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Decision analysis of intracranial monitoring in non-lesional epilepsy

G.C. Hotan [a,1], A.F. Struck [b,1,*], M.T. Bianchi [b], E.N. Eskandar [c], A.J. Cole [b], M.B. Westover [b]

[a] Massachusetts Institute of Technology Department of Brain and Cognitive Sciences, Cambridge, MA, USA
[b] Massachusetts General Hospital Department of Neurology, Boston, MA, USA
[c] Massachusetts General Hospital Department of Neurosurgery, Boston, MA, USA

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ABSTRACT

Purpose: Up to one third of epilepsy patients develop pharmacoresistant seizures and many benefit from resective surgery. However, patients with non-lesional focal epilepsy often require intracranial monitoring to localize the seizure focus. Intracranial monitoring carries operative morbidity risk and does not always succeed in localizing the seizures, making the benefit of this approach less certain. We performed a decision analysis comparing three strategies for patients with non-lesional focal epilepsy: (1) intracranial monitoring, (2) vagal nerve stimulator (VNS) implantation and (3) medical management to determine which strategy maximizes the expected quality-adjusted life years (QALYs) for our base cases.
Method: We constructed two base cases using parameters reported in the medical literature: (1) a young, otherwise healthy patient and (2) an elderly, otherwise healthy patient. We constructed a decision tree comprising strategies for the treatment of non-lesional epilepsy and two clinical outcomes: seizure freedom and no seizure freedom. Sensitivity analyses of probabilities at each branch were guided by data from the medical literature to define decision thresholds across plausible parameter ranges.
Results: Intracranial monitoring maximizes the expected QALYs for both base cases. The sensitivity analyses provide estimates of the values of key variables, such as the surgical risk or the chance of localizing the focus, at which intracranial monitoring is no longer favored.
Conclusion: Intracranial monitoring is favored over VNS and medical management in young and elderly patients over a wide, clinically-relevant range of pertinent model variables such as the chance of localizing the seizure focus and the surgical morbidity rate.

1. Introduction

Up to one third of patients with epilepsy develop medication-refractory epilepsy [1]. Surgery is often an effective treatment for these patients. Several studies, including a randomized controlled trial and a decision analysis [2,3], demonstrate the effectiveness of surgery in temporal lobe epilepsy. These patients have up to an 80% chance of post-operative seizure freedom. Similarly high rates of success are seen in lesional extratemporal epilepsy [4].

Patients without an MRI-evident structural lesion as the etiology for their epilepsy do not fare as well with surgery. These patients have reported post-operative seizure freedom rates between 30% and 40% [5,6]. For patients with non-lesional epilepsy, intracranial EEG monitoring is often necessary to localize the epileptogenic zone. However, intracranial monitoring comes with inherent surgical risks, including hemorrhage, CNS infections, stroke and death [7]. Furthermore, in a significant minority of patients, the epileptogenic focus can remain poorly localized even with extensive electrode coverage [8]. An important unresolved question is whether the population of epilepsy patients who are non-lesional and under consideration for intracranial EEG monitoring generally derives net benefit rather than harm from the extensive work-up and inherently invasive nature of intracranial monitoring necessary to determine candidacy for resective surgery.

Alternatives to intracranial monitoring include vagal nerve stimulator (VNS) implantation and further use of anti-seizure medications. These alternatives carry less upfront risk than intracranial monitoring but also have less chance of achieving seizure freedom, tending to result in seizure improvement instead. A comparison between the potential benefits and risks of these treatment options is necessary to optimize treatment protocols for patients with non-lesional epilepsy.

* Corresponding author at: Fruit Street Wang 7, Boston, MA 02114, USA. Tel.: +1 617 726 3311; fax: +1 617 726 9250.
E-mail address: astruck@mgh.harvard.edu (A.F. Struck).
[1] Shared first-authorship.

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A randomized controlled trial is the ideal methodology to address the question of whether the expected benefits of intracranial monitoring outweigh its expected risks for patients with non-lesional medication refractory epilepsy. However, the high cost and logistical difficulties of conducting an adequately powered randomized controlled trial are substantial. Decision analysis offers a viable alternative methodology for weighing the risks and benefits of various treatment options. In a decision analysis, the treatment options under consideration and the possible outcomes from each treatment are modeled as branches in a decision tree. Sensitivity analyses are then performed on parameters of interest to define the parameter range over which a specified treatment is favored. This allows for the "best" treatment option to be found (e.g. the option producing the highest quality of life or the lowest cost, depending on the metric used in the study) for each range of values of a parameter of interest. Base cases are constructed by inputting parameter values that apply to patients of a certain demographic, and the best treatment option for each base case is determined.

The present study comprises a decision analysis comparing three treatment strategies for patients with non-lesional medication refractory focal epilepsy who are under consideration for intracranial EEG monitoring: 1) intracranial monitoring with the intention of resective surgery, 2) VNS implantation and 3) continued medical management. The metric used to decide between the treatment strategies is the quality-adjusted life years.

2. Methods

2.1. Model structure

All modeling was conducted with TreeAge Pro HealthCare (Williamstown, MA). The decision analysis employs a decision tree. The first branch lists the decisions under consideration then proceeds through branch points that represent stochastic events such as the mortality from a surgery. The tree ends in the possible outcomes.

In this model we restrict attention exclusively to patients who are potential candidates for resective surgery after intracranial monitoring. The model thus begins at a decision node which branches into three treatment strategies: intracranial monitoring with the intention of resective epilepsy surgery, VNS implantation, and medical management. The potential complications include death and permanent morbidity from electrode implantation, resective surgery, or VNS placement. Potential outcomes include seizure freedom with or without morbidity, failure to achieve seizure freedom with or without morbidity, and death. While seizure improvement without seizure freedom is another potential outcome, a prior quality-of-life (QOL) study indicates that seizure improvement alone does not substantially improve QOL [9]. We therefore chose not to include this outcome in the model. The decision tree is illustrated in Fig. 1.

Medical management carries a low risk of permanent morbidity and death, so the possible outcomes from medical management are seizure freedom (without morbidity) and no seizure freedom (without morbidity). VNS may result in permanent morbidity; thus, seizure freedom and no seizure freedom, either with or without permanent morbidity, are possible outcomes from VNS.

Intracranial monitoring may lead to death with a low probability. In the likely event that the patient survives the electrode implantation procedure, morbidity may or may not result from the procedure. If the patient develops permanent morbidity it is assumed that they do not proceed to resective surgery and instead go on medical management. For patients that do not develop morbidity, their seizures are either localized or not localized. If intracranial monitoring fails to localize the seizures,

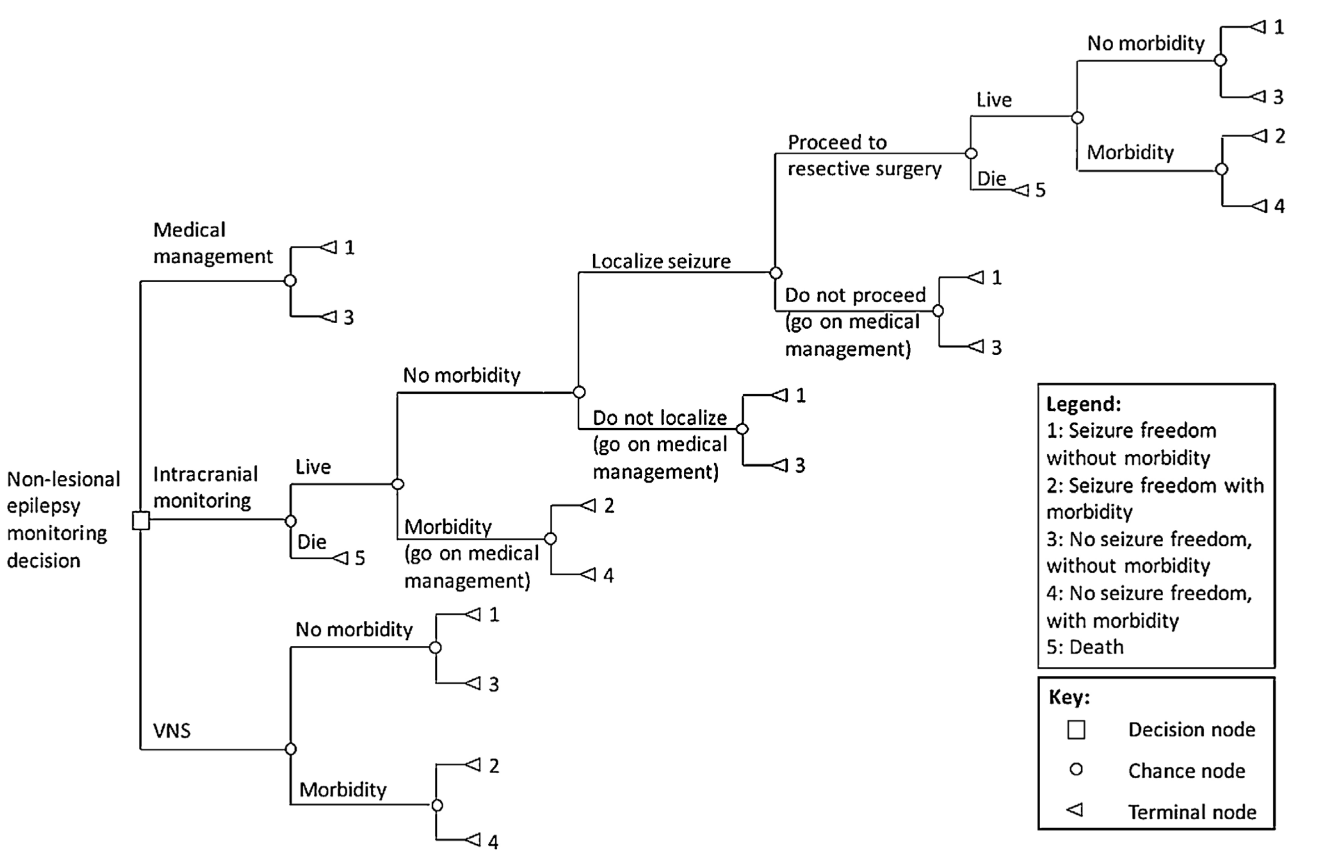

Fig. 1. Decision tree model. The possible outcomes are: (1) seizure freedom without morbidity, (2) seizure freedom with morbidity, (3) no seizure freedom, without morbidity, (4) no seizure freedom, with morbidity, or (5) death.

the patient does not proceed to resective surgery and instead goes on medical management. If the seizures are localized, resective surgery may be performed. If the resective surgery is performed it carries the risk of surgical death and the risk of surgical morbidity. It is also possible that resective surgery may not be performed even if the seizure focus is localized, for instance in cases where the seizure focus is close to eloquent cortex. In the case where resective surgery is not performed, the patient proceeds to medical management.

We performed sensitivity analysis for clinical variables of interest such as the chance of localizing seizures to a single operable (non-eloquent) focus. In each sensitivity analysis, the probability p of an outcome of interest is varied from 0 to 1 (all possible values). The quality-adjusted life years (QALYs) at each end node in the tree are calculated for each value of p. The QALY is a measure of life expectancy factoring in decreases in the quality of life due to medical conditions. For each value of p, the decision branch with the highest QALYs is considered the best option. One-way sensitivity analysis plots show the QALYs of each branch as a function of p. Two-way sensitivity analysis plots show the branch that yields the highest QALYs for a pair of parameter values, p and q, where p is the probability of the first outcome of interest and q is the probability of the second outcome of interest. Both p and q are varied from 0 to 1 (i.e. The entire range of their possible values). For each coordinate (p, q), the decision branch yielding the highest QALYs is shown on the 2D graph.

The next step in the decision analysis is to examine base cases of clinical relevance. For instance, a base case might be a 21-year-old otherwise-healthy male epilepsy patient. We would obtain his probability of seizure freedom, p_{base}, from the existing medical literature. We would then determine the best treatment option for him by identifying the treatment option which gives the highest QALYs for $p = p_{base}$ from the sensitivity analysis graph.

The decision analysis method therefore allows one to simulate the outcomes of several treatment options for all possible values of the probability of a particular outcome of interest. By doing so, one can obtain the range of values of p for which a particular treatment option is the "best". For the purposes of our study, the best treatment option is the option which yields the highest QALYs.

2.2. Model parameters

Two base cases were selected based on common clinical scenarios. Parameters relevant for the base cases are listed in Table 1. Sensitivity analysis was carried out on parameters of interest to assess the effect of these parameter values on the overall model conclusions. Since specific surgical risk data for epilepsy surgery is not available for all demographics, surgical risk was modified for higher-risk populations by extrapolating from general surgical risk data [10].

While the mean standardized mortality ratio for patients who become seizure-free after treatment is 1.11, the mean standardized mortality ratio for patients who do not become seizure-free is 5.64 for patients who underwent surgery and 5.40 for patients on medical management [2]. The increased mortality ratio for patients who are not seizure-free factors in deaths due to SUDEP as well as other causes of increased mortality for patients with epilepsy such as accidents. The mortality ratio is related to the death rate by adjusting the baseline probability of dying for a given age obtained from the US life Tables [49] and is a factor accounting for any increased risk of dying relative to the healthy population.

The mortality ratio is related to the death rate by $MR(x) = (1-e^{-r(x)R(x)\Delta x})/(1-e^{-r(x)\Delta x})$, where x is the age in years, $r(x)$ is the death rate at age x, $R(x)$ is the adjusted death rate at age x due to illness and Δx is the time step. We used a time step of $\Delta x = 1$ year. The death rate $r(x)$ is related to $q(x)$, the probability of dying between ages x and $x + 1$, by $r(x) = (1/\Delta x)\ln(1-q(x))$. $q(x)$ is the baseline probability of dying between ages x and $x + 1$ obtained from the US life Tables [49]. For each of the base cases below, the adjusted death rate, $r(x)^*R(x)$, was calculated from the relevant mortality ratio value for each outcome branch. The outcome branches included (1) seizure freedom, (2) no seizure freedom after surgery and (3) no seizure freedom after medical management. The adjusted probability of dying, $q_1(x)$, was obtained from the adjusted death rate and used to calculate a life table corresponding to the base case's gender. The life expectancy corresponding to the base case's age was read off the life table and multiplied by the QOL for the outcome to obtain the QALYs for that outcome branch.

2.3. Base cases

We explored two base cases which capture different potential clinical situations in which the question of whether intracranial monitoring should be employed arises. A base case represents a putative clinical situation in which the model parameters are different. In the first base case, the model was run for the typical epilepsy surgery patient, who is relatively young and healthy. In the past, epilepsy surgery was limited primarily to younger patients, but more recent studies [50] have indicated that elderly patients can also benefit from surgery. Thus, the second base case was developed for an elderly person without significant medical comorbidities. We present these bases cases as vignettes.

2.3.1. Patient 1 (young healthy patient)

A 24 year-old right-handed man with a 10-year history of medication refractory focal epilepsy. He has a single seizure semiology of a positive sensory aura rapidly followed by a generalized tonic clonic (GTC) seizure. He has tried >5 AEDs with incomplete control and still typically has at least one GTC a week. He has no other medical comorbidities. His MRI on repeated occasions is normal. Prior EMU admissions have found a single area of interictal abnormality and seizure onset zone broadly over the right frontal region. The model parameters for base case 1 follow those in Table 1. His life expectancy if he becomes seizure-free is 54.5 years. If he undergoes surgery or VNS treatment but does not become seizure-free, his life expectancy is 36.0 years. If he goes on medical management but does not become seizure-free, his life expectancy is 36.5 years.

2.3.2. Patient 2 (elderly healthy patient)

A 65 year-old right-handed woman with a history of medication refractory epilepsy for 40 years. She was in a car accident in her teen years and suffered a head trauma with a brief loss of consciousness, but was not hospitalized. Several years later she developed seizure primarily occurring at night where she appears to awaken then extends her left arm and flexes her right, rarely followed by a GTC. She has tried several medications through the years but her husband reports that she still has 1–2 seizures a month. Her MRIs have been normal with no evidence of prior contusions or hemorrhage. Her prior EMU admissions have shown bifrontal epileptiform discharges but with a consistently higher amplitude over the right. Her seizure onsets are broadly bifrontal, but typically have a phase lag with the right leading the left. The model parameters for base case 2 follow those in Table 1, except that her risk of complications from surgery is elevated to 6% [10]. Her risk of mortality from surgery is <1% [10], similar to base case 1. Her life expectancy if she becomes seizure-free is 19.5 years. If she undergoes surgery or VNS treatment but does not become seizure-free, her life expectancy is 8.7 years. If she goes on medical management but does not become seizure-free, her life expectancy is 9.4 years.

Table 1
Decision analysis model parameters.

Model parameters		
Parameter	Source	Value
Intracranial monitoring		
Chance of death from intracranial monitoring	Hamer et al., 2002 [11] 1/187 Fountas and Smith, 2007 [12] 2/185 Wong et al., 2009 [13] 2/71 Mullin et al., 2016 [14] 5/2624	10/3067 = 0.00330
Risk of permanent morbidity from intracranial monitoring	Van Gompel et al., 2008 [15] 26/198 Rydenhag et al., 2001 [16] 13/205 Wellmer et al., 2012 [17] 49/469 Gonzalez-Martinez et al., 2013 [18] 3/100 Behrens et al., 1997 [19] 2/279 Mullin et al., 2016 [14] 121/2624 Hamer et al., 2002 [11] 9/187	223/4062 = 0.0549
Chance that intracranial monitoring successfully localizes seizure	Siegel et al., 2001 [8] 37/43 Gonzalez-Martinez et al., 2013 [18] 96/100	133/143 = 0.930
Chance of proceeding to resective surgery given that intracranial monitoring successfully localizes seizure	Siegel et al., 2001 [8] 28/37 Gonzalez-Martinez et al., 2013 [18] 75/96	103/133 = 0.774
Resective surgery		
Chance of death from resective surgery	Lee et al., 2008 [20] 2/118 Polkey et al., 2016 [21] 7/818 Schramm et al., 2008 [22] 3/2000 Tanriverdi et al., 2009 [23] 0/2449 Jensen, 1975 [24] 18/2282 Rasmussen, 1968 [25] 15/1300 Olivier, 1991 [26] 0/526 Engel et al., 1983 [27] 1/130 Van Buren, 1987 [28] 3/300 Ojemann, 1991 [29] 1/250	50/10173 = 0.00490
Risk of permanent morbidity from resective surgery	Rydenhag et al., 2001 [12] 14/449 Behrens et al., 1997 [19] 13/429 Lee, 2008 [20] 3/118	30/996 = 0.0301
1-year seizure-free rate for resective surgery	Cohen-Gadol et al., 2006 [30] 311/399 Elwes et al., 1991 [31] 56/101 Wiebe et al., 2001 [32] 15/40 Jutila et al., 2002 [33] 56/88	438/628 = 0.698

Table 1 (*Continued*)

Model parameters

Parameter	Source	Value
5-year seizure-free rate for resective surgery	Cohen-Gadol et al., 2006 [30] 295/399 Edelvik et al., 2013 [34] 56/134 Elsharkawy et al., 2009 [35] 308/434 Elwes et al., 1991 [31] 46/69 Jutila et al., 2002 [33] 26/52 Sperling et al., 1996 [36] 62/89 de Tisi et al., 2011 [37] 239/615 Yoon et al., 2003 [38] 126/175	1158/1967 = 0.589
10-year seizure-free rate for resective surgery	Cohen-Gadol et al., 2006 [30] 287/299 Edelvik et al., 2013 [34] 61/144 Elsharkawy et al., 2009 [35] 307/434 de Tisi et al., 2011 [37] 227/615 Yoon et al., 2003 [38] 98/175	980/1667 = 0.588
VNS		
Chance of morbidity from VNS	Ben-Menachem, 2002 [39]	0.0015
1-year seizure-free rate for VNS	McHugh et al., 2007 [40] 2/48 Scherrmann et al., 2001 [41] 4/95	6/143 = 0.0420
5-year seizure-free rate for VNS	Elliott et al., 2011 [42] 32/436 Wheeler et al., 2011 [43] 11/169	43/605 = 0.0711
10-year seizure-free rate for VNS	Elliott et al., 2011 [42] 16/65	16/65 = 0.246
Medical management		
1-year seizure-free rate for medical management	Wiebe et al., 2001 [32] 1/40 Bootsma et al., 2004 [44] 17/177 (Topiramate) Sander et al., 1990 [45] 0/125 (Lamotrigine) Beydoun et al., 2003 [46] 4/42 (Oxcarbazepine)	22/384 = 0.0573
5-year and 10-year seizure-free rate for medical management[a]	Callaghan et al., 2007 [47] 3/246 Choi et al., 2008 [48] 33/187	36/433 = 0.0831

Preference-based quality of life scores

Final health state	Quality of life (QOL) score	
	Surgery	Medical management
(1) Seizure freedom, without surgical morbidity [2]	0.970	0.960
(2) Seizure freedom, with surgical morbidity [2]	0.770	–[b]
(3) No seizure freedom, without surgical morbidity[2]	0.780	0.750
(4) No seizure freedom, with surgical morbidity [2]	0.660	–[b]
(7) Death	0.000	0.000

[a] This number reflects a 4 to 5 year follow-up period but is the longest term data directly ascertaining the annual incidence of seizure freedom. It approximates a steady state of remission and relapse.

[b] Medical management does not result in morbidity.

Quality of life (QOL) scores were obtained from a decision analysis study by Choi et al. [2], in which QOL values were obtained via the standard gamble technique. For each base case under consideration, QALYs for each outcome are given by the product of the QOL for the outcome and the life expectancy of the base case.

3. Results

Sensitivity analyses were performed to verify the findings of the model for clinically relevant ranges of the independent variables. Intracranial monitoring with the intention toward resective surgery produced the highest QALYs for both base cases.

3.1. One-way sensitivity analyses

Since the goal of intracranial monitoring is to localize the seizure focus so that resective surgery can be performed, we examined the effect of changing the probability of localizing the seizure focus on the favored management strategy in Fig. 2a,

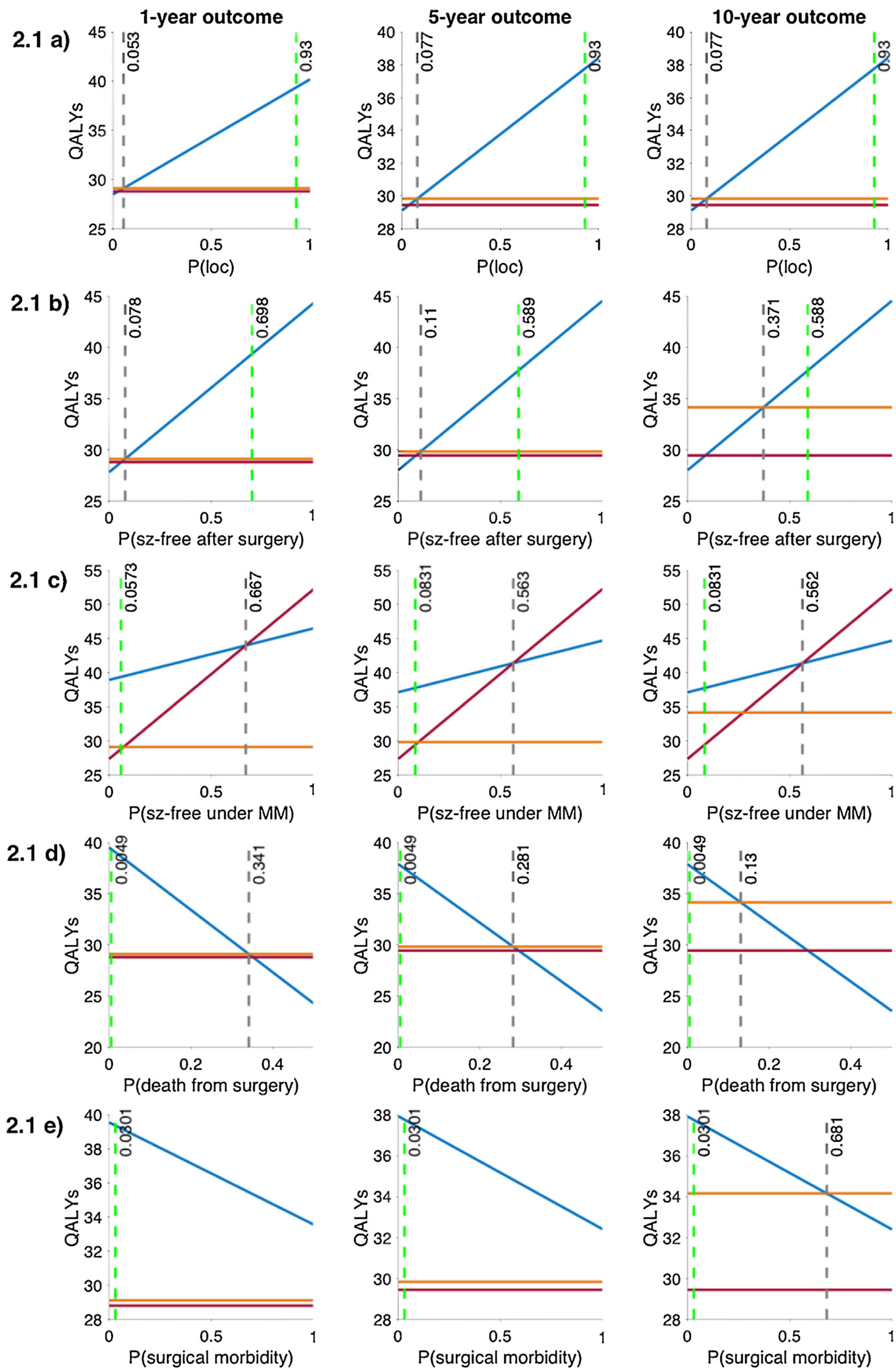

Fig. 2. One-way sensitivity analyses for 1-year, 5-year and 10-year outcomes. The blue lines correspond to intracranial monitoring, the red lines to medical management and the orange lines to VNS. The green dotted line on each graph shows the value of the parameter in question for each of the base cases. The grey dotted line indicates the threshold value of the parameter above which a different treatment option produces the highest QALYs. Intracranial monitoring produces the highest QALYs for both base cases 1 (2.1) and 2 (2.2). Abbreviations used: "P(loc)" for "Probability of localizing seizure"; "MM" for "medical management"; "sz-free" for "seizure-free".

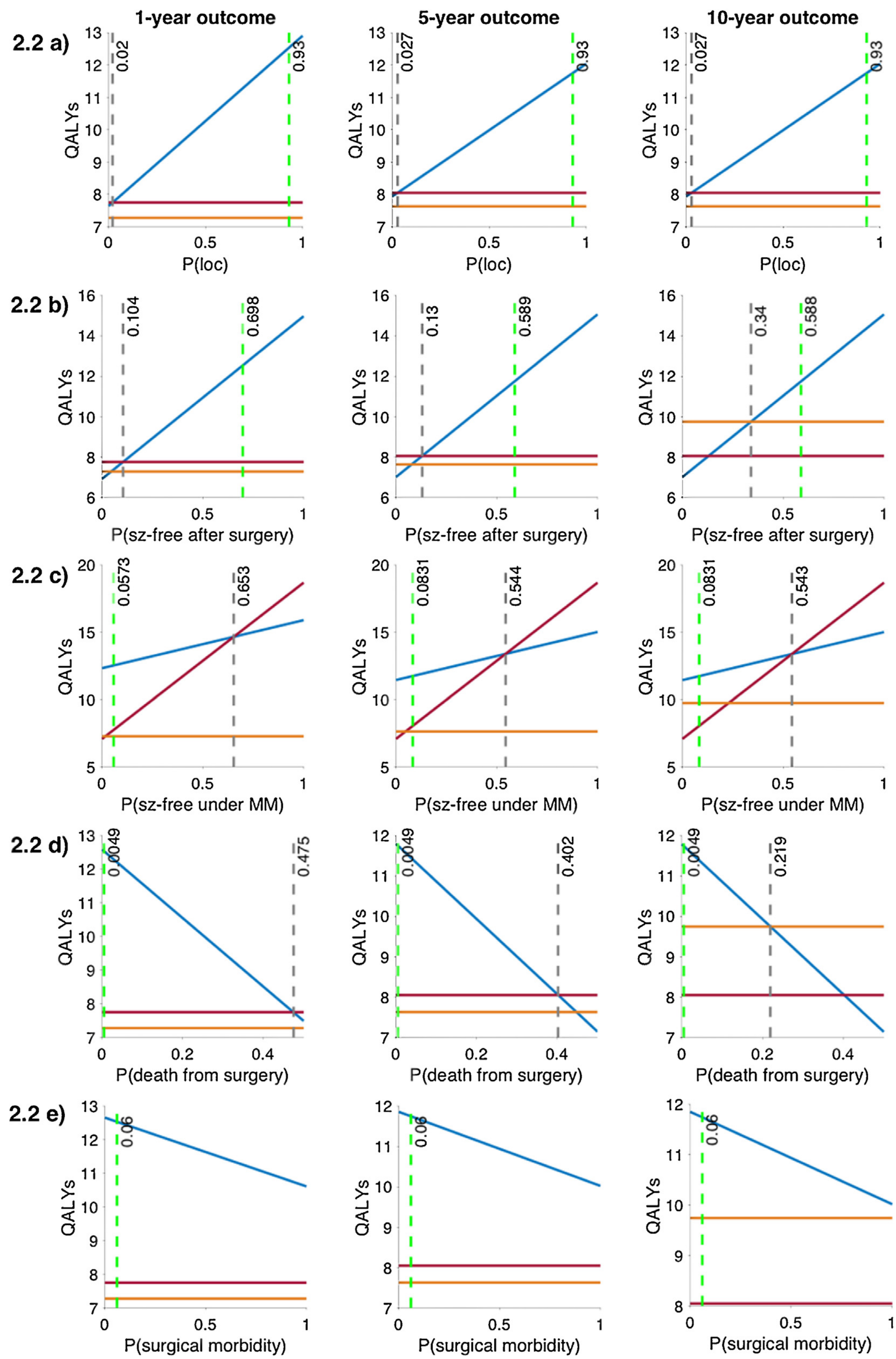

Fig. 2. (*Continued*).

where we define the favored strategy as the strategy producing the highest QALYs. At the 1-year mark, intracranial monitoring is favored for base case 1 above a localization probability of 5.3% (Fig. 2.1a) and becomes favored above a localization probability of 2.0% for base case 2 (Fig. 2.2a). The actual reported effectiveness of the procedure in localizing seizures is 93.0% (Table 1); thus, intracranial monitoring is the favored treatment option for base cases 1 and 2. Intracranial monitoring continues to be favored at the 5-year and 10-year marks.

3.2. Two-way sensitivity analyses

Since the aim of resective surgery is complete seizure freedom, the rate of seizure freedom after surgery is explored in Fig. 2b). At the one-year mark, intracranial monitoring is favored over VNS and medical management for seizure-free rates from surgery above 7.8% for base case 1 (Fig. 2.1b) and 10.4% for base case 2 (Fig. 2.2b). Since the estimated 1-year seizure-free rate after resective surgery is 69.8%, intracranial monitoring is favored for both base cases. Intracranial monitoring is also favored for both base cases at the 5-year and 10-year marks, where the seizure-free rates from resective surgery are 58.9% and 58.8% respectively. This is in spite of the fact that intracranial monitoring carries higher morbidity and mortality risks than VNS or medical management, as accounted for in our model. Thus, intracranial monitoring is expected to produce higher QALYs than

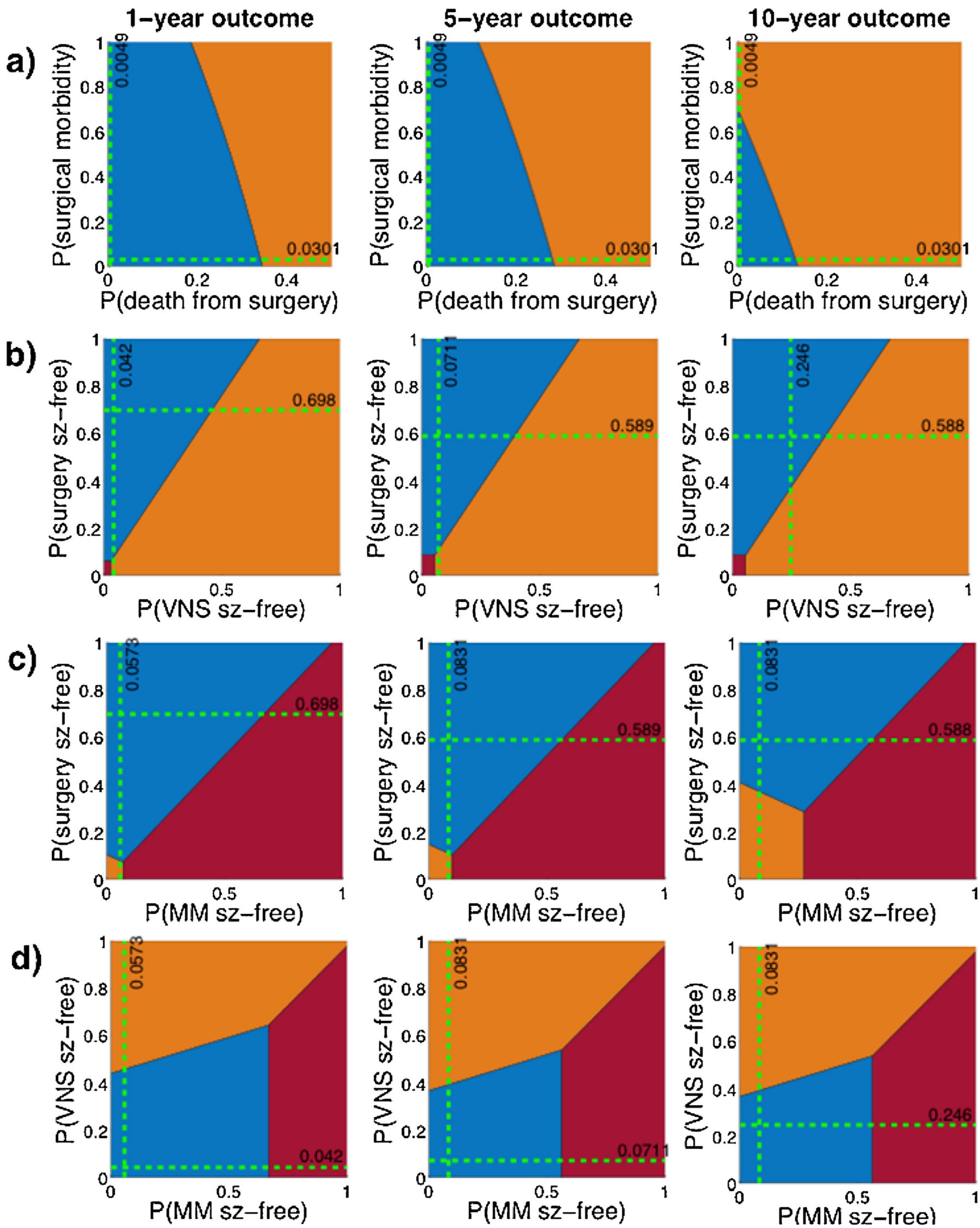

Fig. 3. Two-way sensitivity analyses for 1-year, 5-year and 10-year outcomes. Regions colored in blue correspond to where intracranial monitoring yields the highest QALYs. Regions colored in orange are regions where VNS yields the highest QALYs, and regions colored in red are regions where medical management yields the highest QALYs. The green dotted lines show the values of the two parameters for each of the base cases. The point of intersection between the green dotted lines indicates which treatment is expected to result in the highest QALYs. Intracranial monitoring produces the highest QALYs for both base case 1 (3.1) and 2 (3.2). Abbreviations used: "sz-free" for "seizure-free"; "MM" for "medical management".

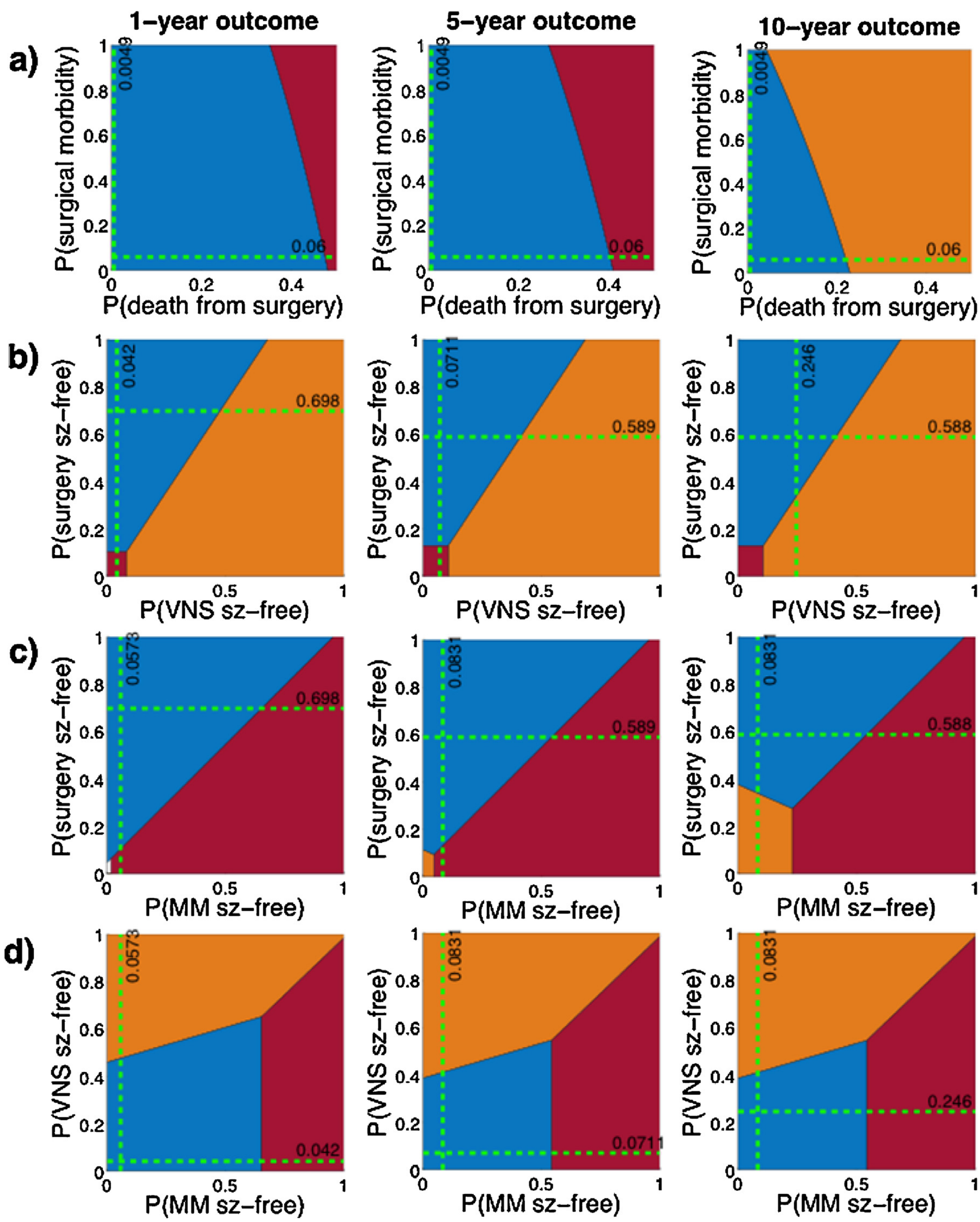

Fig. 3. (*Continued*).

VNS or medical management in the short term and long term despite its higher risks.

In Fig. 2c the probability of becoming seizure-free under medical management is examined to probe how effective medical management would have to be in order for it to be favored over intracranial monitoring. A hypothetical medical treatment plan would have to produce one-year seizure-free rates of 66.7% for base case 1 (Fig. 2.1c) and 65.3% for base case 2 (Fig. 2.2c) in order to be preferred over intracranial monitoring. Current medications for epilepsy achieve a 1-year seizure-free rate of 5.73%. Therefore, intracranial monitoring is currently a better treatment option than medical management for the base cases. This result holds in the longer term, with the 5-year and 10-year seizure-free rates for medical management being 8.31%.

Resective surgery contains an inherent mortality risk which is examined in Fig. 2d. 1-year surgical mortality rates would have to exceed 34.1% for base case 1 (Fig. 2.1d) and 47.5% for base case 2 (Fig. 2.2d) before medical management would become preferred to intracranial monitoring. The actual mortality rate for base cases 1 and 2 is 0.49%. In Fig. 3a surgical morbidity and mortality are varied in tandem. At the 1-year, 5-year and 10-year marks, the morbidity and mortality rates for base cases 1 and 2 fall well in the region where intracranial monitoring is favored. These results reflect the fact that the 1-year, 5-year and 10-year rates of seizure freedom after resective surgery are much higher than the corresponding seizure-free rate for VNS and medical management, and thus the overall QALYs for resective surgery are still higher than for VNS and medical management despite the fact that resective surgery is riskier initially.

In Fig. 3b–d the probabilities of becoming seizure-free with surgery, VNS and medical management are varied and compared with each other. For all combinations of seizure-free rates, intracranial monitoring is preferred not just for the base cases, but over a broad range of the clinically relevant parameter space, in both the short term and the long term.

In Fig. 2e a sensitivity analysis on surgical morbidity is performed. In the longer term, at the 5-year and 10-year marks, the threshold above which medical management or VNS becomes preferred to intracranial monitoring decreases, but given the surgical morbidity rates of 3.01% for base case 1 and 6.00% for base case 2, intracranial monitoring is still clearly preferred in the short and long term.

4. Discussion

In this study we performed a decision analysis to assess the utility of intracranial EEG monitoring for non-lesional medication refractory focal epilepsy. Sensitivity analyses were performed over the range of clinically relevant parameters to address the question of whether intracranial monitoring with the intention toward resective surgery is a better treatment strategy than VNS or medical management in terms of maximizing the QALYs for two base cases. The sensitivity analyses show that intracranial monitoring is expected to result in the highest QALYs as compared to VNS or medical management for both base cases in the short (1 year) and long (5 and 10 years) term, despite the fact that intracranial monitoring and resective surgery carry higher morbidity and mortality risks than VNS and medical management.

A previous study by Choi et al. [2] presented a decision analysis incorporating a Markov model and Monte Carlo analysis to show that anterior temporal lobe resection is expected to produce greater QALYs than medical management for patients with medication refractory temporal lobe epilepsy who are eligible for surgery. Their patient population comprised patients whose seizures could be localized by magnetic resonance imaging or functional tests. Our study builds on this work to examine the population of patients with non-lesional medication refractory epilepsy which cannot be localized by non-invasive procedures. By definition, our study only reflects those patients requiring intracranial EEG monitoring to localize their epileptogenic focus before resective surgery. These patients incur additional risks of morbidity and mortality associated with the implantation of electrodes during intracranial monitoring. Our study demonstrates that for otherwise healthy patients, the benefits of intracranial monitoring are expected to outweigh its risks. The clinical implication of our study is that intracranial monitoring with the intention of resective surgery is expected to produce higher QALYs than VNS or medical management in healthy patients with non-lesional medically-refractory epilepsy. In addition, the findings were fairly robust to changes in the model assumptions. For example, our model suggests that intra-cranial monitoring followed by resective surgery is still favored for a young healthy patient even if the chance of seizure freedom is only 10%.

4.1. Choice of model and modeling assumptions

A straightforward decision tree model was used rather than a Markov model or Monte Carlo simulation because it reduces the number of assumptions needed, especially for long-term seizure relapse and remission rates after non-lesional epilepsy surgery, VNS and medical management. A Markov model would include at least three states- seizure freedom, continued seizures, and death. Available longitudinal patient studies do not extend beyond the fifth year after treatment, so assumptions would have to be made regarding the probability of transitioning between these Markov states in later years. A Monte Carlo analysis would require that assumptions be made regarding the distributions of parameters for each tree node since the actual distributions are not known. By performing sensitivity analyses using a simple decision tree model we avoid having to make additional assumptions regarding transition probabilities and probability distributions in deriving our conclusions. To examine the long-term expected QALYs from the three treatment strategies, we ran the model with the 5-year and 10-year seizure-free rates for resective surgery, VNS and medical management. A longitudinal study of QALYs for patients who underwent intracranial monitoring, VNS and medical management would produce better estimates, but is currently unavailable.

Medical management and VNS tend to result in seizure improvement rather than seizure freedom. The chance of a $>$50% reduction in seizures under VNS is 31.0% [43]. The chance of seizure improvement under medical management is on the order of 36.8% [51–54]. Since resective surgery is far more effective at producing seizure freedom than VNS or medical management, it may seem like we are biasing the study to favor intracranial monitoring by considering seizure freedom but not seizure improvement as one of our outcomes. However, significant improvements in QOL scores, as measured by several metrics for QOL, consistently occur only for patients who become seizure-free, not for patients who experience seizure reduction [9]. Thus, our model includes only complete seizure freedom as the desired goal of the treatment options.

We made the assumption that the surgical risk of VNS was the same for both base cases. Although base case 2 had an increased risk of mortality and morbidity from surgery, her risk of morbidity and mortality from VNS implantation was assumed not to be elevated. Given the lack of data quantifying the increased risk in this population, we made this assumption because the risk of VNS implantation is relatively low compared to the risks of intracranial electrode implantation and of resective surgery.

This study does not consider the question of dual therapy with resective surgery and VNS placement. Many patients undergo both of these therapies and this study does not directly address the question of which should be offered first. However, the results of the study indirectly suggest that resective surgery would be the preferred first treatment, as the chance of seizure freedom with VNS is low and implantation would likely defer resective surgery and in doing so lower the overall expected QALYs.

4.2. Utility of the model

For actual patients, the values of parameters in the model will vary from those of our two base cases due to differences in size and location of the epileptogenic zone. For instance, a large resection creates a larger morbidity risk than a small resection. Procedures such as corpus callosotomies and hemispherectomies carry a far larger morbidity risk than the targeted resections which are the focus of our analysis. The decision model presented here can serve as a guide to evaluate treatment options (among intracranial monitoring, VNS and medical management) for patients with differing surgical mortality and morbidity risks, probabilities of seizure localization via intracranial monitoring, probabilities of seizure freedom and values of other model parameters, by referring to the sensitivity graphs for various values of the parameter of concern.

We also note that the risk of morbidity related to resective surgery is not limited to complications such as hemorrhage or stroke. Potential morbidities of epilepsy surgery also include neurologic deficits directly caused by resection, such as a quadrantanopia related to temporal lobectomy. The number used in our base case analysis is the risk of unexpected complications, estimated based on available published data. However, to apply the model to any particular patient the morbidity risk would need to be estimated based on the specific risks for the target area. For example, if the risk of memory decline after temporal lobectomy is estimated at 50%, the risk of morbidity should be changed to 50%. The resulting decision from this parameter adjustment would be found in the one-way sensitivity analysis where the surgical morbidity risk is 50% on the x-axis. Similarly, if aphasia, paresis or vision loss are risks these would need to be estimated and evaluated in the sensitivity analysis plots. Depending on the degree of disability an adjustment to the QOL should could also considered as discussed below.

Another concern not directly addressed by our study is the adjustment of the QOL for expected neurologic deficits after resective surgery, such as the risk of memory decline after dominant temporal lobectomy. This concern is mainly limited to non-lesional temporal lobectomy and has been addressed in other decision analysis studies [55]. The model in our study is intended for non-eloquent resective surgery. If epilepsy surgery is considered in regions that would result in neurologic deficits a patient-specific model adjustment would be necessary. For instance, a moderate decrease in QOL after memory decline was modelled as a QOL discount of -0.25 by Akama-Garren et al. [55], based on other studies assessing QOL of patients suffering from ischemic stroke, intracerebral hemorrhage and dementia [56–58].

5. Conclusions

This study supports current clinical practices. Despite the risks associated with intracranial monitoring and resective surgery, intracranial monitoring yields higher QALYs overall than VNS or medical management for both young and elderly patients with epilepsy that is presumed focal but is MRI-negative. The conclusions of the model hold even when parameters such as the chance of seizure freedom or likelihood of localizing seizure freedom are widely varied. The results for base case 2 affirm reports [50] that intracranial monitoring with the intention of resective surgery is of benefit not only to the typical young patient of base case 1, but also to elderly patients.

The analysis presented herein could be further refined by incorporating more precise model parameters for the base cases as further data regarding the risks and outcomes of intracranial monitoring, resective surgery, VNS and medical management of epilepsy become available. In particular, incorporating high-quality longitudinal data regarding long-term relapse and remission rates could strengthen our decision model. Nonetheless, through the use of sensitivity analysis, this study's findings are robust over the parameter ranges that are clinically observed. Until alternative treatment options with higher seizure-free rates are developed, intracranial monitoring with the intention toward resective surgery is favored for most otherwise-healthy patients with focal but MRI-negative epilepsy.

Conflicts of interest

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