Case Report

Salvage gamma knife radiosurgery in the management of dysembryoplastic neuroepithelial tumors: Long-term outcome in a single-institution case series

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Abstract

Background: Dysembryoplastic neuroepithelial tumors (DNT/DNET) are rare epileptogenic tumors. Microsurgery remains the best treatment option, although case reports exist on the use of gamma knife radiosurgery (GKRS) in selected cases. We investigated the long-term outcome of GKRS-treated DNTs at our institution in the context of current diagnostic and treatment options.

Case Descriptions: We conducted a retrospective review of three consecutive adult patients (≥18 years) treated with salvage GKRS between 2002 and 2010 at Karolinska University Hospital, Stockholm, Sweden. The case series was supplemented by a review of current literature. A 20-year-old male underwent subtotal resection (STR) in 1997 and 2002 of DNT resulting in temporary control of intractable epilepsy despite antiepileptic drug treatment (AED). Long-term seizure control was obtained after GKRS of two separate residual DNT components along the surgical margin (2005 and 2010). A 27-year-old male undergoing gross total resection of the contrast-enhancing portion of a DNT (1999) resulted in temporary control of intractable epilepsy; lasting clinical control of seizures was achieved in 2002 after GKRS of a small, recurrent DNT component. A 28-year-old male underwent STR of DNT (1994 and 2004) resulting in temporary control of intractable epilepsy. Lasting seizure control was gained after GKRS of a residual tumor (2005).

Conclusion: GKRS as performed in our series was effective in terms of tumor and seizure control. No adverse radiation effects were recorded. Prospective studies are warranted to establish the role of GKRS in the treatment of DNTs.
INTRODUCTION

Dysembryoplastic neuroepithelial tumors (DNTs or DNETs) were first reported by Daumas–Duport et al. in 1988. These rare tumors usually develop within the supratentorial cortex, with a preferential location in the temporal lobe (62%) and the frontal lobe (31%), although more unusual locations such as the caudate nucleus, the cerebellum, the pons, the septum pellucidum, the thalamic region, and the ventricular walls have also been reported. The majority of patients are below 30 years of age at the time of diagnosis, with a peak incidence within the two first decades and male gender predominance with a 1.4:1 male-to-female ratio. DNTs are World Health Organization (WHO)-grade I tumors frequently associated with different grades of focal cortical dysplasia (FCD) and usually result in epilepsy, often drug-resistant and intractable. DNTs may account for 0.8–6.8% of all intractable epilepsy cases. 65% of tumors collected at the European Epilepsy Brain Bank are reported to be DNTs and gangliogliomas combined. Because of their complex nature, thorough histopathological analysis and advanced imaging is often necessary to achieve the correct diagnosis. Micosurgery is widely accepted as the only treatment option, although cases of postsurgical recurrence and malignant transformation have been reported. Adjunct conventional radiotherapy and systemic treatments are generally regarded as ineffective, although reports exist on the successful use of radiosurgery in selected cases. We present our experience with long-term outcome using gamma knife radiosurgery (GKRS) as salvage therapy in this patient category, together with a review of the current literature.

MATERIALS AND METHODS

With institutional approval, we conducted a retrospective review of three consecutive adult patients (≥18 years) treated with GKRS as salvage therapy between 2002 and 2010 at Karolinska University Hospital, Stockholm, Sweden. The data were collected from hospital medical records and our Leksell Gamma Plan system. The case series was supplemented by a review of the current literature. Reviewing the current literature published on PubMed, only two case reports on GKRS treating DNTs were found. 

CASE SUMMARIES

Case 1

A 20-year old male developed complex partial seizures by the age of 3 (April 1996). Magnetic resonance imaging (MRI) revealed a nonenhancing T2/FLAIR hyperintense, well-defined mass in the left frontal lobe. After a subtotal resection (STR) in 1997, histopathological analysis concluded that the tumor was a DNT of so-called simple form [Figure 1 and Table 1]. After surgery, the seizures diminished in intensity and frequency but did not cease. He remained on antiepileptic drug treatments (AEDs) with acceptable therapeutic effect. In 2001, the patient deteriorated with increased electroencephalography (EEG) verified complex partial seizures. A diagnostic MRI showed residual, nonenhancing tumor in the left frontal lobe, which led to a second STR in 2002 [Figure 2-a-c]. Histopathological analysis confirmed the tumor to be a DNT of simple form without malignant transformation. After the second surgery, the patient developed a right-sided spastic palsy, and in later years, signs of cognitive dysfunction, especially with respect to learning skills. The seizures gradually diminished in frequency and intensity, reaching an Engel Epilepsy Surgery Outcome Scale (ES) of 2 in 2003, although the patient remained on AEDs. Follow-up MRI in January 2003 [Figure 3a-c] showed nonenhancing residual tumor, without radiological signs of malignant transformation. A 11C-methionine positron emission tomography (MET-PET) performed in 2005 confirmed the absence of malignant transformation, with MET uptake lower than in the contralateral frontal cortex. A third surgical resection was deemed too high risk, while both fractionated radiotherapy with LINAC as well as chemotherapy were judged likely to be ineffective, with salvage radiosurgery by GKRS assessed to be the only viable treatment option. The patient was treated in 2005 with a peripheral prescription dose of 10 Gy at the 50% isodose line [Table 2]. Follow-up MRI revealed tumor regression, with no signs of adverse radiation effect (ARE); nevertheless, his epileptic status remained unchanged. Follow-up MRI in 2009 showed a 7-mm contrast-enhancing lesion/presumed recurrence in the surgical margin, but without relation to the previous GKRS target and no suspected malignant transformation. A new GKRS treatment was performed with a prescription dose of 12 Gy to the 50% isodose line (2010). Serial follow-up MRIs between 2010 and 2015 have shown no progress of residual tumor and no signs of ARE. Seizures gradually decreased in frequency and intensity after the second GKRS. Remaining on AEDs, the patient has been seizure-free (ES 1) since early 2013. Major clinical impairment at present consists of a minor right foot palsy, while a neuropsychological assessment performed in April 2014 showed no major...
cognitive impairment. His overall quality of life remains good.

**Case 2**
A 27-year-old male had developed intermittent numbness and right-sided neuralgia with upper limb predominance at the age of 11 (1999). A diagnostic MRI demonstrated a 3 cm mass with asymmetrical, nodular, and curvilinear contrast enhancement located in the left postcentral gyrus with an appearance deemed at the time consistent with a low-grade glial tumor. The EEG revealed an epileptic focus in the left frontal-temporal regions. AEDs proved ineffective for seizure control. A functional MRI located the hand motor cortex anterior to the tumor. The patient underwent gross total resection (GTR) in 1999. The initial microscopic evaluation could not differentiate between pilocytic astrocytoma and DNT. Further re-examination based on immunohistochemistry and molecular analyses (MA) proved the lesion to be a complicated type of DNT, displaying mosaic-like patterns composed of complex structures together with nonspecific elements (low-grade glioma-like structures, see Figure 4 and Table 1).

The seizures ceased almost immediately after surgery (ES 1). Postsurgical MRI demonstrated a nonenhancing residual tumor. Two years after surgery, the sensory seizures recurred. A follow-up MRI showed a new

**Table 1: Summary of immunohistochemical (IHC) and molecular marker (MM) analysis**

|          | Case 1 | Case 2                  | Case 3         |
|----------|--------|-------------------------|----------------|
| Type     | Simple | Complex + Non-specific  | Complex        |
| IHC      |        |                         |                |
| Atrx     | Positive | Positive            | NA             |
| AT       | No      | No                      | NA             |
| GFAP     | Negative | Negative             | Negative       |
| Oligo    | Positive | Positive            | NA             |
| IDH1/Mutation | Negative/No | Negative/No | NA             |
| MaP 2    | Positive | Positive            | NA             |
| S-100    | Positive | Positive            | Positive       |
| Oligo 2  | Positive | Positive            | NA             |
| Neu N and NSE | In neuronal cells | In neuronal cells | NA             |
| CD34     | Negative | Expressed in some tumour cells | NA             |
| Ki-67 Synaptoad | Low (<1%) | Low (1%)         | Low (<1%)     |
| MA       |         | NA                      | NA             |
| PS3 mutation | No      | No                      | NA             |
| BRAF mutation | No      | No                      | NA             |
| IDH1 or IDH2 mutation | No      | No                      | NA             |
| Deletion in 1p 19q | No      | No                      | NA             |

NA: Not available

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**Figure 1:** Top left: HE (Magnification x200); DNT simple form with oligodendroglial-like cells. Top right: GFAP (Magnification x400); immunostaining GFAP is negative in tumour cells. Bottom left: S100 (Magnification x400); immunostaining S100 is positive in tumour cells. Bottom right: Ki-67 (Magnification x600); immunostaining Ki-67 proliferative index is low <1%.

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**Figure 2:** (a-c) Axial, coronal and sagittal 3D T1 FFE MR images of the lesion for preoperative planning in 2002, showing the lesion’s inferior extension in the white matter to within a few millimetres of the superolateral edge of the left lateral ventricle.

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**Figure 3:** (a-c) Postoperative axial, coronal and sagittal SET1 (above) and axial T2 (below) MR images in January 2003 demonstrate a small amount of residual DNT tissue (thin graphic circle) at the inferior resection margin in the white matter extending to the left lateral ventricle.
contrast-enhancing lesion within the surgical margins. Open surgery was assessed to be highly hazardous due to the tumor’s close relation to adjacent motor fibers. GKRS was deemed to be the best treatment alternative. The patient was treated in 2002 with a peripheral dose of 12 Gy at the 50% isodose line [Figure 5a-c and Table 2]. The seizures ceased shortly after treatment (ES 1) and the patient remained free from AEDs and seizures thereafter. Serial follow-up MRIs between 2004 and 2006 showed a gradual decrease in tumor volume and contrast enhancement. There have been no signs of recurrence or radiation necrosis/edema on subsequent annual MRI from 2008 to 2013 [Figure 6a and b]. With the last clinical follow-up in 2015, the patient remained AED and seizure-free (ES 1) and showed no neurological impairment.

Case 3
A 28-year-old male had developed complex partial seizures at the age of 6. MRI (without IV contrast) revealed a T1 hypointense/T2 hyperintense, well-delineated, possibly multilobular mass located in the inferomedial aspect of the right temporal lobe including hippocampus [Figure 7a and b]. Contrast-enhanced images were not available at the time of writing of this paper; as such it remains unclear whether or not the tumor was originally contrast-enhancing.

In this case, we could not find evidence of prior diagnostic EEG. The patient underwent STR in 1994 and, despite the subtotal nature of the resection, seizures ceased shortly after (ES 1) and AEDs were discontinued. The histopathological analysis revealed a DNT of complex form with specific glioneuronal elements and associated FCD [Figure 8 and Table 1].

The patient remained stable until 2001, when a follow-up MRI demonstrated a suspect nodular contrast enhancement in the region of the residual tumor located in the right hippocampus and posterior aspect of the medial temporal lobe [Figure 9a-c]. A follow-up MRI in 2003 showed clear signs of local contrast-enhancing tumor progression. The patient underwent STR in early 2004. No pathology report from the second operation is available to us. Because seizures recurred prior to surgery, AEDs were restarted. The seizures ceased after surgery, but the patient was kept on prophylactic AEDs. Follow-up MRI the same year (2004) and subsequent follow-up examination the year after showed gradual progression of the contrast-enhancing residual tumor. The lesion was located in the posteromedial aspect of the right temporal lobe, including the hippocampus and parahippocampal gyrus, bulging into the quadrigeminal plate cistern with subtle mass effect on the midbrain. Volumetric studies assessed the tumor to be 2 cm$^3$ (18 × 16 × 15 mm). Despite the above, the patient was still seizure-free (ES 1). Because open surgery was not an option due to the tumor location, the patient underwent GKRS in 2005. The lesion was treated with a peripheral dose of 12 Gy at the 50% isodose [Figure 10a-c and Table 2]. Serial MRI imaging between 2006 and 2013 showed a gradual decrease in tumor size, ultimately without any signs of ARE [Figure 11a-d]. No signs of neurocognitive dysfunction have been described. The patient remains seizure-free and leads a normal and active life. Mainly due to the patient’s line of work, he has been kept on prophylactic AEDs.

DISCUSSION
As illustrated by our case series, DNTs might have a more complex and complicated evolution than once originally thought. The diagnostic workup of DNTs is multidisciplinary and often quite demanding. The simpler forms (described below) may be easier to diagnose due to their more distinctive histopathologic traits and underlying imaging. Even in these cases, misdiagnoses may still occur, particularly with limited histologic material. Although microsurgery is crucial in the management of DNTs, it is not always feasible and/or...
successful. We will discuss the impact the diagnostics and available treatment modalities (surgical and nonsurgical) have on DNTs (in general as well as in our case series) and their long-term clinical repercussions.

**Histopathology**

DNTs are composed of glioneuronal elements (columns of axons lined by uniform oligodendroglia-like cells) with interventional floating cortical neurons in mucin pools. Rare mitotic figures are also commonly found. The heterogeneous appearance of these tumors is due to the presence of astrocytic, oligodendrocytic, and neuronal components. Histologically, they are classified as simple form (specific glioneuronal elements consisting of small/round monotonous cells, so-called oligodendroglia-like cells), complex form (presence of glial nodules with intermodular-specific glioneuronal elements and FCD/adjacent cortical dysplasia), and nonspecific form (unspecified glioneuronal elements, low-grade glioma-like features). As described earlier, our study included all the above types. As illustrated in Table 1, DNTs’ immunohistochemical fingerprint is generally complex. The Ki-67 labeling index is usually low, below 1–2%. As illustrated in Table 1, DNTs’ immunohistochemical fingerprint is generally complex. The Ki-67 labeling index is usually low, below 1–2%. As illustrated in Table 1, DNTs’ immunohistochemical fingerprint is generally complex. The Ki-67 labeling index is usually low, below 1–2%.

Specific glioneuronal elements may deploy a number of neuronal markers, including synaptophysin, neurofilament proteins, NeuN, neuron-specific enolase, and MAP2. The majority of underlying oligodendroglia-like cells are positive for S-100 protein and Oligo-2 (as in Cases 1 and 2), but generally negative (as in all our cases) for glial fibrillary acidic protein (GFAP). Nevertheless, glial nodules themselves may contain variable numbers of GFAP-positive astrocytes. As the chromatin remodeler (transcriptional regulator) ATRX is frequently expressed in tumor cells, lacking mutation in the alpha thalassemia/mental retardation syndrome X-linked gene (Cases 1 and 2, Table 1). DNTs, particularly nonspecific types, might prove positive for MAP2 as it was the case for patients 1 and 2. Complementary MA proved valuable to differentiate our DNT cases from low-grade gliomas (such as pilocytic astrocytoma, diffuse astrocytoma, or oligodendroglioma), particularly in our second case. DNT’s molecular profile shows no mutations in IDH1/IDH2; no 1p/19q-deletions or TP53 gene mutations have thus far been reported.
matching the MA findings in our series, as illustrated in Table 1.

BRAF analysis is also included in MA profiling. A study by Chappé et al.\[10\] including 96 children with benign cortical glioneuronal tumors identified BRAF\(^{V600E}\) mutation and expression on 30% of all DNTs, including specific and nonspecific tumors. Interestingly, Suh\[40\] noted that BRAF\(^{V600E}\) mutations were more frequent in extra-temporal locations and more common in classical DNTs than in the nonspecific type. BRAF\(^{V600E}\) immunostaining is strongly positive in glial nodules and usually negative in the floating neurons.\[40\] In our cases, BRAF mutation did not coexist with other markers.

The expression of CD34 in DNTs has been variously reported.\[4,40,44\] Once again, Suh (2015) observed that CD34 expression was more frequently observed in nonspecific types. The author also pointed out the importance of combining CD34 and MAP2 – analysis to achieve best differential diagnosis between DNTs and other diagnostically challenging (DNT-mimicking) tumors.\[40\] Other authors seem to share this conclusion.\[3\] No strong prognostic correlations have yet been established with the above markers. Nevertheless, Thom et al.\[44\] (2011) suggested a trend of positive seizure-free outcome with CD34-positive tumors. Other authors seem to share this conclusion.\[3\] No strong prognostic correlations have yet been established with the above markers. Nevertheless, Thom et al.\[44\] (2011) suggested a trend of positive seizure-free outcome with CD34-positive tumors. In our cases, CD34 expression was sporadically found in Case 2 (complex/nonspecific form, MAP2 positive) bringing some support to the suggestions above.

**Imaging**

The diagnostic, pre- and postsurgical follow-up neuroimaging is mainly based on MRI. DNTs are classified as WHO Grade I under neuronal and mixed neuronal glial tumors under tumors of the central nervous system.\[24\] They typically present as well delineated and cortically based with a pseudocystic or multicystic appearance. T1-weighted sequences demonstrate low-signal intensity and T2-weighted sequences high-signal intensity. Contrast enhancement is seen in approximately 20%.\[40\] Noncontrast computed tomography scans reveal hypoattenuating lesions with cystic appearance in half of the cases; calcifications may be present in 15–36%.\[6\] Minimal mass effect and absence of perilesional edema are typical features. Expansion/scalloping of the overlying skull is seen in 20%.\[40\] As pointed out by Chassoux and Daumas-Duport,\[49\] MRI characteristics closely correlate with DNTs microscopic differentiation, the combination of which aids in classifying DNTs as type 1 (low signal on T1-weighted images with cystic/polycystic formations), type 2 (heterogeneous signal, nodular-structured), and type 3 (dysplastic-like, iso- to low signal on T1, poor delineation, grey-white matter blurring). Simple or complex DNTs correspond to type 1 whereas nonspecific DNTs are either type 2 or type 3.\[30,49\] In our material, the first and third cases correspond to type 1 whereas the second case corresponds to type 2. MR spectroscopy in 22 patients with pathologically proven DNT presented significantly higher myoinositol to creatine ratios compared to normal brain parenchyma.\[6\] However, low-grade astrocytomas, the major differential diagnosis for DNT, may also demonstrate elevated myoinositol on MR spectroscopy. With MR perfusion, lower cerebral blood volume values and with diffusion higher apparent diffusion coefficient values are seen in DNT compared to normal brain parenchyma.\[6\] Presurgical investigation may include \(^{99m}\)Tc-HMPAO ictal single-photon emission computed tomography (SPECT) imaging co-registered to MRI (SISCOM) to better delineate the epileptogenic focus and the presence and the extent of associated cortical dysplasia.\[28,30\] and often correlates to a hypometabolic region on interictal \(^{18}\)F-FDG PET. Amino acid MET PET has been described to have a rather high specificity (90%) and sensitivity (89%) for DNTs.\[36\]
with lower uptake ratios for DNT compared to other epileptogenic brain neoplasms, which is also consistent with the findings in our first case.

**Neurophysiology**

Focal (dyscognitive) seizures with impairment of consciousness (formerly complex partial seizures) are the main epileptic manifestation of DNT; followed by generalized tonic-clonic, focal motor (formerly simple partial seizures), and focal seizures evolving to bilateral convulsive seizures (formerly secondarily generalized tonic-clonic seizures). Resection alone (including lesionectomy, extended lesionectomy, lobectomy) is widely regarded as the most effective curative option, particularly in early stages.[8,25,40] The aim of surgery is to improve quality of life by achieving seizure freedom as well as to avoid future complications.[18,21] In clinical terms, epilepsy surgery outcome is usually graphed using the Engel (class I–IV) and ILAE (class 1–6) classifications.[15,29,37,47] Careful preoperative assessment of epileptic activity by means of video-EEG, ictal SPECT, FDG PET, interictal magnetoencephalography (MEG), functional and structural MRI might prove useful to successfully achieve postsurgical seizure freedom. Examinations such as intralesional stereo-EEG and subdural electrocorticography recordings also may provide more precise information regarding underlying epileptic activity.[8,25,32,49] Presurgical focal cortical function is often evaluated using noninvasive techniques such as navigated transcranial magnetic stimulation or MEG,[41,46] especially in eloquent areas.[49] However, it must be noted that while GTR is associated with positive seizure outcome, the addition of invasive neurophysiology has not shown any improvements in terms of postsurgical outcome.[18,19] In our series, we have obtained seizure-freedom for all three cases after radiosurgery.

**Microsurgery**

A quantitative and comprehensive systematic literature review of seizure outcome after surgical resection of epileptogenic glioneuronal tumors (including a total of 910 patients from 39 studies) by Englot et al.[18] concluded that early operative intervention and gross-total aimed resections were crucial factors in achieving seizure freedom, hence improving quality-of-life. Chassoux and Daumas-Duport (publ 2013) also observed that the main prognostic factors for seizure-free outcome (83% of 78 studied cases) were complete and early tumor and epileptogenic-region removal, short epilepsy duration and absence of cortico-subcortical damage. The authors even suggested that surgical resection might be more restrictive for MRI type 1 tumors but should be more extensive/radical in other MRI types, especially in type 3.[49] Chang et al. reviewed 50 cases who underwent DNT surgery between 1990 and 2006: seizure freedom was predicted by complete or extended resection as well as extratemporal topography. The group suggested the relevance of using intraoperative electrocorticography to map possible extralesional interictal activity, which would subsequently lead to extended lesionectomy or lobectomy. Better outcome was achieved when extralesional spiking foci were detected (94% seizure-free) compared with when they were absent (43% seizure-free).[8] A review on long-term epilepsy associated tumors (including glioneuronal tumors) by Giulioni et al. (publ 2014) drew

### Table 2: Summary of clinical and radiological outcome

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| **MRI Type** | 1 | 2 | 1 |
| **SPECT** | No | No | No |
| **FDG-PET** | No | No | No |
| **MET-PET** | Yes | No | No |
| **Age at onset** | 3 (1994) | 11 (1999) | 6 (1994) |
| **EP type at onset** | Complex partial seizures | Simple partial sensory seizures | Complex partial seizures |
| **Surgery type** | STR (1997), STR (2002) | GTR (1999) | STR (1994), STR (2004) |
| **DNT type** | Simple (1997), Simple/no malignancy (2002) | Complex (1999) | Complex (1994), No pathology report available (2004) |
| **Engel Score (EP post surgery)** | 2 (after op 1997), 2 (2003) | 1, recurrence 2002 | 1 |
| **GKRS** | 10 Gy-50% (2005), 12Gy-50% (2010) | 12 Gy-50% (2002), 12 Gy-50% (2005) | |
| **MRI final** | No progress, residual tumor or ARE (2015) | No progress, residual tumor or ARE (2015) | No progress, residual tumor or ARE (2013) |
| **Engel Score final** | 1 (since early 2013) | 1 | 1 |
| **Neuro final** | Minor right foot palsy | No neurological deficits | No neurological deficits |
| **Cognition final** | No major impairment | No major impairment | No major impairment |
| **Overall life quality final** | Good | Good | Good |
| **Ongoing AED by latest MRI** | Yes | No | Yes |
similar conclusions: early tailored epilepsy surgery aims to obtain seizure freedom and avoid the potential side effects of prolonged AED as well as the risk for local recurrence and possible malignant transformation. The latter is even more concrete in the case of DNTs with atypical traits. Adjuvant conventional radiotherapy and systemic treatments are still regarded as ineffective. Some groups have even hypothesized a possible relation between adjunctive treatment (radiation and chemotherapy) and secondary malignant transformation.

A recent published review by Bonney et al. (publ 2015) covering 29 articles on seizure outcome after varyingly performed DNT surgery showed a median postsurgery seizure-free rate of 86% (though one study reported < 60% seizure freedom rate). Four studies concluded seizure freedom to be associated with more extensive surgeries. The number of seizure-free patients who discontinued AEDs varied widely. Interestingly, some groups have reported minor outcome differences between GTR and STR in terms of tumor-free survival time and seizure control. Consales et al. made an ENGEL class-based analysis on seizure outcomes related to lesionectomy in 22 patients with epileptogenic glioneuronal tumors (publ 2013). GTR was achieved in 15 patients (68.2%). At the last follow-up (mean 4.7 years), 90.9% of patients were ES 1 and 9.1% were ES 3. Six of seven (85.7%) patients who underwent STR were assessed as ES 1. There was no statistical difference between seizure outcome and tumor type, location (temporal vs. nontemporal), and surgical extension. In our series, Case 2 underwent single GTR while Cases 1 and 3 were operated twice, achieving STR at each procedure. However, in accordance with the above-mentioned reports, both Cases 2 and 3 were seizure-free (ES 1) after microsurgery, though only temporarily in Case 2.

However, as pointed out previously, cases of local recurrence and histological evolution/malignant transformation of DNT have been reported; although, the latter seems to be associated with STR. A few cases of recurrence (with or without malignant transformation/histological evolution) after GTR have also been illustrated. If GTR is not possible) without adjuvant therapy.

Radiosurgery

The role of radiosurgery in DNT cases remains unclear, perhaps because of unreported cases. Kwon et al. (2006) reported a case of a nonresectable epileptogenic DNT lesion in the right parahippocampal gyrus treated with GKRS. The target volume (described as tumor volume + margins = 6.9 mm³) was covered by 25 Gy at the 50% isodose line. The corresponding tumor volume was 1.5 mm³, and over 95% of the tumor was covered by 30 Gy. The seizures gradually decreased after radiosurgery. Seizure freedom and neuropsychological improvement were achieved 2 years after treatment. The tumor decreased dramatically; radiation induced edema was noticed 6 months after radiosurgery, but subsequently yielded without corticosteroid treatment. Sayuthi et al. (2006) reported a case of a temporal lobe DNT treated with surgery, postsurgical fractionated radiotherapy, and AED resulting in seizure freedom for a period of 6 months. Because of renewed epileptic activity with a rate of 10–15 attacks a month, left vagus nerve stimulation and AED were initiated; which resulted in decreasing the seizure frequency to 3–5 simple partial attacks a month. MRI 12 years after surgery showed enlargement of the residual tumor. Because the recurrence was located in a high risk/eloquent area, the idea of open surgery was soon abandoned. Radiosurgery was applied to the tumor with satisfactory results. By the time the paper was submitted, follow-up imaging showed no tumor progression and the ES was 2. The authors did not mention the type of radiation device used (Gamma knife or accelerator-based instrument) or the prescription dose applied. It is unclear if tumor growth (prior to radiosurgery) had a negative impact on ES.

Although still a vivid subject of discussion, some centers currently use epilepsy radiosurgery to treat recurrent/
residual mesial temporal lobe epilepsy with various results.\textsuperscript{13,14,15,16} Different papers have also described the role of radiosurgery in the management of low-grade gliomas\textsuperscript{1,16,17,27,28} and less common lesions including gangliogliomas.\textsuperscript{3,9,10} The above might suggest the inclusion of salvage GKRS in the management of DNTs, particularly in cases of STR and in tumors proven to be of more complicated nature/unstable evolution.

Finally, the management of malignant transformation of DNT is rather complex and might, depending on the case, require a more conventional management, including surgery, chemotherapy, and radiation.\textsuperscript{9,25}

**CONCLUSION**

Traditionally, DNTs have been considered to be epileptogenic glioneuronal tumors with rather stable evolution after open surgery; however, recent publications are showing otherwise. In this material, GKRS resulted in long-lasting seizure-freedom (ES 1) in all cases, with two of them (Cases 1 and 3) remaining on prophylactic AED, with no observed GKRS-associated neurological deficits or cognitive dysfunction. Follow-up MRI on a regular basis has demonstrated no progression of the lesion and no ARE. In our experience, delivering 10–12 Gy to 50% isodose surface seems to be an efficient and safe strategy.

DNTs might prove difficult to diagnose; a comprehensive neurophysiological assessment, thorough neuroimaging, and complete histopathologic analysis should be included in the identification of DNTs. Surgery remains the treatment of choice and is usually performed to achieve seizure control; early surgical intervention appears to be associated with better Engel class outcome. Some cases of recurrence (with and without malignant transformation) have been reported in recent years. Despite access to advanced diagnostic technology and modern surgical tools, GTR is not always possible. The above may suggest the use of GKRS as a complementary, adjunctive treatment to STR (regardless of postsurgical Engel score outcome) and as salvage modality in cases of DNT recurrence (with or without refractory seizures) where reoperation (STR/GTR) is deemed unachievable or contraindicated. Prospective studies are warranted to establish the role of GKRS in the treatment of DNTs.

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**Conflicts of interest**

There are no conflicts of interest.

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