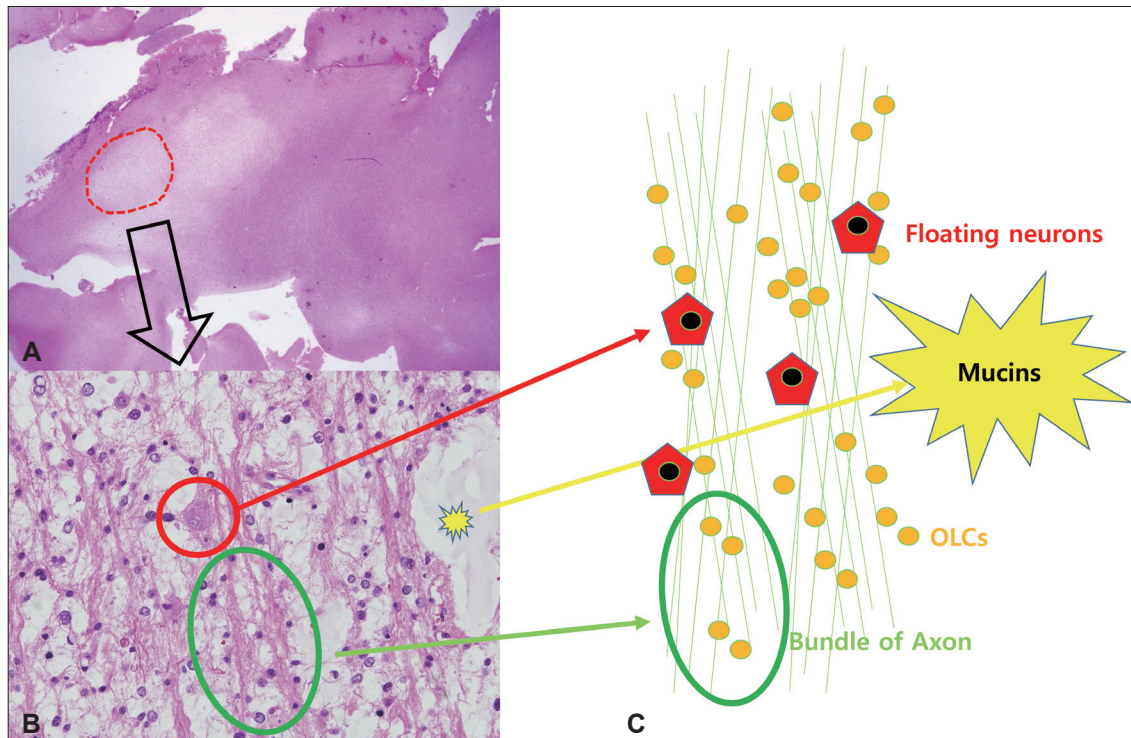


Fig. 4. Diagram of the typical histological features of a dysembryoplastic neuroepithelial tumor (DNET). A: Multinodular pattern. B: Glioneuronal elements with floating neurons. C: Diagram of the DNET architecture. OLCs, oligodendroglia-like cells.

Essential
Cortical glioneuronal tumour
AND
Presence of the specific glioneuronal element
AND (for unresolved lesions)
FGFR1 gene alteration (FGFR1 internal tandem duplication [ITD], fusion, missense mutation)
OR
Methylation profile of DNET
Desirable
Early-onset

Fig. 5. Diagnostic criteria for DNET (according to the 2021 WHO classification). DNET, dysembryoplastic neuroepithelial tumor. Adapted from Pietsch et al. *Central Nervous System Tumors* (5th ed); 2021. p. 123-6, with permission of International Agency for Research on Cancer [18].

OLCs in a DNET are neither mature glial cells nor neuronal cells. Therefore, OLCs show glial markers OLIG2 and PDGFRA but not GFAP. MAP2 expression is typically faint in OLCs. The floating neurons can express NeuN. DNETs show variable BRAF (V600E) and CD34 immunoreactivities which are more commonly expressed in gangliogliomas [18]. If there is expression of IDH (R132H), it is not DNET.

With new technologies and molecular knowledge, the above-mentioned term LEAT can be more subdivided and classified [18]. DNETs have FGFR1 alterations including internal tandem duplication, fusion, and missense mutation [19,20]. The tyrosine kinase domain of FGFR1 is particularly known to

be specific to DNET, although not exclusively. Recently, DNA methylation or transcriptional profiling has shown a distinct pattern of DNET, and they can be helpful for the diagnosis of unresolved lesions. The new 2021 WHO classification of brain tumors suggests the diagnostic criteria (Fig. 5) [18].

TREATMENT AND OUTCOME

DNET is a benign, low-grade glioma with an excellent prognosis. Although oncogenic mutations/duplication of the FGFR1 gene is documented in the majority of DNETs, the tumor is still regarded as a dysplastic neoplasm with limited, very low malignant potential. Some reports of the malignant transformation of DNET are anecdotal and the validity of the initial diagnosis should also be reconsidered [21,22]. Daumas-Duport et al. [2] emphasized the benign nature of the disease and reported that 44% of their patients had an incomplete resection but no clinical or radiological progression was observed. The clinical stability of DNET has long been regarded as true. However, evidence has accumulated that tumor progression is common after incomplete resection, and reoperations for seizure recurrence are also not uncommon [17,23]. A small but meaningful series from St. Jude Children's Research Hospital showed that tumor recurrence/progression occurred in 4 (36%) out of 11 patients [24].

Many studies have emphasized that complete resection is

crucial factor for tumor control and seizure outcome. Gross total resection was reported in 60%–90% of patients with DNETs [25]. However, complete resection of DNETs is often hampered by ill-defined borders in T2/FLAIR images, multi-gyral involvement, tumor location in the eloquent cortex, and the presence of satellite lesions. As mentioned above, satellite lesions are mainly located on the medial side of the tumor, sometimes near the ventricle, where the pyramidal tract or optic radiation can be encountered [17]. Some remnant satellite lesions did not grow during the follow-up, but we experienced slow but steady growth of a residual satellite lesion that led to overt tumor recurrence and reoperation.

After surgery, the reported seizure freedom rates were 60%–80% [25]. Even partial removal of the tumor can give sufficient seizure control to the patients, although temporarily. However, tumor progression is often heralded by a breakthrough seizure attack with or without antiseizure medications. Therefore, complete resection is of utmost importance for long-term seizure freedom [17]. The extent of resection beyond the DNET margin to achieve a good seizure outcome has been controversial. A wider cortisectomy beyond the tumor boundary is required for DNETs for adequate seizure control because DNETs are accompanied by a surrounding rim of the dysplastic cortex where the ictal onset zone is located [26]. Tailored resection is recommended based on invasive monitoring or electrocorticography data to delineate the ictal onset zone [27]. However, lesion (tumor)-directed surgery can also be applied to many patients because complete tumor resection yields favorable seizure control. The presence of satellite lesions is a poor prognostic factor for seizure control after surgery [17]. Whether this reflects the difficulty of complete resection and subsequent seizure recurrence, or the presence of widespread pathologic lesions beyond the observable satellite lesions is unclear but is an interesting question.

CONCLUSIONS

The distinctive clinical features and histological architectures make DNET a unique and important entity among a variety of brain tumors. DNETs are highly associated with chronic epilepsy, and molecular research revealed that DNETs are driven by one or a few oncogenic mutations. Recent studies reported higher recurrence rates of DNETs than previously thought. It is true that complete resection leads to long-term tumor control and seizure freedom, but there are still questions on how to achieve total resection for DNETs with indistinctive borders, with satellite lesions, or located in the eloquent cortex. Piecing together the histology, molecular biology and imaging studies will produce meaningful answers to the unsolved queries.


Ethics Statement


Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iDs

Ji Hoon Phi  <https://orcid.org/0000-0002-9603-5843>

Se Hoon Kim  <https://orcid.org/0000-0001-7516-7372>

Author Contributions

Conceptualization: Ji Hoon Phi, Se Hoon Kim. Writing—original draft: Ji Hoon Phi, Se Hoon Kim. Writing—review & editing: Ji Hoon Phi, Se Hoon Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This work was jointly supported by a grant from the Seoul National University Hospital (No. 26-2019-0010; to Phi JH) and a grant from the Creative-Pioneering Researchers Program through Seoul National University (800-20210571; to Phi JH).

REFERENCES

1. Feindel W. Osler vindicated: glioma of the leg center with Jacksonian epilepsy; removal and cure, with a 50-year follow-up. Historical vignette. *J Neurosurg* 2009;111:293-300.
2. Dumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER Jr, Vredenne C. Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. *Neurosurgery* 1988;23:545-56.
3. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol* 2021;23:1231-51.
4. Scheithauer BW. Development of the WHO classification of tumors of the central nervous system: a historical perspective. *Brain Pathol*;19: 551-64.
5. Dho YS, Jung KW, Ha J, Seo Y, Park CK, Won YJ, et al. An updated nationwide epidemiology of primary brain tumors in Republic of Korea, 2013. *Brain Tumor Res Treat* 2017;5:16-23.
6. Cho KT, Wang KC, Kim SK, Shin SH, Chi JG, Cho BK. Pediatric brain tumors: statistics of SNUH, Korea (1959-2000). *Childs Nerv Syst* 2002; 18:30-7.
7. Luyken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* 2003; 44:822-30.
8. Slegers RJ, Blumcke I. Low-grade developmental and epilepsy associated brain tumors: a critical update 2020. *Acta Neuropathol Commun* 2020;8:27.
9. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N Engl J Med* 2017;377:1648-1656.
10. Campos AR, Clusmann H, von Lehe M, Niehusmann P, Becker AJ, Schramm J, et al. Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. *Neuroradiology* 2009;51:433-43.
11. Dumas-Duport C. Dysembryoplastic neuroepithelial tumours. *Brain Pathol* 1993;3:283-95.
12. Sakuta R, Otsubo H, Nolan MA, Weiss SK, Hawkins C, Rutka JT, et al. Recurrent intractable seizures in children with cortical dysplasia adja-

- cent to dysembryoplastic neuroepithelial tumor. *J Child Neurol* 2005;20:377-84.
13. Chassoux F, Landré E, Mellerio C, Laschet J, Devaux B, Daumas-Duport C. Dysembryoplastic neuroepithelial tumors: epileptogenicity related to histologic subtypes. *Clin Neurophysiol* 2013;124:1068-78.
 14. Urbach H. MRI of long-term epilepsy-associated tumors. *Semin Ultrasound CT MR* 2008;29:40-6.
 15. Phi JH, Paeng JC, Lee HS, Wang KC, Cho BK, Lee JY, et al. Evaluation of focal cortical dysplasia and mixed neuronal and glial tumors in pediatric epilepsy patients using 18F-FDG and 11C-methionine pet. *J Nucl Med* 2010;51:728-34.
 16. Chassoux F, Rodrigo S, Mellerio C, Landré E, Miquel C, Turak B, et al. Dysembryoplastic neuroepithelial tumors: an MRI-based scheme for epilepsy surgery. *Neurology*. 2012;79:1699-707.
 17. Yang J, Kim SK, Kim KJ, Chae JH, Lim BC, Wang KC, et al. Satellite lesions of DNET: implications for seizure and tumor control after resection. *J Neurooncol* 2019;143:437-45.
 18. Pietsch T, Ellison D, Hirose T, Jacques T, Schüller U, Varlet P. Dysembryoplastic neuroepithelial tumour. In: WHO Classification of Tumours Editorial Board, editor. *Central Nervous System Tumors*. 5th ed. Lyon: International Agency for Research on Cancer; 2021. p. 123-6.
 19. Rivera B, Gayden T, Carrot-Zhang J, Nadaf J, Boshari T, Faury D, et al. Germline and somatic FGFR1 abnormalities in dysembryoplastic neuroepithelial tumors. *Acta Neuropathol* 2016;131:847-63.
 20. Qaddoumi I, Orisme W, Wen J, Santiago T, Gupta K, Dalton JD, et al. Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. *Acta Neuropathol* 2016;131:833-45.
 21. Chuang NA, Yoon JM, Newbury RO, Crawford JR. Glioblastoma multiforme arising from dysembryoplastic neuroepithelial tumor in a child in the absence of therapy. *J Pediatr Hematol Oncol* 2014;36:e536-9.
 22. Heiland DH, Staszewski O, Hirsch M, Masalha W, Franco P, Grauvogel J, et al. Malignant transformation of a dysembryoplastic neuroepithelial tumor (DNET) characterized by genome-wide methylation analysis. *J Neuropathol Exp Neurol* 2016;75:358-65.
 23. Maher CO, White JB, Scheithauer BW, Raffel C. Recurrence of dysembryoplastic neuroepithelial tumor following resection. *Pediatr Neurosurg* 2008;44:333-6.
 24. Qaddoumi I, Ellison DW, Morris EB, Broniscer A, Boop F, Merchant T, et al. Dysembryoplastic neuroepithelial tumors and cognitive outcome: cure at a price? *Cancer* 2010;116:5461-9.
 25. Bonney PA, Boettcher LB, Conner AK, Glenn CA, Briggs RG, Santucci JA, et al. Review of seizure outcomes after surgical resection of dysembryoplastic neuroepithelial tumors. *J Neurooncol* 2016;126:1-10.
 26. Giulioni M, Rubboli G, Marucci G, Martinoni M, Volpi L, Michelucci R, et al. Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomesial glioneuronal tumors: lesionectomy compared with tailored resection. *J Neurosurg* 2009;111:1275-82.
 27. Tandon N, Esquenazi Y. Resection strategies in tumoral epilepsy: is a lesionectomy enough? *Epilepsia* 2013;54 Suppl 9:72-8.