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Consideration of epilepsy surgery in adults should be independent of age

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ABSTRACT

Objectives: Epilepsy surgery is performed less frequently in persons over 45 years of age than in younger individuals, probably reflecting biases among patients, referring physicians and neurologists.
Methods: We report on a clinically heterogenous cohort of patients aged 45 years or older who underwent epilepsy surgery for medically intractable epilepsy.
Results: Over a 15-year period, 42 patients with a mean duration of epilepsy of 27.3 years underwent elective surgery. The mean follow-up period was 48 months. Thirty-two patients had an Engel class I outcome, of which 23 were totally seizure-free (Ia). Six patients had a class II outcome (rare disabling seizures), one had a class III outcome (worthwhile improvement), and three had a class IV outcome (no worthwhile improvement). The majority of patients reported an improved quality of life and satisfaction with the epilepsy surgery. A subjective improvement in cognition was reported in 7 patients while a decline was reported in 10 patients. New neuropsychiatric difficulties were reported in three patients while three patients reported improved anxiety after surgery. Only one patient became newly employed after surgery while 23 returned to driving. Permanent complications occurred in four patients (thalamic infarct during a Wada test ($n = 1$) and asymptomatic visual field defect ($n = 3$)).
Conclusions: We report a favorable outcome from epilepsy surgery in a large series of older adults and conclude that age *per se* is not a contraindication to epilepsy surgery. We emphasize the lack of correlation between outcome from surgery and pre-operative duration of epilepsy.

1. Introduction

Despite the increasing recognition of medical intractability and advances in the pre-surgical evaluation of patients, epilepsy surgery is underutilized [1]. In part, this may reflect lack of access to centers with expertise in epilepsy surgery. Nonetheless, the average time to referral for pre-surgical evaluation in the US remains more than 20 years from onset of epilepsy and more than 10 years after recognition of medical intractability [2]. Surgical intervention is a useful therapeutic option for disabling, medically refractory epilepsy in carefully selected patients [3]. Among epileptologists, attention is paid to the early identification of appropriate surgical candidates, particularly those with a well-defined etiology associated with medical refractoriness. These patients are usually young adults, typically under 40 years of age.

Less attention has been paid to older patients with intractable epilepsy [4]. This likely reflects bias among patients, referring physicians and neurologists. Traditionally, increasing age was thought to be a relative contraindication to epilepsy surgery [4–8]. This viewpoint reflects the perception of increased surgical risk for the older patient and reduced chances of a good therapeutic outcome. Intuitively, one might assume that the 'average' older patient with intractable epilepsy will have a longer clinical history of epilepsy with more psychosocial and medical co-morbidities. There is evidence that increasing duration of epilepsy before surgical intervention lessens the chance of permanent abolition of seizures, possibly due to formation of secondary epileptic foci remote from the original focus [8,9]. The patient may have a reduced chance of significant seizure reduction and may have a greater risk of medical, surgical and neuropsychological complications. Lastly, the patient may struggle to rehabilitate and thus not get the psychosocial benefit of epilepsy surgery.

However, many carefully selected older patients may experience benefit from epilepsy surgery [10]. This is particularly true for intractable focal epilepsy of temporal lobe origin [11–16]. We report

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our experience with epilepsy surgery in persons over 45 years of age with intractable temporal and extra-temporal epilepsy.

2. Patients and methods

2.1. Patient selection

We performed a retrospective analysis of patients aged 45 years of age or older operated on for disabling, medially refractory partial epilepsy at the Massachusetts General Hospital over a 15-year period (1992–2006). All patients underwent epilepsy surgery solely on the grounds of disabling, medically intractable partial epilepsy. Specifically, we excluded patients who had seizures in the setting of structural abnormalities (in particular growing tumors or vascular malformations) where the surgery was undertaken due to the nature of the structural abnormality rather than refractory epilepsy related to the lesion. Intractability was defined as occurrence of more than one complex partial or convulsive seizure per month despite appropriate use of at least three appropriate anti-seizure medications. A minimum 1-year follow-up was required for inclusion. The complete medical record was reviewed (particular attention was paid to the consensus opinion reached at the epilepsy surgery conference) and, in addition, all patients were contacted directly in follow-up by telephone interview by D.C. The telephone interview was structured and focused on the evaluation of the outcome parameters. Institutional Research Board approval was obtained for the study.

2.2. Pre-operative evaluation

All patients underwent detailed neurologic history and examination, magnetic resonance imaging (MRI), interictal positron emission tomography (PET), and surface EEG-video recordings in the pre-operative period. Selected patients underwent neuropsychological evaluation, Wada testing or intracranial EEG recording.

2.3. Surgical procedure and complications

Patients were recommended for surgery based on proven medical intractability, secondary disability, and concordant pre-operative data, usually with an associated candidate structural lesion. Medical co-morbidities were factored into the decision-making process on a case-by-case basis. Complications related to the pre-operative work-up and early post-operative period were recorded.

2.4. Seizure outcome

Seizure outcome was determined by review of the medical record in addition to telephone interview in all patients. Seizure outcome was classified according to Engel's classification of epilepsy surgery outcome (Table 1) [17]:

2.5. Histopathology

The final neuropathological diagnosis was extracted from the formal neuropathological report.

2.6. Neuropsychological assessment

Each medical record was assessed for evidence of neuropsychiatric complications or cognitive decline in the post-operative period. In selected cases, where formal neuropsychometric assessments were performed before or after surgery, this data was reviewed. All patients were questioned regarding problems with memory and intellectual function before and after surgery and the impact of surgery.

Table 1
Engel classification of epilepsy surgery outcome.

Class I (free of disabling seizures (excludes early post-op seizures))
1A: Completely seizure-free since surgery
1B: Non-disabling simple partial seizures only since surgery
1C: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
1D: Generalized convulsion with AED withdrawal only
Class II (rare disabling seizures "almost seizure-free")
2A: Initially free of disabling seizures but has rare seizures now
2B: Rare disabling seizures since surgery
2C: More than rare disabling seizures after surgery, but rare seizures for at least 2 years
2D: Nocturnal seizures only
Class III (worthwhile improvement)
3A: Worthwhile seizure reduction
3B: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years
Class IV (no worthwhile improvement)
4A: Significant seizure reduction
4B: No appreciable change
4C: Seizures worse

2.7. Mental health assessment

Symptoms of depression and anxiety were sought and their relationship to surgery was established. Particular attention was paid to the prescription of new psychotropic medications after surgery.

2.8. Assessment of impact of epilepsy surgery on employment and driving status, anti-seizure medication prescribing, and patient satisfaction with epilepsy surgery

Each patient was questioned on employment status and their ability to drive before and after surgery. Changes in anti-seizure medication prescribing were recorded. Five-point rating scales assessing the patient's satisfaction with epilepsy surgery and impact on quality of life were used. The patients were given five possible answers to the question 'How much did the surgery improve your quality of life?' namely, 'marked worsening, mild worsening, no change, mild improvement, or marked improvement'. In addition, the patients were given five possible answers to the question 'How satisfied are you with the results of the surgery for your epilepsy?' namely, 'very dissatisfied, dissatisfied, no opinion, satisfied, or very satisfied'.

3. Results

3.1. Demographic parameters

From a total of 244 patients who underwent surgery for intractable partial epilepsy during a 15-year period (1992–2006), 42 patients were 45 years of age or older. This represents 17.2% of the total cohort. There was an equal gender distribution with 21 female and 21 male patients. The distribution of age was as follows: 45–50 years (23 patients), 51–55 years (10 patients), 56–60 years (7 patients), 61–65 years (1 patient) and >65 years (1 patient).

3.2. Clinical parameters

In the overall cohort of 244 patients, the mean age at surgery was 33.1 years with a standard deviation of 12.2 years. In the overall cohort, age 45 represents one standard deviation above the mean

age at surgery. In the 'older' cohort of 42 patients, the mean age at surgery was 51 years (median 50 years; range 45–66 years). The mean age at first afebrile seizure was 23.9 years. Twenty-three patients had epilepsy onset before age 20 years and 19 patients had epilepsy onset after age 20 years. The mean pre-operative duration of epilepsy was 27.3 years (median 31.5 years; range 0.5–55.5 years). At the time of surgery, the mean pre-operative monthly frequency or complex partial or secondary-generalized convulsive seizures was 17 per month (median of 8 seizures per month). None of the patients who underwent surgery had any major or potentially life-threatening medical co-morbidities.

3.3. Pre-operative clinical diagnosis

Among the 42 patients, there was a wide variety of pre-operative working diagnoses—mesial temporal lobe epilepsy ($n = 19$), malformation of cortical development/focal cortical dysplasia ($n = 5$), non-lesional epilepsy ($n = 5$), single cavernous angiomas ($n = 4$), benign tumor ($n = 3$), post-traumatic encephalomalacia ($n = 3$), post-encephalitic epilepsy ($n = 1$), Tuberous Sclerosis Complex ($n = 1$), and post-infarct epilepsy ($n = 1$). Of note, in those patients who had a tumor, vascular or other structural abnormality, the surgery (usually lesionectomy) was undertaken for the primary purpose of seizure control rather than removal of the structural lesion *per se*.

3.4. Pre-operative imaging

All but two patients underwent epilepsy-protocol 1.5 or 3.0 Tesla MR imaging. These two patients had pacemakers in situ. The most common MRI finding was unilateral or markedly asymmetric mesial temporal sclerosis in 17 (right-sided in 9, left-sided in 8). Focal lesions were evident in 13 patients. Multifocal or extensive lesions were present in five patients. Five MRI studies were normal and patients were deemed 'non-lesional'. Interictal 18-FDG PET imaging was performed in 38 patients. This imaging modality was abnormal in 29 patients and unremarkable in 11 patients. Ictal single photon emission computerized tomography (SPECT) was performed in two patients—it was not informative in either case. Pre-op MR spectroscopy was performed in one patient.

3.5. Pre-operative EEG data

All patients underwent elective inpatient phase I (surface) video-EEG monitoring. Interictal EEG abnormalities were detected in 38 patients and at least 2 habitual electroclinical seizures were recorded in all patients. Invasive phase II recordings were undertaken in seven patients—foramen ovale electrode recordings in two patients (to clarify mesiobasal temporal ictal onsets where surface EEG was uninterpretable), bilateral orthogonal depth electrode recordings in two patients (to lateralize ictal onsets where surface EEG recordings were ambiguous) and a combined depth electrode/grid study (to localize ictal onsets within a previously defined brain region) in three patients. Intra-operative corticography was utilized in 17 patients.

3.6. Pre-operative language and memory assessment

During routine pre-operative clinical assessment, 21 patients reported subjective cognitive difficulties while 19 reported no cognitive difficulties (in 2 patients the presence of subjective cognitive difficulties was unknown). Formal neuropsychometric testing was performed in all cases where possible but particularly in the following circumstances, (i) left anteromedial temporal lobectomy was planned, (ii) either imaging or EEG findings suggest bilateral mesial temporal disease, (iii) any patient who reported significant cognitive difficulties, (iv) 'high functioning' patients with minimal cognitive complaints, (v) planned resection of normal-appearing mesial temporal structures. In selected cases, a Wada test was performed, but particularly in the following circumstances: removal of normal-appearing mesial temporal structures was proposed (especially on the left side), the pre-surgical evaluation suggested bilateral mesial temporal disease, when neuropsychometric testing confirmed both verbal and non-verbal memory deficits, and to characterize language lateralization when neocortical surgery was planned. A formal pre-operative neuropsychometric evaluation was undertaken in 17 patients. Wada testing was performed in 17 patients; of these, 8 patients subsequently underwent left hemispheric surgery and 9 patients underwent right hemispheric surgery. Functional MRI (fMRI) testing of language was undertaken in two patients; of these, one patient subsequently underwent left hemispheric surgery and one patient underwent right hemispheric surgery.

3.7. Resection types

Of 42 individual surgical resections, 11 patients underwent a standard left anterior-medial temporal lobectomy (including amygdalohippocampectomy), 17 patients underwent a standard right anterior-medial temporal lobectomy, 3 patients had a limited left frontal resection, 3 patients had a limited right frontal resection and 2 patients had a left temporal lesionectomy (without removal of the amygdalohippocampal complex). The following operations were performed in single patients—right temporal neocortical resection of extensive malformation of cortical development, right posterior temporal resection, left posterior temporal resection, right temporal lesionectomy, corpus callosotomy, and left parietal lesionectomy. Intra-op mapping of language was performed in two patients. The median length of hospital stay was 4 days.

3.8. Neuropathological diagnosis

From the 42 resections, the most common final neuropathological diagnoses was hippocampal sclerosis ($n = 20$). Other neuropathological findings were as follows: vascular malformation ($n = 5$), non-specific changes or 'no diagnostic abnormality' ($n = 5$), focal cortical dysplasia ($n = 5$), non-specific gliosis ($n = 3$), dysembryonic neuroepithelial tumor ($n = 1$), non-specific encephalitis ($n = 1$), ganglioglioma ($n = 1$), and post-traumatic gliosis ($n = 1$).

3.9. Peri-operative complications

In total, eight patients experienced complications in the peri-operative period. One patient experienced a thalamic infarct during a Wada test, presumably related to angiography. This resulted in diplopia for 2 weeks, which resolved fully. Four patients experienced wound infections. Of these, three were treated with antibiotics and dressings while one patient needed surgical debridement under general anaesthesia. Three patients were found to have asymptomatic visual field defects in the immediate post-operative period.

3.10. Epilepsy outcome

Fig. 1 outlines the epilepsy outcome among the 42 patients at last clinical interview, according to the Engel outcome scale. Of note, the mean follow-up was 4.0 years (range 1.1–14.4 years).

There did not seem to be a correlation between seizure control obtained after epilepsy surgery and age. Of 23 patients aged 45–50 years, 11 patients had a class 1A outcome, 3 patients had a class

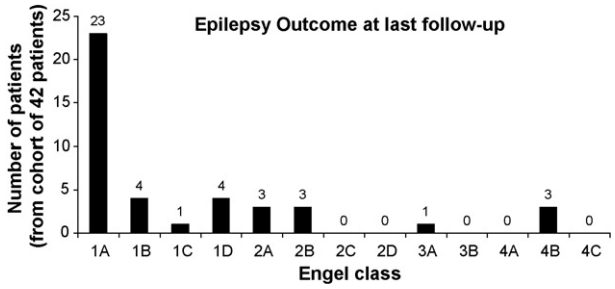

Fig. 1. Epilepsy surgery outcome at last clinical interview (mean duration of follow-up 4.0 years (range 1.1–14.4 years)). The outcome was scored according to frequency of seizures during the previous 12 months.

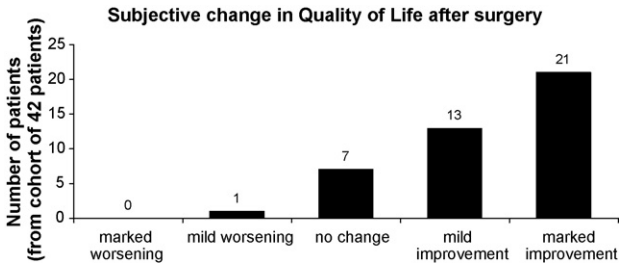

Fig. 2. Subjective change in quality of life after elective epilepsy surgery. The patients were given five possible answers to the question 'How much did the surgery improve your quality of life?' namely, 'marked worsening, mild worsening, no change, mild improvement, or marked improvement'.

2B outcome, 2 patients had class 1B, 1D, 2A, 4B outcomes, and 1 patient had a class 3A outcome. Of 10 patients aged 51–55 years, 8 patients had a class 1A outcomes and 1 patient had a class 1B, 1D outcome. Of seven patients aged 56–60 years, four patients had a class 1A outcome, one patient had a class 1C, 1D, 2A outcome. The single patient aged 61–65 years had a class 1B outcome and the patient aged >65 years had a class 4B outcome.

3.11. Post-operative cognitive changes

Twenty-five patients reported unchanged cognition after surgery. Of the 17 patients who reported a change in cognition after surgery, 7 patients felt that they experienced an improvement while 10 patients reported a decline in intellectual function. Of the 10 patients that reported a subjective decline in cognition, 9 patients reported mild memory problems. Of these 10 patients, 4 patients underwent neuropsychometric testing—2 patients had evidence of a mild decline in verbal memory; 1 patient had unchanged performance scores and 1 patient had improved performance scores compared to pre-operative testing. Four patients experienced transient (<3 weeks) word-finding difficulties. One patient received speech and language therapy and recovered to baseline by 3 months; the other patients improved quickly in the first post-operative week.

Of the 10 patients who experienced subjective cognitive decline, their mean age at surgery was 52 years (median 53 years). Their mean pre-operative duration of epilepsy was 30.3 years (median 34 years, range 5–47 years). Four patients were female and six were male. Six patients had a right anterior-medial temporal lobectomy, three patients had a left anterior-medial temporal lobectomy, and one patient had a limited left frontal resection. Their epilepsy outcome included class 1A ($n = 6$), 1B ($n = 2$), 1D ($n = 1$), and 2A ($n = 1$). The final neuropathological diagnosis was hippocampal sclerosis ($n = 5$), focal cortical dysplasic ($n = 2$), dysembryonic neuroepithelial tumor ($n = 1$), non-specific changes ($n = 1$), and post-traumatic gliosis ($n = 1$). At last follow-up, seven patients were on AED monotherapy while three patients were on the same AED regimen. Despite reporting subjective cognitive decline, seven patients were 'very satisfied' with the outcome of the epilepsy surgery, two patients were 'satisfied' and one patient was 'mildly dissatisfied'. Five patients reported a 'marked improvement' in their quality of life since the epilepsy surgery, four patients reported a 'mild improvement' and one patient reported 'no change' in quality of life since surgery.

3.12. Mental health complications

After reviewing the medical notes and upon interview, of the 42 patients, 2 patients reported a substantial and persistent worsening of pre-existing depression while 2 reported the development of depression *de novo* within 6 months of elective surgery. Each patient was prescribed an anti-depressant by a psychiatrist. One patient reported a substantial and persistent worsening of pre-existing anxiety while one patient reported the development of anxiety *de novo* within 6 months of elective surgery. Three patients reported an improvement in their mental health after surgery—specifically, a lessening of chronic anxiety. The remaining patients ($n = 33$) did not notice any change in mental health after surgery compared to beforehand.

3.13. Employment and driving status

From a total of 42 patients, 16 were actively employed before surgery, 2 had had full careers but retired and 24 patients were unemployed due to medical disability. After surgery, only one previously unemployed person returned to active employment. Except for one patient, all those who were employed before surgery returned to active employment after surgery. From a total of 42 patients, 5 patients reported regular driving before surgery. At last follow-up after surgery 28 patients were legally driving.

3.14. AED withdrawal

Prior to surgery, each patient was prescribed at least two AEDs, i.e. polytherapy. At last follow-up by telephone interview, four patients were taking the same AED combination at the same doses, five patients remained on the same AED combination but at reduced doses, and four patients were no longer taking medications. The remaining 29 patients (69%) were prescribed a single AED, i.e. monotherapy.

3.15. Quality of life

Fig. 2 shows the subjective changes in quality of life due to the elective epilepsy surgery reported by the patients at last telephone interview.

3.16. Patient's satisfaction with epilepsy surgery

Fig. 3 demonstrates the satisfaction expressed by the patient with their decision to undertake elective epilepsy surgery at last telephone interview.

4. Discussion

In this retrospective study of 42 adults aged 45 years or older who underwent elective epilepsy surgery, we report favorable post-operative seizure control along with meaningful functional benefits. Previous reports on epilepsy surgery in older adults focused on temporal lobe surgery and primarily paid attention

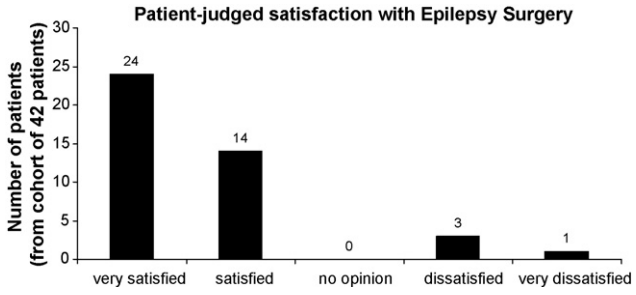

Fig. 3. Subjective patient-judged rating of satisfaction with epilepsy surgery. The patients were given five possible answers to the question 'How satisfied are you with the results of the surgery for your epilepsy?' namely, 'very dissatisfied, dissatisfied, no opinion, satisfied, or very satisfied'.

to epilepsy and neuropsychometric outcomes. In this study, we report on patients who underwent either temporal ($n = 34$) or extra-temporal ($n = 8$) surgery and we examined the patient-reported satisfaction with their decision to undergo epilepsy surgery, when this therapeutic option was offered to them.

Eight of the patients (19%) had a complication related to the pre-surgical evaluation (Wada-related infarct) or surgery (wound infection or visual field defect). Four patients experienced transient language disturbances, all in the setting of left hemispheric surgery (three temporal lobe resections and one frontal lobe resection). Post-operative cognitive and neuropsychiatric complications were unpredictable and usually mild. None of the patients reported a marked subjective deterioration in cognition. One difficulty with interpretation of the cognitive outcomes is that pre-operative neuropsychometric evaluations were only performed in 40% of the patients. Post-operative neuropsychometric testing was obtained in a smaller fraction of patients, typically patients who reported cognitive changes after surgery. This incomplete data set is further confounded by the impact of mood and affect on subjective perception of cognitive function so the 25 patients (60%) who did not report cognitive changes may have had measurable changes masked by improved quality of life.

At last follow-up, 23 patients (55%) were completely free of seizures and 38 patients (90%) had a class I or II outcome. Only one patient achieved a return to gainful employment though 28 patients were driving. Twenty-one (50%) patients experienced a 'marked' improvement and 12 (28.5%) patients experienced a 'mild' improvement in their quality of life after surgery. Six (14%) patients did not notice a change in their quality of life but no patient reported a deterioration in their quality of life after surgery. Twenty-four (57%) patients reported being 'very satisfied' and 14 (33%) were 'satisfied' with the effect of surgery. Three (7%) patients were 'dissatisfied' and 1 (2%) patient was 'very dissatisfied' with the results of surgery. The dissatisfaction expressed by four patients related to the lack of substantial improvement in seizure control after undertaking epilepsy surgery. These self-reported assessments in quality of life and satisfaction are confounded by the fact that the patient reported directed to a physician (D.C.) affiliated with the epilepsy center where the surgery was performed, increasing the likelihood of the patient over-estimating their gains from surgery.

Nonetheless, despite these potential confounding influences, the majority of patients seemed to gain a marked improvement in seizure control with a commensurate improvement in quality of life at the cost of a 1:5 risk of peri-operative complications and a small but unpredictable risk of post-operative cognitive or neuropsychiatric decline. Our findings extend the findings of previous studies in older patients with intractable epilepsy, by emphasizing the enduring psychosocial benefits to patients with both temporal and extra-temporal epilepsy surgery [18,19]. The parameters used to determine quality of life were admittedly somewhat one-dimensional—return to driving, employment status, and single questions asking patients about their level of satisfaction and improvement in quality of life. The five-point assessment of patient-reported satisfaction and quality of life scores are not validated rating tools but do provide a simple albeit crude survey of patient opinion. These measures were generally concordant for a given patient.

Other groups have reported that the benefit of epilepsy surgery in the older adult is generally commensurate with the benefits seen in younger adults [10–16]. The incidence of epilepsy increases with age and is highest among older adults. Though older patients may cope better with the psychological aspects of epilepsy, chronic epilepsy is frequently associated with significant co-morbidities including general medical disorders, depression and anxiety [20]. There remains no clear consensus on an appropriate upper age limit for consideration of epilepsy surgery. No clear expert consensus arose after the 2nd Palm Desert Conference where the participants reported an upper age limit varying from 40 to 70 years [5]. Reasons to undertake surgery in the older adult include likely persistence of seizures, resultant physical injuries, intolerance of medical therapies and significant co-morbidities including cognitive decline, depression and anxiety [20]. Advancing age in the setting of intractable epilepsy is associated with an increased likelihood of cognitive decline, though the duration of epilepsy does not always predict the degree of cognitive decline [21].

Possible barriers against undertaking epilepsy surgery in older adults include a longer duration of epilepsy in most patients with greater potential for secondary epileptogenesis, increased risk of cognitive dysfunction, the presence of established epilepsy-related co-morbidities, concurrent medical and psychiatric co-morbidities, increased peri-operative risk, less post-operative adaptability with less likelihood of achieving an improved quality of life, and reduced likelihood of psychosocial rehabilitation. For many patients, satisfaction with epilepsy surgery is related to a variety of factors including employment status, ability to drive, modification of anti-seizure medications, mental health changes, as well as improvement in seizure control [22].

In our experience and the experience of others [15], the pre-operative duration of epilepsy did not negatively influence seizure outcome. In our study, 15 of the 22 patients with class IA outcomes had long-standing epilepsy of at least 20 years duration (average 32.8 years duration). Patients with longer duration of epilepsy responded as well as those with shorter duration of epilepsy, suggesting that the outcome from epilepsy surgery does not diminish with time.

5. Conclusions

This large series adds to the evidence against treating older patients differently when it comes to consideration of epilepsy surgery. Biases in the selection of older patients for surgical intervention may limit the utilization of epilepsy surgery but paradoxically may ensure careful selection of appropriate candidates. In this study, older patients were selected by the same process as younger patients though it is likely that a greater degree of confidence that the proposed surgery would help the patient was required before surgery was offered. Discordant pre-operative data may have excluded a greater proportion of older patients from surgery. Epilepsy surgery is a reasonable and potentially curative intervention in carefully selected older patients with medically refractory epilepsy. As with all patients, case selection is crucial to good clinical outcome. Elderly patients who are medically intractable and have concordant pre-surgical findings are appropriate surgical candidates. This study, in conjunction with previous

studies, provides compelling evidence that neither chronological age nor duration of epilepsy should exclude patients from consideration of epilepsy surgery.

Disclosure

Funding was needed or obtained for the generation of the presented data.

Conflict of interest

None of the authors have any financial disclosures or conflicts of interest to declare.

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