



# First Randomized Study of Epilepsy Surgery: 20 Years Later What Has Changed?

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**Commentary on: Marks WJ. First Randomized Study of Epilepsy Surgery. *Epilepsy Currents*. 2002;2(1):11-12. doi:10.1111/j.1535-7597.2002.00003.x.**

The modern era of surgical treatment for epilepsy began in the late 19th century, and increased application accompanied the advent of electroencephalography in the 1950s and magnetic resonance imaging (MRI) in the 1990s. Nevertheless, by the turn of the century, epilepsy surgery remained among the most underutilized of all accepted biomedical therapeutic interventions. A common explanation for this seemingly inexplicable failure to fully utilize an accepted treatment for drug-resistant seizures was there had never been a “gold standard” randomized controlled trial (RCT) to prove efficacy. This changed with the landmark Canadian RCT of surgery for temporal lobe epilepsy (TLE) by Wiebe et al, published in the *New England Journal of Medicine* in 2000,<sup>1</sup> and reviewed in the first issue of *Epilepsy Currents* in 2002.<sup>2</sup>

The primary reason RCTs had not been performed previously was lack of the necessary equipoise; it was so obvious to those working in epilepsy surgery centers that surgery is effective, that it was considered unethical to assign candidates to the medical arm of a randomized trial and increase their risk of morbidity and mortality. Wiebe et al circumvented this obstacle because, in Canada, the waiting list for surgery was over a year; they reasoned it would be ethical to operate on some patients immediately, thus the medical arm would be no longer than the usual delay. Although 1 year of postoperative follow-up was less than the recommended 2 years, it was considered to be sufficient to obtain a reasonable estimate of outcome. The results of this study were clear, 58% in the surgical arm, and only 8% in the medical arm were seizure free at the end of a year. Interestingly, the 58% figure was based on intention to treat and not all patients in the surgical arm actually received surgery; the outcome for those who received surgery was 64%, almost identical to the 68% average outcome for over 2500 patients with TLE reported from 118 centers worldwide at the second Palm Desert Conference held in 1992.<sup>3</sup>

So, did the Canadian RCT influence practice? It certainly should have because, based on the existence of this Class 1 study, and a thorough review of the literature, the American

Academy of Neurology (AAN), along with the American Epilepsy Society and the American Association of Neurological Surgeons, published a Practice Parameter in 2003<sup>4</sup> recommending surgery as the treatment of choice for drug-resistant TLE with the highest, Level A, rating. In addition to the Class 1 RCT, the literature review identified 1952 patients from 24 independent case series of surgery for TLE with an average of 67% seizure free after 2 to 5 years, compared to a meta-analysis of drug trials for a similar population of patients with drug-resistant TLE, where the best outcome was a 50% seizure reduction in 54% of participants.<sup>5</sup> Even though the percent seizure free following surgery in the TLE RCT was essentially identical to the Palm Desert report, and the literature review for TLE, a similar analysis of outcome following surgery for extra-temporal epilepsy was not sufficient for a Level A rating because there was no Class 1 RCT.

The 2000 Commentary in *Currents* ended with a tentative prediction: “Perhaps this evidence will finally compel the referral of a greater number of patients with uncontrolled epilepsy to consideration for surgical treatment.”<sup>2</sup> There are 2 measures that would help to determine whether the Canadian RCT and the AAN Practice Parameter had such an effect: an increase in referrals to surgical epilepsy centers and a reduction in time to referral. It shouldn’t have been too difficult to improve on performance in the United States (US): it was estimated that less than 1% of potential surgical candidates were being referred to epilepsy centers<sup>6</sup> and, for those who were referred, the delay from onset of epilepsy to referral was, on average, over 20 years.<sup>7</sup> Sadly, data collected by the National Association of Epilepsy Centers has subsequently found that the rate of referral and surgery has remained fairly steady,<sup>8</sup> while studies from 2 US epilepsy surgery centers found no difference in delay to surgical referral from before to after the RCT and Practice Parameter.<sup>9,10</sup> Indeed, one study of hospital referrals for epilepsy in the United States between 1990 and 2008<sup>11</sup> found a decrease in referrals to high volume hospitals where surgeries are done, and an increase to low volume hospitals that



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do not do surgery. Experience outside the United States has been similar, with the exception that technological developments have contributed to an encouraging increase in the development of epilepsy surgery programs in countries with limited resources.<sup>12</sup>

Now, there has been a second RCT of surgery for TLE, the Early Randomized Surgical Epilepsy Trial (ERSET), published in the *Journal of the American Medical Association* in 2012.<sup>13</sup> The equipoise for this study was based on a design to operate within 2 years of failure of 2 appropriate drug trials, the International League against Epilepsy definition of drug resistance,<sup>14</sup> at a time when it was unclear whether further drug trials might yet be successful. The Early Randomized Surgical Epilepsy Trial differed from the Canadian RCT in several important ways. Not only were participants enrolled early but they met rigid criteria for a diagnosis of mesial temporal lobe epilepsy (MTLE), were determined to be surgical candidates before randomization, and were followed for 2 years after surgery. Whereas the Canadian RCT randomized participants before presurgical evaluation and therefore included some patients who did not have typical TLE, ERSET represented a relatively pure culture of early MTLE. Early referral and recruitment were difficult and the total population of ERSET was small, but the results were definitive: 0/23 (0%) in the medical arm, and 11/15 (73%) in the surgical arm were completely seizure free (no auras) for 2 years in the intention to treat analysis, where participants with incomplete data had to be scored as not seizure free. If only those participants with complete data were included, 11/13 (85%) were seizure free. Furthermore, health-related quality of life and measures of socialization were better in those who had surgery compared with those who did not.

The sample size for ERSET was too small to assess the effect of anteromesial temporal lobe resection on memory, which remains a concern for early resection of mesial temporal structures in the language dominant hemisphere when material-specific memory may not yet be compromised by the disease. One study, however, of 138 patients from multiple centers,<sup>15</sup> concluded that a new memory deficit does not adversely impact quality of life when patients become seizure free. There does remain a risk to quality of life for a small number of patients who experience memory deficit and continue to have seizures postoperatively.

It has been 8 years since the publication of ERSET and there is no clear evidence that this study has had much impact on referrals for surgery. Indeed, there appears to be a clear relative reduction in temporal lobe surgery in the United States and in Europe, leading some to suggest that we have essentially “fished out” the population of patients with classical hippocampal sclerosis (HS).<sup>16</sup> Given that less than 1% of patients with drug-resistant epilepsy are referred for surgery, however, it is difficult to reach conclusions about the total population based on the small percentage seen at epilepsy centers. Perhaps, the 1% of neurologists who refer their patients have “fished out” their HS population, but a more likely explanation is that referrals to epilepsy centers in general have decreased,<sup>11</sup> for

inexplicable reasons, but that extratemporal referrals have suffered less because of high resolution MRI and the emergence of pediatric epilepsy surgery, which only rarely involves HS. With continued improvements in diagnostic approaches and surgical techniques, including neuromodulation and laser ablation, the real success story in the recent history of epilepsy surgery has been the identification of small resectable epileptogenic lesions, particularly focal cortical dysplasias,<sup>17</sup> and the increasing application of surgery to infants and small children.<sup>18</sup> Neither of these advances can be attributed to the 2 RCTs. And there is now a third RCT of pediatric epilepsy surgery from India,<sup>19</sup> which not only highlights the importance of epilepsy surgery in children but also the rapid expansion of epilepsy surgery centers in countries with limited resources, where the vast majority of people with drug-resistant epilepsy live.

Because treating physicians in industrialized countries continue to be reluctant to consider surgical therapy, despite 3 RCTs, and continuing advances in diagnostic approaches and surgical techniques, it may be time to stop asking them to refer their patients for surgery. A more effective approach going forward would be to promote the comprehensive benefits of full-service epilepsy centers, and maintain that *all patients* whose lives are compromised by drug-resistant epilepsy, defined as failure of 2 appropriate trials of antiseizure medications, deserve a consultation with a team of multidisciplinary epilepsy specialists at a full-service epilepsy center.<sup>6</sup> It would then be the responsibility of the epilepsy center physicians to determine who is a surgical candidate.

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