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Early epilepsy surgery for non drug-resistant patients

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ABSTRACT

The aim of epilepsy treatment is to achieve seizure freedom. Surgery is often still considered a late option when pharmacological treatments have failed and epilepsy has become drug-resistant.

We analyse the clinical features and surgical outcome in patients who underwent surgery without experiencing drug-resistance comparing with those observed in patients who became drug-resistant.

Two-hundred and fifty patients with symptomatic focal epilepsy (12.1% of patients who underwent surgery at the "Claudio Munari" Epilepsy Surgery Center) were selected on the basis of initial period of seizure freedom and followed-up for at least 12 months. Patients were divided into two groups: those who underwent surgery during the initial period of seizure freedom (n = 74), and those who underwent surgery after an initial seizure-free period followed by drug-resistance (n = 176).

Outcomes were significantly better in non-drug-resistant patients ($p < 0.001$), all of whom had Engel class Ia or Ic. In the drug-resistant group, 136 patients (77.3%) had class Ia or Ic. The median post-operative follow-up was respectively 75.0 and 84.0 months.

Epilepsy surgery is a successful treatment, especially for non-drug-resistant patients with focal epilepsy with structural etiology. The timing of surgery affects the outcomes, and "early" surgery should be preferred to prevent likely drug-resistance and to improve prognosis.

1. Introduction

One-third of patients with focal epilepsy with structural etiology are not made seizure-free by their first anti-seizure medication (ASM) and have minimal chances of achieving seizure freedom with subsequent medications [1-5]. In a selected group of patients, epilepsy surgery offers the opportunity to obtain seizure freedom and to potentially withdraw ASMs, thus improving cognitive and psychosocial function and quality of life [6,7]. This is particularly crucial in paediatric patients who have a longer life expectancy Fig. 1 and Fig. 2.

Epilepsy surgery is conventionally offered to patients who are drug-resistant, defined by the International League Against Epilepsy as those who failed to achieve sustained seizure freedom after adequate trials of two appropriately chosen and tolerated ASMs, used alone or in combination [5]. Epilepsy surgery is an established treatment for drug-resistant temporal lobe epilepsies [8], resulting in short- and long-term seizure remission rates of more than 80% [9-12]. In extra-temporal lobe epilepsies, the seizure remission rate is 50–55% [13,14]. The presence of an anatomical lesion is associated with a more favorable clinical outcome [15,16], whereas a long disease duration is an unfavorable prognostic factor [17,18]. The complications of epilepsy surgery are comparable with those associated with other neurosurgical procedures [19-25].

In addition to the widely recognized indications for epilepsy surgery, it is worth considering that patients with non-drug-resistant (NDR) symptomatic focal epilepsies with well established anatomo-electro-clinical correlations may benefit from "early" surgery. In these patients, surgery could prevent the development of drug-resistant epilepsy, and increase the probability of a good clinical outcome. "Early" surgery in patients who have not yet become drug-resistant, could reduce disease duration and improve significantly post-operative outcome, thereby reducing the need for long-term ASM treatment and influencing positively quality of life.

In order to evaluate this hypothesis, we selected retrospectively from the large cohort of consecutive patients who have undergone epilepsy surgery at "Claudio Munari" Epilepsy Surgery Center, those who had experienced an initial seizure-free period. We compared clinical features and surgical outcome in patients who

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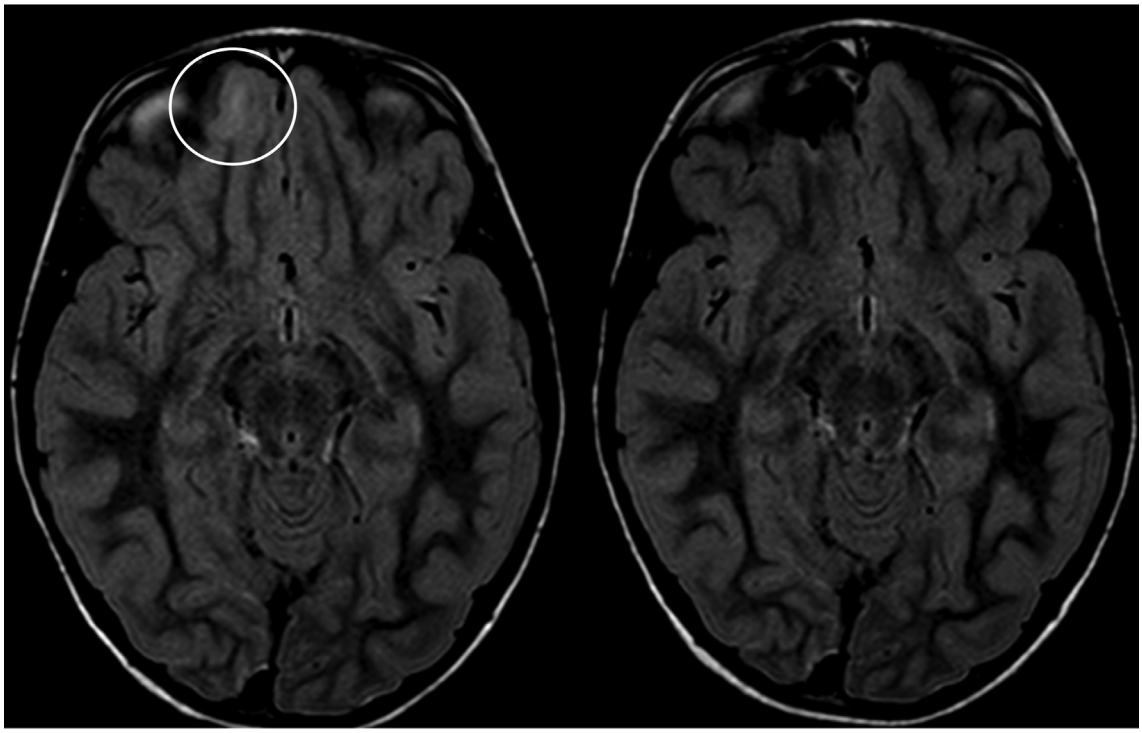

Fig. 1. MRI axial FLAIR T2-W sequences (1.5 T machine Philips ACS-III-NT, 3 mm thickness). a) Right fronto-orbital focal cortical dysplasia in a six-year-old patient with non-convulsive status epilepticus at the onset, and seizure-free since the introduction of ASM treatment. b) Surgery (lesionectomy) was performed one year after the onset. The patient, in class Ia, stopped ASMs one year later. The entire duration of epilepsy was 30 months.

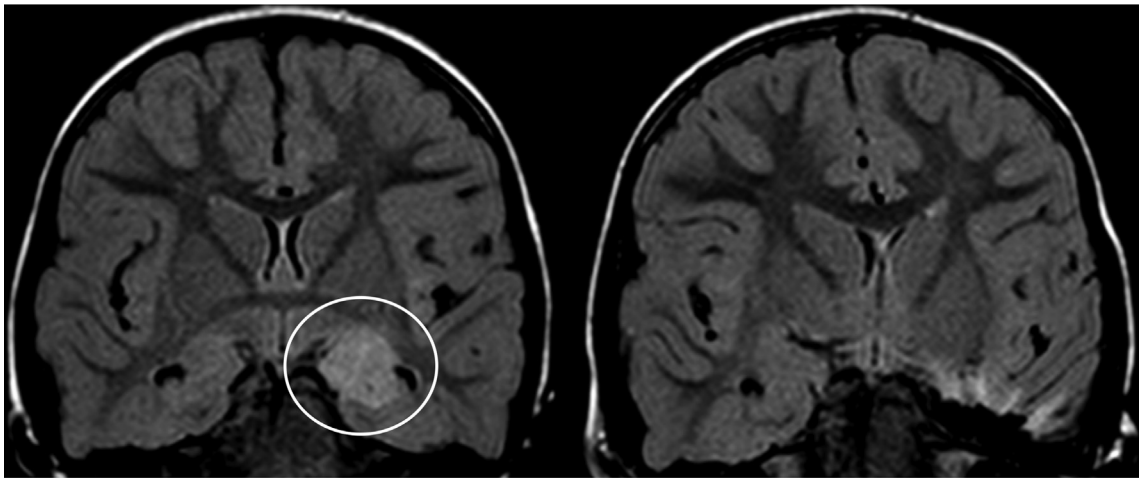

Fig. 2. MRI coronal FLAIR T2-W sequences (1.5 T machine Philips ACS-III-NT, 3 mm thickness). a) A two-year-old patient, six months after seizure onset for a preoperative left mesial temporal glioneuronal tumor. b) A Left antero-mesial temporal lesionectomy and cortectomy was performed, based on the anatomo-clinical correlations. Twenty-four months later the patient is class Ia and does not require ASM.

underwent surgery prior to developing drug-resistance with those recorded in patients who became drug-resistant and underwent surgery then. The findings were used to outline criteria for considering epilepsy surgery in symptomatic and non-drug-resistant patients.

2. Patients and methods

2.1. Patients

We retrospectively analyzed 2075 consecutive patients who underwent resective surgery at Claudio Munari Epilepsy Surgery Center from May 1996 up to December 2019 on the basis of the concordance of their anatomo-electro-clinical characteristics (clinical features, seizure semiology, neuroradiological and interictal electro-encephalography [EEG] findings), and enrolled 250 patients (12.1%) who fulfilled the following inclusion criteria:

i) initial period of drug responsiveness (a first seizure-free period of at least three months after the onset of epilepsy);

ii) at least 12 months' post-operative follow-up;

iii) the presence of a brain lesion revealed by the magnetic resonance imaging (MRI).

These patients were then divided in two groups: those who had experienced a seizure-free period during ASM treatment and never had been drug-resistant (the NDR group) and those who had experienced an initial seizure-free period subsequently followed by

drug-resistance (the DR group). Their clinical, demographic and neuroradiological characteristics and post-surgical outcomes were compared.

2.2. Statistical analysis

The continuous variables (age at the time of epilepsy onset, disease duration, and age at the time of epilepsy surgery) were summarized as median values and interquartile ranges (IQR), and compared using a two-tailed Mann-Whitney *U* test. The categorical variables of outcome (Engel class Ia *vs* the other classes), complete ASM discontinuation and video-EEG monitoring, were evaluated by means of contingency analysis, and the independence of the rows and columns in the tables was verified using Fisher's exact test.

The effect of possible confounding variables was evaluated by means of multivariate analysis using a forward stepwise (conditional) logistic regression in which the dependent variable was outcome (0 for NDR, 1 for DR) and the covariates were surgery confined to the temporal lobe, duration of epilepsy since surgery, study group (DR or NDR) and histology (tumour, cavernoma, gliosis, tuberous sclerosis, malformation of cortical development, hippocampal sclerosis [HS] or other).

All of the analyses were made using SPSS version 25 software (IBM Corp., Armonk, NY, USA) and a p value of ≤ 0.05 was considered significant.

Table 1
Neuroradiological findings, site of surgery and histology.

	NDR patients (n. 74)	DR patients (n. 176)
Neuroradiological findings		
Glioneuronal tumor	51 (68,9%)	47 (26,7%)
Hippocampal sclerosis	2 (2,7%)	41 (23,3%)
Malformation of cortical development	9 (12,2%)	62 (35,2%)
Post-traumatic/hemorrhagic/ischemic injury	0	14 (7,9%)
Cavernous angiomas	10 (13,5%)	8 (4,5%)
Isolated tubers	2 (2,7%)	4 (2,4%)
Site of surgery		
Frontal	25 (33,8%)	41 (23,3%)
Temporal	35 (47.3%)	99 (56.3%)
Parietal	1 (2.6%)	4 (4.4%)
Central	3 (4,1%)	6 (3.4%)
Occipital	2 (2,7%)	5 (2,8%)
Bilobar surgery	3 (4,1%)	12 (6.8%)
Multilobar surgery	3 (4,1%)	5 (2,8%)
Histology		
Tumor	44 (59,5%)	48 (27,3)
Malformation of cortical development	9 (12,2)	47 (26,7)
Cavernoma	9 (12,2)	8 (4,5%)
Gliosis	4 (5,4%)	18 (10,2%)
Hippocampal sclerosis (HS)	2 (2,7%)	40 (22,7%)
Tuberous sclerosis	3 (4,1%)	5 (2,8%)
Other	3 (4,1%)	10 (5,7%)

No significant differences between the two groups.

3. Results

3.1. Non Drug-Resistant patients

Seventy-four NDR patients (46 males and 28 females) were identified (3.6% of the total number of patients who underwent surgery and 29.6% of the selected population). Their median age at the time of epilepsy onset and surgery were respectively 10.0 years (IQR 5.0–21.0) and 16.0 years (IQR 7.0–23.0); 46 (62.2%) were aged $\leq$ 18 years at the time of surgery. Median epilepsy duration was 2.0 years (IQR 1.0–5.0), and the median post-operative follow-up was 75.0 months (IQR 50–144).

Nineteen patients (25.7%) had significant anamnestic risk factors for epilepsy (a family history of epilepsy in seven cases, a dystocic delivery in seven, a threatened miscarriage in four, febrile convulsions in five): the remaining 55 (74.3%) have no risk factors.

At the time of surgery, the patients had been seizure free for 3–260 months (median seizure-free period 17.0 months; IQR 9.0–36.0), being therefore in the initial period of drug-responsiveness; none of them had ever been drug-resistant.

They fell into three major categories: 10 (13.5%) had only experienced one or two seizures before starting ASM then became seizure-free, and then underwent surgery within three years of the first seizure; 20 (27.0%) had epilepsy for less than one year before surgery, being seizure-free for at least three months; and 44 (59.5%) had epilepsy between 2 and 40 years (mean 9.4 years) and had been seizure-free for at least six months (mean 38.0 months).

Seven patients underwent surgery three months after their first evaluation. Sixty patients (81.1%) had achieved seizure freedom with only one ASM, and thirteen (17.6%) with two ASMs alone or in combination; one patient (1.3%) was not yet treated and immediately operated on (MRI indicated a low-grade tumour).

All patients underwent a pre-surgical evaluation. Ten patients (13.5%) underwent a short video-EEG monitoring before surgery (only interictal EEG findings); the remaining 64 patients underwent just standard interictal EEGs elsewhere. All the EEG recordings were analysed during the pre-surgical evaluation. No patient required stereo-EEG invasive monitoring. All the patients had a positive MRI.

Table 1 shows the neuroradiological findings, type and site of surgery, and the histological findings Table 2.

3.2. Drug-Resistant patients

One-hundred seventy-six patients (80 female and 96 males; 8.5% of the total number of patients who underwent surgery and 70.4% of the selected population) were considered DR on the basis of the ILAE definition.

Median age at the time of epilepsy onset and surgery was respectively 7.0 years (IQR 2.0–14.0) and 30.0 years (IQR 18.0–38.0); 47 patients (26.7%) were aged $\leq$ 18 years at the time of surgery. Median epilepsy duration was 17.0 years (IQR 9.0–28.0).

All the patients experienced an initial period of drug-responsiveness (median duration of initial seizure freedom

Table 2
The table reports the differences about age at epilepsy onset, epilepsy duration, age at surgery, initial seizure freedom period.

	NDR	DR	*p*
Age at epilepsy onset (years)	10 (IQR 5–21)	7.0 (IQR 2–14)	= 0.029
Epilepsy duration (years)	2 (IQR 1–5)	17 (IQR 9–28)	<0.001
Age at surgery (years)	16 (IQR 7–23)	30 (IQR 18–38)	<0.001
Initial seizure freedom period (months)	17 (IQR 9–36)	48 (IQR 24–84)	<0.001

(Mann-Whitney *U* test).

48.0 months; IQR 24–84) followed by the occurrence of drug-resistance. The median post-operative follow-up was 84.0 months (IQR 48–162).

Seventy-five patients (42.6%) had significant anamnestic risk factors for epilepsy (family history of epilepsy in 22, dystocic delivery in 31, traumatic brain injury in 6, febrile seizures in 18, threatened miscarriage in 8, and one had infection). 101 (57.4%) did not have any risk factors for epilepsy.

One-hundred thirty-five patients (76.7%) underwent pre-surgical video-EEG monitoring. The remaining patients underwent only interictal EEGs elsewhere. No patients underwent stereo-EEG.

Table 1 shows the neuroradiological findings, type and site of surgery, and the histological data.

The decisions concerning surgical strategy were based on neurophysiological, neuroradiological and clinical findings.

3.3. Post-operative outcomes

Seizure outcomes in the NDR patients were excellent: 71 (95.9%) had Engel class Ia and three patients were in class Ic outcomes; none of the patients fell into class II, III or IV.

Among the DR patients, 111 (63.1%) were in class Ia, four (2.3%) class Ib, 25 (14.2%) class Ic, two (1.1%) class Id. Moreover, six (3.4%) were in class II, 23 (13.1%) in class III and five patients (2.8%) in class IV.

Outcomes in the two groups were significantly different: patients NDR had a better post-surgical outcome than those who underwent surgery who were drug-resistant ($p < 0.001$).

Antiseizure therapy was discontinued in 62 NDR patients (83.8%) and reduced in eight (10.8%) remaining unchanged in four patients (5.4%).

ASMs were discontinued in 87 DR patients (49.4%) and reduced in 31 (17.6%); therapy remained unchanged in the other 58 patients (33%).

Therefore, NDR patients discontinued ASM therapy more often than the DR patients ($p < 0.001$).

Moreover, comparing the two groups of patients the NDR were older at the time of epilepsy onset ($p = 0.029$), had a shorter disease duration ($p < 0.001$), younger at the time of surgery ($p < 0.001$), and had a shorter initial seizure-free period ($p < 0.001$) (see table 2).

Another difference was the diagnostic burden required in the two populations with only 18.4% of NDR patients necessitating long-term video-EEG monitoring, compared to 76.7% of the DR patients ($p < 0.01$).

Finally, the multivariate analysis showed that a better outcome was associated with the NDR group (OR 8.1, CI 95% OR 2.31–28.52I, $p = 0.001$), a shorter duration of epilepsy (OR 0.97, CI 95% OR 0.94–0.99) but was not associated with temporal lobe epilepsy or the histological diagnosis.

4. Discussion

By definition, the main goal of epilepsy surgery is to achieve seizure freedom. To date, epilepsy surgery is indicated in drug-resistant focal epilepsies with or without a structural etiology. Despite the ILAE definition of drug-resistance being the failure of adequate trials of two appropriately chosen and tolerated ASMs [5], surgery is still underutilized being considered by some to be "the last choice" despite ongoing disability from many years of illness, seizures and ASM. This is in contrast to available information from randomized controlled trials (RCTs) that has shown surgery to be more effective than best medical therapy [26].

Many patients may prove resistant from the very beginning of the disease, but a portion can become drug-resistant over time, possibly as a result of recurrent seizures, the intrinsic pathogenesis of the disease, or the underling etiology [27].

A lesional etiology is usually associated with an increased risk of drug-resistant epilepsy [28,29]. Undoubtedly drug-resistance is a multifactorial process; one of the mechanisms could be the "*transporter hypothesis*", proposing the structural abnormalities damaging the capillary endothelial cells that constitute the blood–brain barrier, leading to an overexpression of efflux transports and then to the drug-resistance [3].

Among the many possible etiologies, in particular HS, glioneuronal tumours and FCD type II [18,30-33] appear to be associated with almost certain drug-resistance.

Glioneuronal tumours, such as gangliogliomas and disembryoplastic neuroepithelial tumors, are associated with drug-resistant epilepsies in up to 90–100% of patients [3]. Focal cortical dysplasia (FCD) is also frequently associated with drug-resistance [34,35]; FCD type II is the most frequent histopathology in children and the third most common aetiology in adults undergoing epilepsy surgery [18,36]. Furthermore, HS is one of the most common cause of drug-resistant temporal lobe epilepsy [37,38].

Therefore, in most cases of epilepsy when the etiology is unambiguous, it is possible to predict (or strongly suspect) a tendency to become drug-resistance at seizure onset and suggest surgery from the beginning of the disease. Furthermore the presence of an anatomical lesion makes it challenging to reduce or to withdraw the ASMs even when seizures are controlled. Moreover, it is equally difficult to predict the duration of the clinical seizure-free stability, as this is influenced by many factors. Oftentimes drug therapy will have to be maintained over long periods of time or even throughout one's life with the resultant burden from ASM and therapies.

Many studies had demonstrated the duration of epilepsy may be influenced by the response to ASM in patients with lesional epilepsies with a longer duration of treated epilepsy [32].

Therefore, the duration of the disease can influence not only the development of drug-resistance, but also the post-surgical outcome in an unfavorable sense, in terms of cognitive and quality of life parameters [12,17,33,39-42].

Hence, considering all these characteristics we have retrospectively analyzed two different groups of patients who underwent epilepsy surgery, those with or those without drug-resistance (who never experienced or reccurred following an initial seizure-free period).

One of the main findings from the study demonstrate a better outcome in the drug-sensitive population ($p < 0.001$). Apparently, waiting many years before proposing and carrying out resective surgery increases the risk of drug-resistance and experiencing a worse post-surgical outcome.

In NDR patients the multivariate analysis found the result of surgery did not depend on its lobar localization, while the literature supports surgery within the temporal lobe had better results than extra-temporal sources [10-13]. In our study, the lack of drug-resistance could explain this difference. In the NDR group the post-surgical outcomes with either temporal or extra-temporal epilepsies were significantly better than reported in the literature, and better than those observed in the group of DR patients (95.9% NDR patients in class Ia and 63.1% DR patients in class Ia, $p < 0.01$).

From the literature, one of the reasons for the scarce use of epilepsy surgery, besides the fear of complications and the doubts about its benefits, is the financial burden [43].

Interestingly, in NDR population not only invasive investigations were not considered mandatory, but also long-term video-EEG was performed in fewer patients compared to the DR group (18.4% NDR patients and 76.7 DR patients, $p < 0.01$). This finding suggests that a majority of NDR patients can undergo successful epilepsy surgery without the need for resource-intensive long-term video-EEG recordings, probably due to the presence of less complex anatomo-electro-clinical correlations in this group. In contrast, DR patients often having a long disease duration with various seizure types and bilateral interictal EEG abnormalities, necessitate a more complex work-up (both video-EEG and invasive recordings in order to verify the anatomo-electro-clinical correlations).

After surgery most of NDR patients (83.8% compared to only 49.4% in DR group) were able to discontinue ASMs, a further positive effect to be considered when an "early" surgery is proposed, especially during childhood. As already known the discontinuation of ASMs and the absence of their side effects improves attention, vigilance and psychomotor promptness [44-47]. The results indicate that "early" surgery reduces the duration of ASMs both before and after surgery, being a further positive element to be considered in determining the proposal for the patient.

In the NDR group the younger age at surgery– median 16.0 years (IQR 7.0–23.0) – and the higher percentage of ASMs discontinuation (83.8%) suggest that the costs of surgery is lower than the cost of long-term ASMs. This also considering the fact that the long-term ASMs can address physical and cognitive side effects and in lesional epilepsies the possibility of reducing or withdrawing ASMs (in the absence of seizures) is probably low and risky regarding seizure recurrence.

Based on the results of our study, epilepsy surgery may be effective in NDR patients with symptomatic epilepsy. Considering improved seizure control, avoiding later risk of drug-resistance, a greater number of seizures over time, and prolonged exposure to ASMs. These aspects have potential consequences on social and personal quality of life. However these issues are better addressed by prospective longitudinal studies.

The present study has some relevant limitations. The population of NDR patients who underwent surgery had more favorable prognostic factors than those with DR. Considering the short duration of the disease, our study is monocentric and retrospective subject to typical biases. Moreover the histology of epilepsy was inhomogeneous between the two groups limiting comparison.

Nevertheless, further studies that are prospective and randomized could confirm our findings and support and strengthen the indications for early epilepsy surgery.

5. Conclusion

As the concordance between anatomo-electro-clinical data have been established, proposing and discussing the surgical choice with patient and the caregivers, should be done at an early stage.

Early epilepsy surgery prior to drug-resistance should weigh the individual's risks and benefits relative to the etiology of a lesion and encompass future disability from recurrent seizures, to personalize prediction of a successful post-operative outcome.

The risk/benefit ratio should be carefully analyzed and discussed with the patient and the caregivers, highlighting the advantages of early intervention in the absence of drug-resistance to balance the known operatory risks.

Ideal candidates for epilepsy surgery are young patients suffering with a symptomatic focal epilepsy, particularly if associated with HS, FCD type II and a glioneuronal tumor. The lack of drug-resistance and the short duration of epilepsy represent a further favorable and determinant factor for a positive post-surgical outcome.

Ethical statement

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The patients gave informed consent to the surgical procedure and to the reviewing of data for scientific purposes. The present retrospective study received the approval of the Niguarda Hospital ethics committee (ID 939–12.12.2013).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We dedicate this work to our mentor and beloved master Claudio Munari.

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