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Low-dose radiosurgery or hypofractionated stereotactic radiotherapy as treatment option in refractory epilepsy due to epileptogenic lesions in eloquent areas – Preliminary report of feasibility and safety

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ABSTRACT

Purpose: The eradication of epileptogenic lesions (e.g. focal cortical dysplasia) can be used for treatment of drug-resistant focal epilepsy, but in highly eloquent cortex areas it can also lead to a permanent neurological deficit. In such cases the neuromodulation effect of low-dose high-precision irradiation of circumscribed lesions may represent an alternative therapy.
Method: A total of 10 patients with eloquent localized lesions causing pharmacoresistant focal epilepsy were prospectively identified. After informed consent, six patients agreed and were treated with risk adapted low-dose radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (hfSRT). Comprehensive data concerning treatment modalities and outcome after short-term follow up (mean = 16.3 months) were prospectively collected and evaluated.
Results: From the six patients, two patients were treated with hfSRT (marginal dose 36 Gy) and four with SRS (marginal dose 13 Gy). Clinical target volume (CTV) ranged from 0.70 ccm to 4.32 ccm. The short-term follow-up ranged from 6 to 27 months. There were no side effects or neurological deficits after treatment. At last available follow-up two patients were seizure-free, one of them being off antiepileptic drugs. The seizure frequency improved in one and remained unchanged in three patients.
Conclusion: Treatment of eloquent localized epileptogenic lesions by SRS and hfSRT showed no adverse events and an acceptable seizure outcome in this small prospective patient series. The relatively short-term follow-up comprises one of the study's drawbacks and therefore a longer follow-up should be awaited in order to evaluate the neuromodulation effect of the treatment. These preliminary results may however justify the initiation of a larger prospective trial investigating whether focused low-dose stereotactic irradiation could be an option for lesions in eloquent brain areas.

1. Introduction

Epilepsy is one of the most common neurological disorders affecting around 50 million people worldwide [1]. About 30% of the epilepsies are resistant to medical treatment and are associated with devastating socioeconomic consequences, diminished quality of life and higher morbidity and mortality rate [2,3]. Although mesial temporal lobe epilepsy (MTLE) is one of the most common forms of pharmacoresistant epilepsy, in approximately one third of the cases seizures arise extratemporally (ETLE, extratemporal lobe epilepsy) [4]. Treatment of ETLE is difficult, which is reflected by

Abbreviations: SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; PTV, planning target volume; CTV, clinical target volume; OARs, organs at risk; LINAC, linear accelerator; MRI, magnetic resonance imaging; RT, radiotherapy; Gy, gray; EEG, electroencephalography; SSW, slow-sharp-wave; FCD, focal cortical dysplasia; ETLE, extratemporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; MAP, morphometric analysis program.

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the relatively low seizure-free rates, rarely being higher than 50% [5]. Besides difficulties in exact localization of the epileptogenic focus, one of the greatest challenges is encountered when the epileptogenic lesion involves eloquent cortex areas. In such cases surgery may be performed but the risk for permanent neurological deficit (up to 25% [6]) should be taken into consideration.

Stereotactic radiosurgery (SRS) or hypofractionated/fractionated stereotactic radiotherapy (hf/fSRT) may represent an alternative and safe treatment option for epileptogenic lesions involving highly eloquent cortex areas like motor cortex, primary visual cortex or insular cortex. Beside their noninvasive nature, both SRS and SRT can be stereotactically applied, thus making them a preferred option for lesions nearby or within eloquent cortex areas. The idea of attempting to eliminate epileptogenic foci by stereotactic means is not novel; it has been pursued since the 1970s [7] and recently a number of different ablation techniques have been used in the treatment of pharmacoresistant epilepsy [8,9]. Although the initial results of stereotactic treatment were heterogeneous and not completely convincing, the better understanding of seizure generation and the concept of the epileptogenic zone have lead to a more successful usage of these modalities [10], so that radiosurgery for e.g. epileptogenic hamartomas and for MTLE have emerged as valuable alternative treatment options [11–13].

Modern radiosurgical techniques include, in addition to the classical SRS (single-stage high-precision radiation), the so-called hypofractionated or fractionated stereotactic high precision radiotherapy (SRT). Fractionated SRT is an increasingly used method of radiotherapy treatment for many benign and malignant brain lesions and has been already carried out for treatment of drug-resistant focal epilepsy, but conclusive evidence is still lacking [14–16]. Although the use of SRS and SRT has been mainly used to treat MTLE or hypothalamic hamartomas, there are other highly epileptogenic lesions, which could benefit from these treatment modalities as well. Such lesions comprise focal cortical dysplasia (FCD), which are characterized by an erroneous cortical architecture and abnormal arrangement of the nerve cells. Currently, FCDs are classified in three types according to neuropathological findings with different electroclinical course, magnetic resonance imaging (MRI) findings and postsurgical outcome [17]. FCD type IIb is the most commonly diagnosed group showing a characteristic tail between the cortex and the lateral ventricles. A complete resection of the cortical malformation is the most important prognostic factor for postoperative seizure freedom. However, removal of the tail is not relevant for outcome, but to spare it reduces the potential surgical risks [18]. The complete microsurgical resection of FCD can be difficult especially in deep-seated and/or eloquent located FCD. In these challenging cases, the complete resection could only be performed with subsequent significant and permanent neurological deficits.

In summary, stereotactic irradiation has already been performed for treatment of pharmacoresistant epilepsies and showed some promising results with an acceptable and less overall side effect profile than microsurgery, but this form of therapy has only rarely been studied in FCD. We postulated that focal pharmacoresistant epilepsies due to FCD are also well treatable with stereotactic irradiation. Here, we investigated the safety and efficacy of a low-dose high-precision irradiation in patients with pharmacoresistant focal epilepsies mainly due to FCD. Our results indicate that low dose irradiation of circumscribed epileptogenic lesions may lead to lasting neuromodulatory effects with an acceptable seizure control, suggesting that low-dose high precision irradiation may be a feasible and efficacious alternative treatment option in pharmacoresistant focal epilepsies arising from highly eloquent areas with possibly fewer side effects as compared to standard microsurgical resection.

2. Methods

2.1. Cohort description and epilepsy diagnostic

This is a single-center prospective study.
Inclusion criteria were:

- Patients >18 years of age
- Pharmacoresistant epilepsy
- MRI suspect for FCD
- Congruent results in the presurgical diagnostic
- Eloquent localization

Exclusion criteria were:

- Suspected FCD without drug resistance
- Non eloquent localization
- Bilateral epilepsy
- Pregnancy

From January 2013 until December 2014 a total of 10 patients were prospectively identified with drug-resistant focal epilepsy which met the eligibility criteria, six patients agreed and were included in the study. All patients presented with an eloquent localized epileptogenic lesion mainly suggestive for FCD. There were four male and two female patients. Further patients' characteristics are presented in Table 1.

All patients underwent presurgical evaluation using a standard protocol [19]. For each patient, 3.0 Tesla MRI, ictal and interictal scalp video-EEG and neuropsychological testing were routinely performed. If necessary additional investigations including ictal and interictal SPECT/PET imaging and MRI-postprocessing methods (MAP, Morphometric Analysis Program) were performed.

In four patients a second-stage invasive diagnostic was needed to confirm the putative epileptogenic lesions, which included the implantation of depth electrodes (sEEG, stereo-EEG) in three and placement of subdural electrodes in one patient. Additional stereotactic biopsy was performed in 2 patients (Tables 2 and 3). Every patient was evaluated by at least one experienced epileptologist. All patients underwent video-EEG monitoring at the Department of Epileptology for seizure recordings. Antiepileptic drugs were usually tapered off to facilitate seizure onset. The correct localization of the depth electrodes was confirmed with MRI [20].

After the presurgical evaluation and confirmation of the epileptogenic focus a surgical intervention was discussed with all patients. Due to eloquent localization of the epileptogenic lesions, consequently leading to a high risk for permanent neurological deficit, all patients were offered a stereotactic irradiation as an alternative treatment option after interdisciplinary discussion. For all patients informed consent was obtained according to the Declaration of Helsinki and the therapy was offered as an individualized treatment.

2.2. Treatment protocol

The Clinical Target Volume (CTV) was defined as the visible epileptogenic lesion using magnetic resonance imaging (MRI) alone or as the zone suggestive for FCD combining MRI, Morphometric Analysis Program (MAP) and active electrode contacts of the sEEG. In FCD Type IIb the typical so-called tail was not included, which also corresponds to an alternative microsurgical procedure. For radiosurgery the Planning Target Volume (PTV) was identical with the CTV without any additional safety margin. In case of fractionated stereotactic irradiation, a safety margin of 1 mm was placed around the CTV. The decision