SURGICAL RCT'S: THE WAY FORWARD?

PROF WALTER VAN DYCK, MA MSC PHD

CHAIR, TECHNOLOGY & OPERATIONS MANAGEMENT AREA
DIRECTOR, HEALTHCARE MANAGEMENT CENTRE
VLERICK BUSINESS SCHOOL

NOVEMBER 2019

FINANCIAL AND COMPETING INTERESTS DISCLOSURE

The Vlerick HMC is fully owned by Vlerick Business School, a Public Utility Foundation, and funded by grants from public institutions and private organisations. To conduct its applied business and policy research, the Vlerick HMC benefits from unconditional partnership grants from MSD Belgium, and Medtronic, and from contract research funds from MSD, Janssen Pharmaceuticals, Novartis, Pfizer and Agentschap Zorg & Gezondheid. Furthermore, Vlerick HMC collaborates with HHZH Lier, Sint-Franciscus Ziekenhuis, AZ Maria Middelares, Ziekenhuis Netwerk Antwerpen, ASZ Aalst, AZ Alma, AZ Nikolaas, AZ Sint-Maria, Europa Ziekenhuizen, Jan Yperman Ziekenhuis and Jessa Ziekenhuis, and Roche Diagnostics united as MINOZ Research Members.

RCT'S: THE MOST RELIABLE FORM OF SCIENTIFIC EVIDENCE?

Courtesy to: Dirk De Ridder MD PhD FEBU, UZ Leuven, Belgium

ADVANTAGES OF RCT'S

CONSORT: Consolidated Standards of Reporting Trials 2010

- Most reliable form of scientific evidence
- Hypothesis testing: superiority, non-inferiority, equivalence
- Efficacy, effectiveness
- Eliminates bias in treatment assignment
- Facilitates blinding of investigators, participants and assessors
- Data can be combined into systematic reviews and meta-analysis

Courtesy to: Dirk De Ridder MD PhD FEBU, UZ Leuven, Belgium

BUT, ALSO PRESENTING SOME LIMITATIONS

- Not appropriate power
- Too large sample sizes studying rare events
- Too long and too costly when outcomes in distant future. *Risk of loss of relevance at time of publication*
- internally valid, but presenting *problem of external validity*

Courtesy to: Dirk De Ridder, MD, PhD, FEBU, UZ Leuven, Belgium

---

I CONCUR WITH NEZHAT ET AL. (2019)

The two Achilles heels of surgical randomized controlled trials: differences in surgical skills and reporting of average performance

Farr R. Nezhat, MD; Cande V. Ananth, PhD, MPH; Anthony M. Vintzileos, MD

"Averaged reporting without considering the variations in surgical proficiency could result in unforeseen adverse consequences, such as the recently released Food and Drug Administration statement that used the trial by Ramirez et al.. as evidence to caution against robot-assisted surgical devices for treatment of patients with cancer...

It is our hope that, contrary to the Food and Drug Administration cautionary statement, minimally invasive surgical approach should not be replaced by open surgery based on the averaged results of the Ramirez et al trial".

230 *American Journal of Obstetrics & Gynecology* SEPTEMBER 2019

Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.

Slide 1

RCT'S: ALSO FOR ROBOT-ASSISTED SURGERY?

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study

John W Yaxley, Geoffrey D Coughlin, Suzanne K Chambers, Stefano Occhipinti, Hema Samaratunga, Leah Zajdlewicz, Nigel Dunglison, Rob Carter, Scott Williams, Diane J Payton, Joanna Perry-Keene, Martin F Lavin, Robert A Gardiner

Summary
Background The absence of trial data comparing robot-assisted laparoscopic prostatectomy and open radical retropubic prostatectomy is a crucial knowledge gap in uro-oncology. We aimed to compare these two approaches in terms of functional and oncological outcomes and report the early postoperative outcomes at 12 weeks.

Lancet 2016; 388: 1057-66
Published Online
July 26, 2016
http://dx.doi.org/10.1016/

Slide 2

RCT COMPARING OPEN AND ROBOTIC SURGICAL APPRAOCHES

Research in context

Evidence before this study
Robotic-assisted radical prostatectomy was introduced without high level evidence. The published literature so far has consisted of non-randomised longitudinal studies of robotically assisted and open prostatectomies (considered the gold standard in terms of treatment) alone or collated in meta-analyses, although there is randomised controlled trial evidence comparing robotically assisted and laparoscopic prostatectomy showing improved functional results for the robotically assisted procedure.

Added value of this study
To the best of our knowledge, this is the first published randomised controlled trial to compare robotic-assisted with

open prostatectomy and shows no significant difference in outcome for standard oncological and quality of life parameters at 12 weeks.

Implications of all the available evidence
Over the past 2 decades, patients and clinicians have embraced robotic-assisted prostatectomy in the belief that this approach will result in better patient outcomes. If the short-term findings from this study are maintained with longer follow-up results, this could have implications for patient choice and for health provider decision making.

Interpretation These two techniques yield similar functional outcomes at 12 weeks. Longer term follow-up is needed. In the interim, we encourage patients to choose an experienced surgeon they trust and with whom they have rapport, rather than a specific surgical approach.

Slide 3

SO, BOTH PROCEDURES YIELD SIMILAR FUNCTIONAL OUTCOMES. HOWEVER, INTER- AND INTRA-SURGEON VARIABILITY ARE SOURCES OF CONFOUNDING AND SHOULD BE MODELLED

- Surgical heterogeneity was well managed while every procedure was done by the same surgeon who had the most expertise in each approach.

- However, the two surgeons had a completely different background at the commencement of the trial: the robotic surgeon had completed a 2-year robotic fellowship followed by 200 robotic prostatectomies, while the open surgeon had 15 years post-fellowship experience and had done 1500 procedures.

- So, robotic surgery helps to achieve the same functional outcomes earlier and faster. In other words, the surgical learning curve of the robotic surgeon appears shorter compared to the open surgeon in terms of functional outcomes.

Adapted from: Fossati, N. & A. Mottrie, Robotic versus open radical prostatectomy: What do we expect from a RCT?, ORSI Academy, Melle, Belgium

Slide 4

HIERARCHICAL FACTORS AFFECTING INDIVIDUAL SURGEON LEARNING CURVES: A PLEA FOR A PROBABILISTIC APPROACH

Cook, J. A., Ramsay, C. R., & Fayers, P. (2001). Statistical evaluation of learning curve effects in surgical trials. Clinical Trials, 1, 421-427.

Slide 5

IN 2001, WE UNDERSTOOD THE PROBLEM, BUT DID NOT HAVE A SOLUTION ROLLED OUT

Robot-assisted surgery: health technology assessment
KCE reports 104C

Comparison of operative time and **surgical outcomes** such as complication rates may be biased by the technical performance of each surgeon and his/her position on the learning curve. Answers to this problem have been looked for in the literature. For example, it could be possible to adjust for learning effects by means of a Bayesian hierarchical model, or by stratification (if the sample size is large enough). Nevertheless, according to Brazier in his 2001 article on economic evaluation of surgery, interventions to be compared should be provided in a routine service setting. Moreover, even if robot-assisted surgery may be considered an emerging technology, the Belgian penetration is already high, cost-effectiveness studies should hence analyse costs induced by experienced surgeons already located on the right part of the learning curve. These analyses are needed to base any reimbursement policy on evidence.

In addition to those RCTs that would give information on 'ideal' practice in experienced centres, effectiveness data should be derived from the performance in daily life. This analysis should clarify whether expected advantages are also obtained in reality. Therefore, the setting up of registries of actual practice, including a rigorous follow-up system and comparison with conventional interventions, could help build the knowledge base to decide whether this robot-assisted technology provides additional value worth its additional cost and if so, for which interventions.

Slide 6

THE NEED FOR A SURGICAL LEARNING SYSTEM: WHAT WE CAN LEARN FROM THE PHARMA EXPERIENCE

Journal of Multidisciplinary Healthcare — Dovepress

PERSPECTIVES

Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making

Valdiur B Katkade
Kafi N Sanders
Kelly H Zou

Abstract: Evidence from medication use in the real world setting can help to extrapolate and/or augment data obtained in randomized controlled trials and establishes a broad picture of a medication's place in everyday clinical practice. By supplementing and complementing safety and efficacy data obtained in a narrowly defined (and often optimized) patient population in the clinical trial setting, real world evidence (RWE) may provide stakeholders with valuable information about the safety and effectiveness of a medication in large, heterogeneous populations. RWE is emerging as a credible information source; however, there is scope for enhancements to real world data (RWD) sources by understanding their complexities and applying the most appropriate analytical tools in order to extract relevant information. In addition to providing information for clinicians, RWE has the potential to meet the burden of evidence for regulatory considerations and may be used in approval of new indications for medications. Further understanding of RWD collection and analysis is needed if RWE is to achieve its full potential. **Keywords:** electronic health records, evidence-based medicine, real world data, real world evidence, randomized controlled trial

Katkade, V. B., Sanders, K. N., & Zou, K. H. (2018). Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. *Journal of multidisciplinary healthcare, 11*, 295-304.

THE FUTURE OF SURGICAL RCT'S: STRATIFIED FOR SURGICAL PROFICIENCY AND LONGITUDINAL IN NATURE

Supervised Learning

Unsupervised Learning

- No need for cohort-based averaged reporting in Kaplan – Meyer plots
- Instead, stratified randomization is needed with variation reported for surgical skills or volume.
- Reporting not only cohort averages and ranges but also;
  - By quartile skill, centre size, centre
  - By surgeon
- Stratification obtained by supervised (Tree-based) or unsupervised learning
- **IMPORTANT NOTICE:** Need for 4V's in data capture: volume, variety, veracity, and velocity

© Vlerick Business School

SURGICAL QUALITY LEARNING SYSTEMS REQUIRE A RWE-BASED INSIGHT-PROVIDING NETWORK

FIGURE 2 | Visualization of the current healthcare data ecosystem (left) and the underlying, federalised, data provider infrastructure, based on a common data model, needed to ensure a smooth transition from real-world data to real biomedical big data (right) characterized by **(A)** interoperable databases with international data reusability (high volume and variety), **(B)** real-time RWD processing information systems (velocity), and **(C)** longitudinal data (variety).

Geldof, T., Huys, I., & Van Dyck, W. (2019). Real-World Evidence Gathering in Oncology: The Need for a Biomedical Big Data Insight-Providing Federated Network. *Frontiers in Medicine, 6*(43),

© Vlerick Business School

CONCLUSION: FROM RCT TO RWE

- Surgical RCT reporting only make sense when stratified for surgeon proficiency
- Surgical Centre-based RWE registries should be set up to longitudinally capture qualitative surgical procedure process data
- Data capture should respect the 4V's as a prerequisite for statistical learning analytics

© Vlerick Business School

THANK YOU!

WALTER.VANDYCK@VLERICK.COM