Seizure outcomes in people with drug-resistant focal epilepsy evaluated for surgery but do not proceed

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INTRODUCTION

Neurosurgery is considered the treatment of choice for suitable people with drug-resistant focal epilepsy who fulfil feasibility criteria. (1, 2) Many of those who complete presurgical evaluation, however, do not proceed to surgery. (3-5) Common reasons for this include an inability to adequately localize the epileptogenic zone, multifocal epilepsy, or the risk of developing a post-surgical neurological deficit. (3, 5, 6) Many candidates suitable for surgery also decide not to proceed, habitually considering that risks outweigh potential benefits. (3, 5)

There are very few studies looking at follow-up outcomes in people who have gone through presurgical evaluation and not proceeded to surgery. Often, these individuals will subsequently try different anti-seizure medications (ASM), vagal nerve stimulation (VNS), or ketogenic diet to reduce seizure frequency. Over the last three decades, there has been a considerable increase in the number of available ASM. Their ability to impart seizure freedom in people with drug-resistant epilepsy, however, remains low. (7, 8) Similarly, while vagal nerve stimulation may improve seizure frequency, seizure freedom rarely occurs. (9)

We describe seizure outcomes in people with drug-resistant epilepsy who completed presurgical evaluation but did not proceed to surgery. This will help inform discussions with those offered epilepsy surgeries, particularly if they decide not to pursue a definitive operation.

METHODS

Our epilepsy surgery program is for adults. Children are evaluated in a separate pediatric service. We reviewed individuals discussed in a weekly adult presurgical epilepsy MDT

meeting from 01 January 2015 to 31 December 2019. At this meeting, results of EEG video telemetry, neuroimaging, neuropsychology and neuropsychiatry assessments, and clinical information regarding adult individuals referred for consideration of epilepsy surgery were reviewed. We identified those in whom a clinical decision was made not to proceed or those individuals who opted not to proceed with epilepsy surgery.

We recorded reported seizure outcomes in the previous year for these people at their most recent follow-up using a modified International League Against Epilepsy (ILAE) postoperative outcome scale. We obtained this by direct follow-up with these individuals, primary care physicians and their consultant neurologists. Seizure outcomes in all cases were directly self-reported by individuals or family members, who were asked to maintain prospective seizure records. Electronic records of seizure frequency at time of presurgical evaluation and prospective follow-up were reviewed in all cases to classify subjects into the ILAE outcome scale. Those who had less than 12-month follow-up were not included. For comparison, seizure outcomes in people who had epilepsy surgery at our center during the study period were also recorded.

This study was approved as part of an ongoing epilepsy surgery audit at University College London Hospitals (registration number 45-202021-SE). As a service evaluation posing no risk, individual informed consent was not required.

RESULTS

A total of 617 individuals were discussed in presurgical epilepsy MDT meetings from 01 January 2015 to 31 December 2019. Of these, 471 completed presurgical evaluation, and 156 had or are on the waiting list for surgery. A definitive decision not to have surgery was made in the remaining 315 individuals, including 39 who were considered suitable candidates but who

declined resective surgery. The reasons why these people did not have surgery are summarized in Table 1 and have been reported in detail elsewhere. (3) Nine (3%) of these 315 people had died in the years following the MDT meeting, and data were not available for 25 (8%), leaving 281 (89%) included for analysis. The median duration of follow-up was 2.4 (IQR 1.5-4) years.

Table 1: Reasons for not having epilepsy surgery

Reason	**N=315 (%)**
No localized source found	104 (33)
Multifocal epilepsy	74 (23)
Declined further investigation	62 (20)
Declined resective surgery	39 (12)
Risk of significant post-surgical deficit	33 (10)
Neurological comorbidity	3 (1)

The median age at the time of the decision not to have surgery was 36 (IQR 28-45) years old, with a median duration of epilepsy of 21 (IQR 13-31) years. Individuals took a median of 3 (IQR 2-4) ASM at the time of the presurgical MDT meeting and had tried a median of 7 (IQR 5-9) ASM. The seizure frequency reported by these individuals over the last 12 months at their most recent follow-up is listed in table 2:

Table 2: Seizure frequency over the last 12 months at most recent follow-up

Modified* ILAE outcome score	Description	N (%)
1	Completely seizure-free; no auras	13 (5)
2	Only auras; no other seizure	2 (0)
3	One to three seizure days per year; +/- auras	7 (3)
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras	61 (22)
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras	180 (64)
6	More than 100% increase of baseline seizure days; +/- auras	18 (6)
*ILAE post-surgical outcome score in the last 12 months where surgery is replaced by 'decision not to have surgery'		

Thirteen (5%) people were seizure-free over the preceding twelve months at the most recent follow-up. In nine, this followed additional drug therapy (one each with the addition of carbamazepine, lamotrigine, oxcarbazepine, lacosamide, zonisamide and topiramate and in two following starting clobazam). In each case, individuals had been previously taking 2-7 ASM before the MDT discussion. Three people became seizure-free following an increase in the dose of a current ASM.

Fifty-three people (19%) had a vagal nerve stimulator implanted. One was seizure-free for three years following VNS insertion, and another only reported auras, having previously experienced frequent focal seizures with impaired awareness. A further 17/53 (32%) reported a >50% reduction of seizures (ILAE outcome class 3 or 4), while 29/53 (55%) experienced no change in seizure frequency (ILAE outcome class 5). Five people (10%) experienced a >100% increase in seizure frequency (ILAE outcome class 6).

Four (1%) people were started on a ketogenic diet. Of these, three reported no change in seizure frequency (ILAE outcome class 5) and one person experienced a modest improvement in seizure control (ILAE outcome class 4).

Thirty-nine people were offered resective surgery but declined an operation. In this subset, 33/39 (85%) had an abnormal MRI scan, and 27/39 (69%) had temporal lobe epilepsy. Outcomes over the last 12 months in this group are shown in Table 3. For comparison, the latest 12-month outcomes in 166 individuals who had epilepsy surgery at our center within the same 5-year period is also presented. Individuals in this surgical group may have been discussed in the MDT before 2015. They included 150/166 (90%) with an abnormal MRI and 123/166 (74%) people with temporal lobe epilepsy.

Table 3: Seizure frequency over the last 12 months in those who decline surgery			
Modified ILAE outcome score		Declined surgery, n=39 (%)	Had surgery, n=166 (%)
1	Completely seizure-free; no auras	5 (13)	85 (51)
2	Only auras; no other seizure	0 (0)	16 (10)
3	One to three seizure days per year; +/- auras	3 (8)	15 (9)
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras	9 (23)	30 (18)
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras	17 (44)	10 (6)
6	More than 100% increase of baseline seizure days; +/- auras	2 (5)	0 (0)
7	Deceased	1 (3)	0 (0)
8	No follow-up available	2 (5)	10 (6)

Of the 9 (3%) individuals who died following the decision not to have surgery, death was epilepsy-related in six, which gives an epilepsy-related death rate of 1/116 people per patient/year. Causes of death included Sudden Unexpected Death in Epilepsy (SUDEP) in four people, and one death each due to suicide by drug overdose, status epilepticus and drowning following a seizure. We were unable to obtain documentation of the cause of death in the remaining two cases.

DISCUSSION

The chance of achieving seizure remission with ASM after having tried three ASM is slight (7), but it does happen. In those who are evaluated for surgery but do not proceed, further ASM and VNS may be associated with seizure remission in 5% and >50% reduction of seizure frequency in a further quarter. This is consistent with previous reports that individuals with previously refractory epilepsy may improve and rarely enter remission with ASM changes. (8, 10, 11) A

previous study that also focused on those who are considered for epilepsy surgery but do not proceed found that approximately 10% were seizure-free over the preceding 12 month period four years after evaluation. (11) While this does not consider relapse and remission patterns, seizure freedom over 12 months is often predictive of more prolonged remission. (12)

Surgery is an effective treatment for selected individuals with drug-resistant temporal lobe epilepsy, and long-term benefits can also be seen in those with extratemporal epilepsy. (1, 2, 13) At our center, approximately half of people having epilepsy surgery are seizure-free five years after surgery, consistent with reports of long-term outcomes elsewhere. (2, 13-15) Many people with focal epilepsy are not, however, suitable for surgery, and up to a third of those who are offered an operation subsequently decline. (4, 6) Our findings suggest that in those who do not proceed to surgery, a worthwhile improvement in seizure control may still be achieved with nonsurgical treatments. Rates of seizure freedom are lower without surgery, and this should be discussed with those who choose not to proceed when an operation is deemed feasible. The epilepsy-related death rate in our cohort was substantially higher than that seen in other epilepsy populations, likely reflecting the consequence of frequent, ongoing seizures in a cohort with severe pharmacoresistant epilepsy. High rates of SUDEP are seen in candidates of epilepsy surgery, with an incidence of 9 per 1000 patient-years previously reported. (16) Discussing this finding with potential surgical candidates may also help inform the decision of whether to proceed to surgery.

Consistent with previous reports, vagal nerve stimulation in our cohort was associated with a >50% reduction in seizure frequency in approximately one-third of people (9, 17) VNS was not curative, and only one individual became seizure-free. VNS is a reasonable palliative procedure in those who are not eligible for a definitive resection, mainly if there are no further ASM options or these have led to adverse effects.

Our findings are limited to a single adult epilepsy surgery center with a very pharmacoresistant cohort who had already tried a median of seven ASM. Our data is observational with no control group, and individuals were not randomized to receiving additional drug therapy or neurostimulation. Outcome data within the cohort was limited to seizure frequency and death, with other adverse events such as side effects of medication not being systematically recorded. Despite these limitations, our data reflect real-world conditions for treating individuals with drug-resistant epilepsy and may help inform discussions with those not suitable for surgery.

CONCLUSION

Further ASM and neurostimulation rarely result in seizure freedom for those with drug-resistant epilepsy who are evaluated for surgery and do not proceed. Nonetheless, these treatments can be associated with a reduction in seizure frequency and should be considered for those not suitable for resection.

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Table Legend

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