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Predictive factors for outcome of invasive video-EEG monitoring and subsequent resective surgery in patients with refractory epilepsy

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ABSTRACT

Objective: This is a descriptive study of patients who underwent invasive video-EEG monitoring (IVEM) at Ghent University Hospital. The aim of the study is to identify predictive factors for outcome of IVEM and resective surgery (RS). These factors may optimize the patient flow following the non-invasive presurgical evaluation towards IVEM and RS or other treatments.
Patients and methods: Over the past 16 years, 68/710 refractory epilepsy patients included in the presurgical evaluation protocol (M/F 41/27, mean age 33 years) underwent IVEM at Ghent University Hospital. Patient features and follow-up data were collected from the patients' medical files and the electronic patient database at the neurology and neurosurgery department. Predictive factors for IVEM outcome were identified by comparing features of patients with a positive IVEM outcome (i.e. ictal onset zone identification) and patients with a negative IVEM outcome. Predictive factors for RS outcome were identified by comparing features of patients with Engel class I and patients with Engel class II–IV outcome.
Results: In 56/68 patients (82%) IVEM outcome was positive. The occurrence of a seizure-free interval in the patient's history and a non-localizing ictal scalp EEG in patients with a structural abnormality on MRI ($p < 0.05$) were predictive factors for a negative IVEM outcome. 32/68 patients underwent RS. In 22/32 (70%) patients RS resulted in an Engel class I outcome. A structural abnormality on MRI was a predictive factor for a positive RS outcome in patients in whom a focal or regional focus was resected ($p < 0.05$).
Conclusion: This study shows that IVEM identifies one or more ictal onset zone(s) in up to 80% of patients. The potential of IVEM to identify the ictal onset zone is unlikely in patients with a seizure-free interval in their medical history and a non-localizing ictal scalp EEG during the non-invasive presurgical evaluation.
Half of these patients underwent RS with long-term seizure freedom in 70%. Patients with structural MRI lesions have the highest chance of seizure freedom. These findings may contribute to the optimization of patient management during both the invasive and non-invasive presurgical work-up.

1. Introduction

In 15–25% of refractory epilepsy patients included in the presurgical evaluation protocol invasive video-EEG monitoring (IVEM) with intracranial electrodes is required to identify the ictal onset zone [1–4].

IVEM is indicated in patients with normal structural imaging, non-localizing scalp video-EEG monitoring (SVEM), or conflicting results between these two "cornerstone" investigations. IVEM is an expensive and labor-intensive technique associated with medical risks [5–8] and therefore strict patient selection is mandatory [9]. A review by Spencer et al. in 1981 showed that IVEM using depth electrodes increased the number of patients eligible for surgery by 36% compared to scalp video-EEG monitoring (VEM) [10]. IVEM also identified candidates unsuitable for surgery, due to the existence of multiple seizure foci in 18% of patients. It was concluded that IVEM had a major influence on the surgical decision in up to 50% of patients [10].

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Table 1
Overview of statistically analysed data to identify predictive factors for IVEM and RS outcome.

General features (prior to IVEM)	1. Gender 2. Age (at the time of IVEM) 3. Risk factors for epilepsy: febrile seizures, head trauma, CNS infections, tumor, earlier epilepsy surgery 4. Relevant medical history 5. Family history 6. Abnormal clinical neurological examination 7. FSIQ-score
Epilepsy features (prior to IVEM)	1. Age of epilepsy onset 2. Years of epilepsy 3. Seizure type 4. Seizure semiology 5. Seizure-free interval (years) 6. Seizure frequency/month prior to IVEM 7. Number of AED/day prior to IVEM 8. VNS treatment prior to IVEM
Presurgical evaluation (prior to IVEM)	1. Subgroup 1: localising ictal scalp EEG ⃠, MRI lesion ⃠ 2. Subgroup 2: localising ictal scalp EEG ×, MRI lesion ⃠ 3. Subgroup 3: localising ictal scalp EEG ⃠, MRI lesion × 4. Subgroup 4: localising ictal scalp EEG ×, MRI lesion ×, but discongruent 5. Subgroup 5: localising ictal scalp EEG ×, MRI lesion ×, congruent but discongruency with other non-invasive tests 6. Subgroup 6: need for functional mapping 7. Localizing ictal scalp EEG 8. Structural abnormality on MRI 9. Extra-T versus T epilepsy based on SVEM 10. m versus n T epilepsy based on SVEM 11. × unilateral HS versus ⃠ unilateral HS on MRI 12. Syndrome of mTLE

×: present; ⃠: absent; IVEM: invasive video-EEG monitoring; extra-T: extra-temporal; T: temporal; m: mesial; n: neocortical; HS: hippocampal sclerosis; mTLE: mesial temporal lobe epilepsy; FSIQ: full IQ score.

In 10–20% of patients undergoing IVEM, the ictal onset zone cannot be identified [11]. Furthermore the surgical outcome in patients who undergo IVEM is reported to be less successful compared to patients considered suitable candidates following non-invasive testing only [12]. The identification of predictive factors for IVEM and RS outcome would therefore be of great value in the optimization of the presurgical evaluation protocol. In this study, data from patients who underwent IVEM were analysed to identify patient features predicting outcome both for IVEM and for RS.

2. Patients and methods

This study is a retrospective survey of the experience with IVEM at the Reference Center for Refractory Epilepsy at Ghent University Hospital. Since 1992, 68 out of 710 patients underwent IVEM following the non-invasive presurgical evaluation. The presurgical evaluation includes SVEM and optimal MRI, PET and neuropsychological testing. Subsequently the patients were discussed at the multidisciplinary epilepsy surgery meeting.

Patients underwent IVEM based on one of the following criteria:

(1) A non-localizing ictal scalp EEG and absence of an MRI abnormality.
(2) A localizing ictal scalp EEG and absence of an MRI abnormality.
(3) A non-localizing ictal scalp EEG with an MRI abnormality.
(4) A discongruent localizing ictal scalp EEG and an MRI abnormality.
(5) A congruent localizing ictal scalp EEG and an MRI abnormality, discongruency with other non-invasive test.
(6) Delineation of the ictal onset zone from functional cortex (functional mapping).

At Ghent University Hospital subdural electrodes with or without depth electrodes are implanted for IVEM. Depth electrodes are stereotactically implanted via a burr-hole to target a given structure not accessible via subdural electrodes (hippocampus, amygdala, insula, lesion, ...). Subdural grids are implanted via a craniotomy. These grids are able to cover a large part of the neocortex. This is especially useful in case of functional mapping. Subdural strips are slid in place using a burr-hole. These strips are often implanted in combination with depth electrodes to be able to differentiate mesial from neocortical temporal lobe ictal onset.

2.1. Data collection

Since 1992, data from refractory patients included in the presurgical evaluation protocol have been prospectively collected in a standardized way [13,14]. Patient features and medical history were obtained from the patients' files at the neurology and the neurosurgery departments at Ghent University Hospital. Follow-up data after IVEM and consequent treatment were obtained using the electronic medical files at the neurology department.

This resulted in four data sets: 1. general patient and epilepsy features, 2. results of the non-invasive presurgical evaluation protocol, 3. results of IVEM, 4. seizure outcome for a given treatment following IVEM (continued AED, epilepsy surgery, neurostimulation).

2.2. Identification of predictive factors

Two statistical comparisons were designed to identify predictive factors for: 1. the outcome of IVEM and 2. seizure outcome following RS.

- *Outcome of IVEM* was considered *positive* when IVEM resulted in the identification of one or more ictal onset zone(s). This comprised patients with focal, regional or multiple ictal onset zones. A focal ictal onset was defined as an ictal onset with EEG discharges observed on 1–4 electrode contacts. A regional ictal onset was defined as an ictal onset with EEG discharges observed on more than 4 electrode contacts. Patients with multiple ictal onset zones

showed focal EEG discharges on at least 2 different electrodes spatially separated from each other for different seizures.
- *Outcome of IVEM* was considered *negative* when IVEM was unable to identify the ictal onset zone. In other words the ictal onset zone was not sufficiently covered by the intracranial electrodes.
- *Outcome following RS* was defined based on the Engel classification [15]. For the statistical analysis only patients who underwent a resection of a focal or regional ictal onset zone identified by IVEM were included. Patients with multiple ictal onset zones were excluded.

To identify predictive factors for IVEM outcome patients were divided into two groups: Group I consisted of patients in whom IVEM outcome was positive. Group II consisted of patients in whom IVEM outcome was negative. Patient features, epilepsy features and results of the non-invasive presurgical evaluation (Table 1) were compared between both groups, and potential predictive factors for IVEM outcome were statistically analysed.

To identify predictive factors for RS outcome, only patients who underwent a resection of a focal or regional ictal onset zone identified by IVEM were included. This subgroup of patients who underwent RS were subdivided into a group of patients categorized as Engel class I outcome and into a group of patients categorized as Engel class II–IV. Patients' features, epilepsy features and results of the non-invasive presurgical evaluation (Table 1) were compared between both groups and potential predictive factors for surgical outcome were statistically analysed.

The literature was searched for predictive factors for RS and the major predictive factors were included in the analysis in this study. The patient features and epilepsy features that were analysed and compared between the groups to identify predictive are summarized in Table 1. Subgroups of patients based on the results of the non-invasive presurgical investigations were identified and are also summarized in Table 1. Specific features that were included in the statistical analysis were temporal versus extra-temporal epilepsy based on the result of SVEM, mesial versus neocortical temporal epilepsy based on the result of SVEM, unilateral hippocampal sclerosis (HS) based on the optimal MRI result and the occurrence of the epileptic syndrome mesial temporal lobe epilepsy (mTLE).

In case of categorical data, contingency tables were constructed and Fisher's exact tests were performed. In case of continuous variables, the non-parametric (exact) Mann–Whitney *U*-test was used. Statistical significance was assumed in case of p-values < 0.05. Trends ($p < 0.1$) are mentioned. All statistical procedures were performed with SPSS-package version 15.0.

The study was approved by the Ethical Committee of Ghent University Hospital.

3. Results

3.1. General patient and epilepsy features

Between 1992 and 2007, 68 out of 710 patients (10%) included in the presurgical evaluation (M/F 41/27) (mean age of 32 (range: 10–50)) underwent IVEM. In 14/68 patients (21%) the neurological examination was considered abnormal. One patient was mentally retarded (mean FSIQ = 97.5 (range: 52–142)). Risk factors for epilepsy were reported in 76% of patients (febrile seizures 27%, head trauma 25%, perinatal complications 16%, CNS infection 16%, brain tumor 16%, earlier epilepsy surgery 4%). For 4 patients epilepsy in first-degree relatives was reported.

Mean age of epilepsy onset was 13 years (range: 1–40). Half of the patients had complex partial seizures (CPS) and the other half had CPS with frequent secondary generalization. One patient had continuous simple partial seizures (SPS) (i.e. epilepsia partialis continua). Mean epilepsy duration was 19 years (range: 0–43). Nineteen percent of patients had a seizure-free interval ranging from 1 to 8 years (mean 4 years). At the time the presurgical evaluation was conducted, patients had a mean of 15 seizures per month (range: 0, 5–120). The mean number of AEDs was 3 (range: 1–4). Two patients were treated with VNS, and this therapy was ongoing.

3.2. Results of the non-invasive presurgical evaluation

The results of the non-invasive presurgical evaluation, the criteria to perform IVEM and the hypothesis on the location of the ictal onset zone are summarized in Table 2. For 49/68 patients a structural abnormality was identified on MRI. In 35/49 this concerned a unique abnormality and in 14/49 patients multiple lesions. In 17/35 patients this concerned unilateral HS and in 7 patients damage was observed in both hippocampi. For 31/68 patients the ictal scalp EEG revealed unilateral frontal, temporal, frontotemporal, occipital or parietal ictal onset during the scalp video-EEG monitoring. In 36/68 patients SVEM suspected temporal lobe epilepsy and in 17/68 patients the ictal onset zone was believed to be extra-temporal. This was unclear in 15/68 patients. In 2 patients with suspected temporal lobe epilepsy it was explicitly mentioned to be mesial temporal and in 1 patient neocortical. In 9 patients the combination of febrile seizures, unilateral HS and mesial temporal semiology was found.

3.3. Results of IVEM

Based on the results of the non-invasive presurgical evaluation, electrode implantation was designed (number, type and localization of electrodes) in a patient-specific way. This resulted in 8 patients with depth electrodes only, 17 patients with subdural electrodes only and 43 patients with a combination of depth and subdural electrodes covering 1 up to 3 lobes (Table 2).

AEDs were tapered during IVEM to record habitual seizures. A mean of 4 habitual seizures was recorded (range: 0–10) during an IVEM-period that averaged 7.5 days (range: 2–31). One patient (marked with (*) in Table 2) removed the implanted depth electrodes during the first seizure and no further seizures could be recorded. Additionally functional mapping was performed in 8 patients (12%).

Complications occurred in 7 patients (10%). All were transient and fully reversible (cortical edema at the implantation site $n = 2$, subarachnoid hemorrhage $n = 1$, meningitis $n = 1$, subcutaneous abscess at the burr-hole site $n = 1$, damage nervus auriculotemporalis $n = 1$, accidental electrode removal $n = 1$).

IVEM outcome per patient is described in Table 2.

For 23/35 patients with a unique lesion on MRI, the lesion was congruent with the ictal onset zone identified by IVEM. For 4/35 the lesion was not and in 7/35 patients the IVEM was negative because the ictal onset zone was not covered by electrodes. For 1/35 patients an additional zone (next to the lesion) in the brain was identified to be responsible for ictal onset by IVEM.

3.4. Seizure outcome

Overall seizure control for a given treatment following IVEM is listed in Table 2.

3.5. Identification of predictive factors

3.5.1. IVEM outcome

In this series of 68 patients, IVEM outcome was positive in 56/68 patients (Group I, 82%). In 12 patients (Group II, 18%), IVEM outcome was negative. In Group I, 42 patients (75%) had a focal ictal onset,

Table 2
Summary of the results of the non-invasive presurgical evaluation, the criteria to perform IVEM, the hypothesis on the ictal onset zone in the brain, the implanted electrodes, IVEM outcome, performed treatment and outcome per patient.

Pt initials	Ictal scalp EEG	Classification based on SVEM	Optimal MRI	mTLE syndrome	PET (hypome-tabolism)	Neuro-psychology (deficit)	Criteria for IVEM	Hypothesis	Type of electrodes implanted	Lobe coverage by IVEM	IVEM outcome	Ictal invasive EEG	Treatment	Outcome (Engel)
VG	LT	T	normal	not mTLE	LFP + T	RPT	2	bilat T or P or L F	D	mT	Pf	LH	RS	I
CQ	bilat T	T	bilat HS	not mTLE	L ant T	broad	3	bilat T	D + S	mT;T	Pf	LH	RS	I
CB	no ictal disch.	extra-T	R FT cyst	not mTLE	–	–	3	RFT	S	T;F	Pf	RF	RS	I
DCL	no ictal disch.	unclear	LHS	mTLE	normal	broad	3	LmT	D + S	mT;T	Pf	LH	RS	I
DF	FT	unclear	LHS	not mTLE	normal	normal	3	bilat T	D + S	mT;T;F	Pf	LH	RS	I
DL	bilat ictal disch.	T	LHS	mTLE	LT	mild T + F	3	bilat T or F	D + S	mT;T;F	Pf	LH	RS	I
HF	no ictal disch.	T	R H cyst	not mTLE	RT	T	3	RT	S	T	Pf	RnT	RS	I
LC	L hemisph.	nT	LHS	mTLE	L FP + mT	F	3	L mT or L FP	D + S	mT;T;F	Pf	LH	RS	I
MC	bilat theta	T	RHS	mTLE	RT	RPTF	3	bilat T	D + S	mT;T	Pf	RH	RS	I
VH	L hemisph.	extra-T	L mT cyst	not mTLE	LT	broad	3	LT	S	F;P	Pf	LSMA	RS	I
LN	bilat ictal disch.	T	L HS + biF signal abnl	not mTLE	L ant nT + mT	broad	3	bilat T or bilat F	D + S	mT;T	Pf	LH	RS	I
BP	L T	T	L HS + L 1 glioma or MD	not mTLE	bilat T	m + nT	4	L T and I	D + S	mT;T;F	Pf	LH	RS	I
DWC	R T rhytm.	mt	R HS + R OT signal abnl	not mTLE	RT + O	RT	4	RTorRO	D + S	mT;T;P	Pf	RH	RS	I
DA	R T rhytm.	T	bilat HS + R T cyst	not mTLE	RT	RT	4	bilat T	D + S	mT;T	Pf	RH	RS	I
SL	L FT	unclear	L basal F cyst	not mTLE	normal	–	4	L basal F or L FT	S	T;F	Pf	LF	RS	I
AH	L T	T	LHS	mTLE	RT	RFT	5	bilat T	D + S	mT;T	Pf	LH	RS	I
SS	R ant FT rhytm.	extra-T	RHS	not mTLE	RT	RT	5	RmT	D + S	mT;F	Pf	RH	RS	I
VHF	L T rhytm.	T	LHS	mTLE	LmT	LT	5	LmT	D	mT	Pf	LH	RS	I
VEC	L pre C	extra-T	L F cavernoma	not mTLE	LF	abnormal	6	LF	S	F	Pf	LF	RS	I
VD	muscle	extra-T	R FP astrocytoma	not mTLE	RFP	normal	6	RFP	S	F;P	Pf	RF	RS	I
BE	LT or F	unclear	normal	not mTLE	bilat mT + L F	normal	1	bilat T or L F	D + S	mT;T;F;P	Pr	RnT	RS	I
AJ	R F slow waves	extra-T	RHS	not mTLE	R ant mT	normal	4	R mT or R F	D + S	mT;T;F;I	Pr	RA	RS	I
VM	T	T	normal	not mTLE	LT	L	1	LT	D + S	mT;T	Pf	LH	RS	II
DCV	R	unclear	normal	not mTLE	RT	not lateralized	1	RT	D	mT	Pf	RH	RS	III
DA	R mT	mT	normal	not mTLE	R FT + L T	RT	2	bilat T and R F	D	mT	Pf	RH	RS	III
VM	no ictal disch.	T	L mT lesion	not mTLE	normal	F	3	L mT or F	D	mT	Pf	LH	RS	II
MS	T	T	L HS	mTLE	normal	IQ comp.	3	bilat T	D + S	mT;T	Pf	LH	RS	IV
VF	R parasagital	extra-T	R P hemosiderine	not mTLE	R P	F	6	R P	S	P	Pf	RP	RS	III
TP	muscle	T	R T cyst	not mTLE	R T	abnormal	3	R T	D + S	mT;TF	Pm	RF+RH	RS	III
DW	RFT	T	bilat HS	not mTLE	R post mT	several	4	bilat mT	D + S	mT;T;F	Pm	4 LnT + 1 RH	RS	III
ML	R T rhytm.	T	bilat HS	not mTLE	RT	RH + T	4	bilat T	D	mT	Pm	most RH + other regions	RS	IV
VJ	T	mT	bilat HS	not mTLE	RT, LF orb + mT	RH + T	3	bilat T or LF	D + S	mT;T	N*	no seizures recorded	RS	III
HT	muscle	extra-T	normal	not mTLE	broad	LF	1	LF	S	F	Pf	LC	MST	I
HK	RpreC	extra-T	R parasagital CD	not mTLE	normal	normal	6	RC	S	P	Pf	RC	MST	IV
VD	muscle	extra-T	R F and P focal CA	not mTLE	I + preF	bilat	3	extra-T	S	F	Pf	R postC	RS + MST	I
VPG	no lat.	extra-T	R preC glioma	not mTLE	R hemish.	normal	3	R preC	S	F;P	Pf	RC	RS + MST	III
VRJ	no ictal disch.	extra-T	L preC cavernoma	not mTLE	normal	Lant	6	LC	S	F	Pf	LpreC	RS + MST	I
BA	bilat FT	T	normal	not mTLE	LnT	LP	1	bilat T or L P	D + S	mT;T	Pf	LH	DBS	III
VLK	LT	T	normal	not mTLE	L ant + mT	F	2	L T or bilat F	D + S	mT;T;F	Pf	RH	DBS	III
MW	RT	T	normal	not mTLE	RT	R hemisph.	2	RT	D + S	mT;T	Pf	RnT	DBS	IV
SW	LFT	unclear	normal	not mTLE	LT	bilateral	2	bilat T	D + S	mT;I	Pf	LH	DBS	IV
CJ	L antFT rhytm.	T	L HS + L T n damage	not mTLE	LmT	mild	4	LT	D + S	mT;T	Pf	LH	DBS	I
GM	LT	T	bilat HS	not mTLE	LF	RmT	4	bilat T or L F	D + S	mT;T	Pf	LH	DBS	III
VMC	LT	T	LHS	mTLE	LT	non-dominant P	5	L mT or P	D + S	mT;P	Pf	LH	DBS	I
SI	bilat F - T	unclear	normal	not mTLE	R m to n T	not focal	1	bilat F or T	D + S	mT;T;F	Pr	RH	DBS	IV
VW	bilatT	T	normal	not mTLE	normal	LFT	1	bilat T or L F	D + S	mT;T	Pm	bilat H(3L;1R)	DBS	IV
BV	extra-T	extra-T	normal	not mTLE	L FT n + bilat mT	T	1	bilat T or L F	D + S	mT;T	Pm	bilatH(5L;1R)	DBS	IV
LG	R FT rhytm.	T	bilat HS	not mTLE	normal	FT	4	bilat T	D + S	mT;T	Pm	bilat H(2R;1L)	DBS	IV
DA	muscle	unclear	normal	not mTLE	normal	LFT	1	LForT	D + S	mT;T;F	N	no focal ictal disch.	DBS	IV

Table 2 (*Continued*)

Pt initials	Ictal scalp EEG	Classification based on SVEM	Optimal MRI	mTLE syndrome	PET (hypome-tabolism)	Neuro-psychology (deficit)	Criteria for IVEM	Hypothesis	Type of electrodes implanted	Lobe coverage by IVEM	IVEM outcome	Ictal invasive EEG	Treatment	Outcome (Engel)
DWA	L hemisph.	T	RHS	not mTLE	LT	normal	3	bilat T	D + S	mT;T;F	Pf	LH	VNS	III
DB	Extra-T	extra-T	LHS	not mTLE	L hemisph.	bilat T + L F	3	bilat T or L F	D	mT;F	Pf	LH	VNS	III
PK	L postT	unclear	L post T CD	not mTLE	L	R	5	L post T or L	D + S	mT;O	Pf	LO	VNS	IV
VCK	LO	unclear	normal	not mTLE	normal	bilat FT	2	bilat T or F or L O	D + S	mT;T	Pr	RnT	VNS	III
PM	RFT	T	normal	not mTLE	bilat	normal	2	bilat T	D + S	mT;T	Pm	bilat H	VNS	IV
KM	R Fpolar and T delta	unclear	L preC, I and put enceph seq	not mTLE	L caput NC + F	R preC	4	Extra-T or T	S	T;F	Pm	bilatF	VNS	IV
VAW	RT	T	normal	not mTLE	bilat mT + L T	bilat T	2	bilat T	D + S	mT;T	N	RnT broad ictal disch.	VNS	IV
VDP	bilat T	T	R H cyst	not mTLE	LFP + T	normal	3	bilat T or L FP	D + S	mT;T	N	no focal ictal disch.	VNS	III
CY	RF	extra-T	R P glioma	not mTLE	normal	C	4	R F or R C	S	P	Pf	RC	AED	IV
VR	RT	T	LHS	not mTLE	LmT	T + F	4	L mT or F	D + S	mT;T	Pr	LnTO	AED	III
DMI	L preC	extra-T	normal	not mTLE	LT	bilat mT	2	L preC or bilat T	D + S	mT;T;F	Pm	bilat H	AED	LFU
VOC	LForT	unclear	normal	not mTLE	–	R + LH (postop)	1	ForT	D + S	mT;T;F	N	L broad ictal disch.	AED	III
CM	bilat T	T	LHS	mTLE	LT	broad	3	bilat T	D + S	mT;T;F	N	no focal ictal disch.	AED	III
ME	bilat - R FT	unclear	L T signal abnl	not mTLE	normal	F	3	bilat T or F	S	T	N	no focal ictal disch.	AED	III
DL	R hemisph.	unclear	ROTMD	not mTLE	RT	R hemisph.	3	RTorO	D + S	mT;T;P	N	R broad ictal disch.	AED	IV
NK	bilat - R T	T	RHS	not mTLE	RmT	abnormal	3	bilat or R mT	D	mT	N	no focal ictal disch.	AED	IV
RK	no ictal disch.	extra-T	bilat F signal abnl	not mTLE	R ant nT	–	3	R nT or bilat F	S	T;F	N	no focal ictal disch.	AED	IV
KE	bilat T	T	RHS	not mTLE	–	bilat T	3	bilat T	D + S	mT;T;O	N	no focal ictal disch.	AED	LFU
AJ	L T theta waves	unclear	L T cavernoma	not mTLE	normal	dominant T	5	LT	S	T;F	N	no focal ictal disch.	AED	I

Abbreviations: T, temporal; F, frontal; O, occipital; P, parietal; C, central; I, insular; L, left; R, right; n, neocortical; m, mesial; bilat, bilateral; ant, anterior; post, posterior; H, hippocampus; HS, hippocampal sclerosis; MD, migration disorder; CD, cortical dysplasia; seq, sequel; put, putamen; enceph, encephalitis; abnl, abnormality; disch, discharges; hemisp, hemisphere; rhytm, rhytmicity; CA, cortical atrophy; NC, nucleu caudatus; A, amygdala; comp, compensation; D, depth electrodes; S, subdural electrodes; P f, positive IVEM outcome with focal ictal onset; P r, positive IVEM outcome with regional ictal onset; P m, positive IVEM outcome with multiple ictal onset; N, negative IVEM outcome; N*, negative IVEM outcome due to accidental electrode removal; SMA, supplemental motor cortex; RS, resective surgery; MST, multiple subpial transections; DBS, deep brain stimulation; VNS, vagus nerve stimulation; AED, anti-epileptic drugs SVEM, scalp video-EEG monitoring; IVEM, invasive video-EEG monitoring patients inside the square marking (– – –) were taken into account for the statistical analysis to identify predictive factors for RS outcome

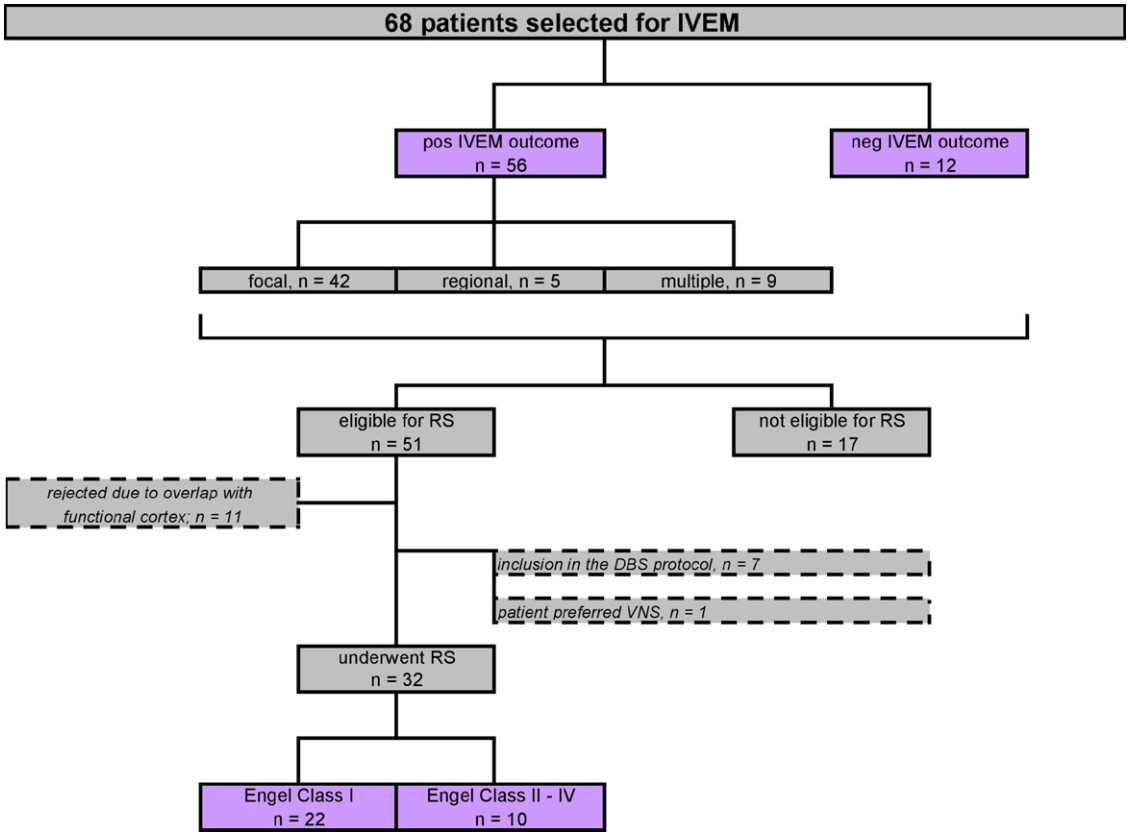

Fig. 1. Patient flow-chart from IVEM to RS abbreviations: IVEM, invasive video-EEG monitoring; RS, resective surgery; DBS, deep brain stimulation; VNS, vagus nerve stimulation.

5 patients (9%) had a regional ictal onset, and 9 patients (16%) had multiple ictal onset zones (Fig. 1).

The statistical comparison between these 2 groups revealed two significant predictive factors for a negative IVEM outcome: (1) a seizure-free interval in the past, and (2) IVEM performed due to a non-localizing ictal EEG but presence of a structural abnormality.

Besides the statistically significant findings, the analysis also revealed statistical trends. There was a trend for a correlation between a negative IVEM outcome and (1) high seizure frequency, and (2) non-localizing ictal scalp onset on EEG in both lesional and non-lesional patients. There was a trend for a correlation between positive IVEM outcome and the presence of a brain tumor ($0.053 < p < 0.083$).

The other patient data and features summarized in Table 1 did not reach statistical significance for predicting IVEM outcome.

3.5.2. *Seizure outcome following RS*

Forty out of 68 patients (58%) were considered eligible for RS. Thirty-two out of 40 patients eventually underwent RS. In 28/32 patients IVEM identified a focal or regional ictal onset zone. In 3/32 patients multiple onset zones were identified. In 2/3 the predominant ictal onset zone was resected and in 1/3 a partial frontal lobectomy was combined with a hippocampectomy. In 1/68 no seizures were recorded due to accidental removal of a depth electrode. Eleven patients with focal/regional ictal onset were rejected for RS due to overlap of the ictal onset zone with functional cortex. Five out of 11 underwent multiple subpial transections (MST) with (3/5) RS or without RS. Seven out of 40 patients who were suitable for RS, participated instead in an ongoing deep brain stimulation (DBS) protocol where patients were allowed to choose between DBS or RS. One out of 40 patients was treated with vagus nerve stimulation (VNS) because the results of IVEM were inconsistent with those of non-invasive testing (Fig. 1).

The 32 surgically treated patients had a mean follow-up of 65 months (range 12–120 months). Twenty patients were classified as Engel class Ia, 2 patients as class Ib. In 5 patients belonging to class Ia, AEDs have been completely tapered. Ten patients were classified as Engel class II–IV. Two out of 10 patients still have rare disabling seizures, and are classified as class II (IIa and IIb). Six patients have a 'worthwhile' improvement in seizure frequency and are classified as class IIIa. Two patient are categorized as class IV, 1 patient has a seizure frequency reduction of 50% and 1 patients did not show any improvement.

Eighteen out of 23 patients with a unique structural abnormality on MRI congruent with the ictal onset zone identified by IVEM underwent RS and 15/18 patients had Engel Class I (83%).

The statistical comparison between patients with Engel class I and Engel class II–IV outcomes, revealed one predictive factor for Class I outcome following RS. The presence of a structural abnormality on MRI was associated with favorable outcome. Besides this statistically significant finding, there was a trend suggesting that patients with a lower mean number of seizures per month before RS have a higher chance of Engel class I outcome ($p = 0.068$).

The other patient features summarized in Table 1 did not reach statistical significance.

4. Discussion

4.1. *Patient selection*

IVEM is indicated when it is reasonable to believe that RS could be performed, but the non-invasively obtained data are inadequate, and more information is needed. During IVEM, intracranial elec-

trodes are used to precisely identify the location of the ictal onset zone and to delineate functional tissue prior to RS. Exact criteria defining what is sufficient concordant or discordant data are not available and therefore differ somewhat from one epilepsy center to another. Specific indications for IVEM evaluation include: 1. insufficient concordance of non-invasively obtained data. This means there remains uncertainty about the localization of the epileptogenic zone. This could be due to the presence of an MRI structural abnormality with non-localized EEG or due to absence of a structural lesion on MRI and localized abnormality of excitability on EEG. 2. discordance of non-invasively obtained data, so that the existence of a single epileptogenic zone must be proven and better localized. 3. epileptogenic lesion within or immediately adjacent to vital cortex so that functional mapping must be performed before resection [9].

For all patients included in this study, the non-invasive presurgical evaluation remained inconclusive and an invasive investigation was considered necessary to continue the presurgical evaluation. At Ghent University Hospital patients are planned for IVEM when one of 6 criteria is fulfilled. This resulted in IVEM in about 10% of patients being included in the presurgical protocol. Other epilepsy centers have reported comparable percentages although in some centers up to 25–50% of refractory epilepsy patients are considered eligible for any kind of IVEM [1–3,9]. These centers have specific expertise in IVEM and may therefore have higher implantation rates. Studies specifically describing selection criteria for IVEM are rare. In one study, Henry et al. prospectively evaluated 6 specific indications for performing IVEM in 50 patients in whom the non-invasive presurgical evaluation resulted in inadequate localization of ictal onset [16]. They found that IVEM is strongly indicated in case of non-localizing or bilateral ictal onset on scalp EEG, and when conflicting scalp video-EEG monitoring and MRI result are found

4.2. IVEM outcome

This retrospective study revealed an indispensable role for IVEM in the presurgical evaluation protocol, as the non-invasive presurgical evaluation had not identified the ictal onset zone well enough to justify RS in any of the included patients. We were able to show that this is also true for patients with a single structural abnormality on MRI. Despite the fact that for 23/35 patients (65%) IVEM showed that their single MRI lesion was congruent with the ictal onset zone, for 13 patients this was not the case. This means that for 1/3 patients a lesionectomy without IVEM would have failed in resecting the epileptogenic zone.

With IVEM, the ictal onset zone was identified in 56/68 patients (82%). The chance of a positive IVEM outcome, independent of what type of implantation strategy used, is reported to range from 60 to 94% [8,11,17–20].

In our series, IVEM identified multiple ictal onset zones in 9 patients (13%). Other studies have reported the identification of multiple foci in 10–30% of patients investigated with intracranial monitoring [8,10,21,22]. In this context, Spencer and colleagues stressed the need and importance of combining subdural and depth electrodes, to be able to identify more than one focus [8]. The major limitation of IVEM is the sampling bias namely that one will only measure activity where the electrodes are placed.

Eighteen percent of our patients had a negative IVEM outcome. In the series described by Siegel et al. IVEM outcome was negative in 14% of patients [22]. In comparison to our study, all patients in Siegel's series had normal findings on MRI. In the subgroup of patients without structural abnormalities on MRI we did not find statistical differences with regards to IVEM outcome.

In case of a negative IVEM outcome, inappropriate sampling of brain tissue has been performed with recording of spreading activity rather than ictal onset zone discharges recorded by the implanted electrodes [19]. In these cases, the hypothesis on which the implantation design was based was incorrect, or at least insufficient. Siegel et al. re-evaluated 9 patients with a second IVEM, after the first IVEM outcome was negative, presumably due to sampling error. For 7/9 patients this resulted in satisfactory localization, 6 patients had RS and 5 became seizure-free. One patient with post-operative seizures was invasively investigated for a third time and did become seizure-free after a limited extension of the resection zone [23]. In our series to date no patients have bee re-evaluated with a second IVEM.

We found a correlation between negative IVEM outcome and a seizure-free interval in the past. It is unclear why these patients would have a less successful IVEM outcome. However, we did find that patients in whom seizures where controlled for some years and afterwards became intractable again, had significantly worse IVEM outcomes. This finding should be examined more closely in a prospective study before we start using it in the counseling of patients who are proceeding towards an invasive evaluation.

The second predictive factor was non-localizing ictal scalp EEG despite the presence of a structural abnormality on MRI. More than half of the patients with a negative IVEM outcome were selected for IVEM based on non-invasive results that turned out to be a predictive factor for negative IVEM outcome. Our findings suggest that patients in whom the ictal scalp EEG does not reveal any clues on the ictal onset localization are the most difficult candidates for IVEM. That is why these patients need more accurate and sensitive non-invasive neurophysiologic evaluation before being investigated invasively. In our research group, and others, magnetoencephalography (MEG) is being investigated in this way because this non-invasive method is able to measure the magnetic activity of the brain more completely to focus intracranial recordings more successfully and in this way reduce the sampling error.

Other diagnostic tools such as ictal SPECT studies have already shown that they can make a contribution to a better working hypothesis for the regional localization of the seizure focus, and thus can guide the placement of intracranial EEG electrodes [24–26].

Other reports indicate that the most successful localization with IVEM is achieved for temporal lobe cases, and in extra-temporal cases when a lesion is found on MRI [8,17–20]. In our population this was also analysed. However temporal lobe or extra-temporal lobe epilepsy were not identified as predictive factors for IVEM outcome. One reason for not reaching statistical significance might have been the small number of patients in the subgroups.

4.3. RS outcome

In general, the proportion of patients undergoing RS following IVEM ranges between 74% and 100% [3,6,7,17,27–29]. Our population differed from the above, as only 32/68 patients (47%) eventually underwent RS, despite the fact that IVEM was positive in 56/68 patients (82%). Eleven patients however dropped out due to overlap of the ictal onset zone with functional cortex. Five out of 11 patients did undergo MST with or without RS. An additional 7 patients, eligible for surgery, preferred to participate in a deep brain stimulation protocol available at Ghent University Hospital [30–32].

In our series, half of the patients who had IVEM eventually had RS, and in 2/3 seizure outcome was excellent after a mean follow-up of 65 months. Drugs were tapered completely and successfully in a minority of patients, which is comparable to other case series in the literature [19]. In studies that report seizure outcome following RS in patients who underwent IVEM, 45–63% of patients become seizure-free [3,6,7,17,28,29,33,34]. One study reported worse seizure outcomes following resection of a unilateral regional ictal onset as defined by IVEM. The definition of 'regional'

Table 3
Summary of reported predictive factors for outcome following resective surgery in literature.

Ref.	Predictive factors (POSitive or NEGative)	'Outcome'	Population
[35]	POS: extensive resection, abnl MRI, MTS, FS, MRI/EEG concordance, tumor; NEG: invasive monitoring, postop discharges	Meta-analysis	Meta-analysis
[12]	POS: MTS, FS, tumors, abnl MRI, MRI/EEG concordance, extensive resection; NEG: postop discharges, invasive monitoring	Systematic review	Systematic review
[38]	POS: MRI/EEG concordance, sz freedom 2 months postop	Seizure-free (+aura)	Multivariate
[39] (a)	NEG: GTC-seizures, aura* (at different FU-times; * last year of FU)	ILAE classification	mTLE and HS
[39] (b)	NEG: early FS, complicated FS, interval between febrile sz and epi onset, early sz, risk factors, longer epi, older age at surgery, type of surgery	Engel classification	mTLE and HS
[37]	POS: abnl MRI, abnl APD; NEG: cortical dysplasia on APD	Engel; I versus II–IV	mTLE
[40]	NEG (2 years postop): preoperative GTC-sz, ictal dystonia; NEG (3 years postop): ictal dystonia, longer epi; NEG (5 years postop): longer epi		TLE and HS
[41]	POS: localizing interictal EEG, absence of GTC-sz; NEG: perinatal complications	Seizure-free (+aura)	MTS (no MRI)
[42]	POS: localizing ictal EEG, tumor, favorable sz situation at 6 months postop; NEG: left-sided surgery, focal cortical dysplasia	'Seizure-free'	nTLE
[43]	NEG: preop GTC-sz (neocortical epil); late surgery (mTLE)	Late recurrence	
[44]	POS: localizing ictal EEG, complete resection	Engel; Ia versus Ib-IV	Post epi (T-P-O)
[36]	NEG: nl MRI, extraF abnl on MRI, non-localizing ictal EEG, acute postop sz, incomplete resection	Seizure-free (+aura + sz 1 week postop)	FLE
[45]	POS: concordant presurgical testing	'Seizure-free'	OLE
[46]	POS: complete resection; NEG: multilobar resection	Engel; I–II versus III–IV	Children
[47]	POS: unifocal lesion MRI, older age onset, unilobar resection, complete lesionectomy, tumor	Engel; I versus II–IV	Children

MTS, mesial temporal sclerosis; FS, febrile seizures; T, temporal; P, parietal; O, occipital; F, frontal; mTLE, mesial temporal lobe epilepsy; nTLE, neocortical temporal lobe epilepsy; FU, follow-up; abnl, abnormal; sz, seizures.

in this study was mesial and neocortical temporal lobe involvement [8]. In these cases, broader resections were suggested. In our series both patients in whom IVEM identified a regional ictal onset and who underwent RS were classified Engel class I. The extent of the resection in these 2 cases was comparable to patients in whom a focal ictal onset on IVEM was identified. However comparison is difficult as our definitions are not identical.

Three out of 9 patients with multiple ictal onset zones identified by IVEM in our series did undergo RS, but none of them achieved an Engel class I outcome. Two out of 3 ended in Engel class III and 1/3 in Engel class IV. The identification of multiple ictal onset zones on IVEM, can therefore be considered a valuable result, as it should probably lead to a decision not to perform RS [10]. Additionally one of our patients underwent RS despite a negative outcome of IVEM because he removed the depth electrodes during the first seizure. His surgery, based on other localization criteria, resulted in an Engel Class III seizure outcome. Excluding patients without a focal or regional ictal onset revealed by IVEM would result in Engel Class I outcome in 22/28 cases (79%). Patients in whom IVEM identified multiple ictal onset zones have been reported to undergo RS. For example, in Cascino's group of temporal lobe epilepsy patients, 83% of patients were considered eligible candidates. These were patients in whom IVEM identified one unique seizure focus, although a few patients had more than one. The latter were considered suitable for resective surgery only when one (out of multiple) ictal onset zones was responsible for ≥80% of seizures [28].

Patients who did not achieve seizure freedom following RS, did show a better outcome when compared to other patients with multiple ictal onsets or negative IVEM who underwent other treatments such as VNS or continued AEDs. Therefore, when the optimal treatment is searched for in this group of patients, despite the lower chances of seizure freedom, RS should be kept in mind. In these cases, risks and side effects of surgery should be balanced against the risks of ongoing refractory epilepsy treated with AEDs and benefits and side effects of other treatment options such as VNS.

As mentioned above, for the statistical analysis to identify predictive factors for seizure outcome following RS patients with multiple ictal onset zones identified with IVEM were excluded. This allowed us to compare patients with different seizure outcomes, all of whom underwent a resection of a focal or regional ictal onset zone identified by IVEM. The identified predictive factor for good seizure outcome following RS was the presence of a structural abnormality on MRI. This has also been a predictor factor in other studies of outcome following RS with or without invasive work-up [12,35–37].

When reviewing the literature, we found that there were striking differences in definitions and classifications of seizure outcome that make comparisons problematic. In the literature various factors predicting excellent surgical outcome in different epilepsy populations, with or without invasive work-up, have been identified. These are summarized in Table 3. Important features in literature besides the presence of a structural abnormality are temporal lobe epilepsy, hippocampal sclerosis and mTLE syndrome. In our population these features were included in the analysis but were not identified to be predictive factors for RS outcome. This might be a consequence of the limited number of patients in the different subgroups that were compared for this statistical analysis.

Besides an extensive description we were able to perform a statistical analysis to identify predictive factors for IVEM and RS outcome within this group of invasively investigated patients. The statistical analysis revealed that IVEM identifies (one or more) ictal onset zone(s) in up to 80% of invasively investigated patients. The potential to localize this ictal onset zone is unlikely in patients with in their medical history of seizure-free interval and a non-localizing ictal scalp EEG during the non-invasive presurgical evaluation.

Half of patients being invasively worked-up became good surgical candidates resulting in long-term seizure freedom in 70%. Patients with structural MRI lesions have the highest chance of

seizure freedom. These findings may contribute to the optimization of patient management during both the invasive and non-invasive presurgical work-up.

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