Revisiting clinical research in surgical oncology: a plea for new directions

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EORTC
The future of cancer therapy
Surgery is the bad boy of clinical research

• 1926: compared to a comic opera (Major Greenwood)
• 1996: blamed by the Lancet Editor (Richard Horton)
• 2014: described “as a waste” (John Ioannidis)
What are we talking about?

- **A trial in surgery**: studying a co-factor of a given surgery that is the same for every patient: neoadjuvant or adjuvant treatments, antibiotics, etc.

- **A surgical trial**: a surgery is compared to another surgery.
  
  Ex: Partial vs total gastrectomy, sentinel LN vs lymphadenectomy, etc.

  *Also applicable to all local treatments: interventional radiology or radiotherapy*
State of... the waste

- An overwhelming majority of retrospective studies
- RCTs are rare:
  - Surgical phase 3 trials are rare, representing only 8% of such publications in 2006
  - 1 in 5 surgical studies is abandoned and 44% of them are never published
- ... and of bad quality:
  - Less than 50% match the CONSORT NPT criteria
  - Recent reduction of the Consort NPT for surgical studies criteria to 10
What are the offered solutions?

• Randomization, randomization and ... randomization!
• 1997, H. Buchwald (Minnesota): “Surgical procedures and devices should be evaluated in the same way as medical therapies, namely, by randomized clinical trials.”
• 2014, Potter (Bristol): “Education of the next generation of surgeons by changing the culture of surgical research may be key to unlocking the potential of randomized controlled trials in surgery.”
Why are RCTs not the good and immediate solution to improve the quality of CR in SO?

- Surgery versus surgery
- Limitation to conduct RCTs in surgery are well known:
  - Lack of equipoise for both surgeon and patient
  - Timing: « always too early, suddenly too late »
  - Accrual concern for patient in surgery: the more selective, the rarer.
  - The more selective, the wider the gap between RCT and true life.
  - Lack of funding
  - Difficult to warrant quality and reproducibility of a local treatment (RCT = 2 local treatments)
3 main dangers with RCTs

- To certify with a scientific label (RCT) something which is wrong
- To burn out the team, the patients and the funding sources
- To block the system by asserting that it is randomization and nothing else
Plea for a new deal

- Quality control
- Other prospective surgical trials
QUALITY CONTROL

- A prospective attitude
- The devil is in the detail (track details)
- Professionalization: work with clinical nurse, data manager, stats etc. Cross check your decision. External viewing
- Surgery: level of experience, prepare a protocol of the procedure with mandatory steps, pictures
- Pathology: aspect of the mesorectum; slicing the liver with a machine to look for missing mets, number of lymph node, etc.
- Outcome reports (Dindo and Clavien, Comet system)
Other prospective studies

- Phase 0
- Phase 1
- Phase 2
- Phase 4
Phase 0

- IDEAL recommendations: preclinical studies on corpses or virtual simulation

- But a phase 0 is more an early clinical exploration

- Scheduled surgery unchanged, administration of low dose of a drug (10X less) during 7 days max

- Proof of concept in humans
Phase 1

- A real concern
  - New implants, devices, tools
  - New procedures

- Precautionary principle completely forgotten
Phase 2 trials

- Appropriate framework easily adaptable to surgery, and a largely untapped methodology in surgical trials
- To establish the efficacy of a new treatment
- To define *a priori* a threshold for efficacy and non-efficacy
- Focused on short-term efficacy
- Power calculation: 30-60
Phase 2 trials

- Simple phase 2
- Phase 2 with a two-stage optimal design (Simon)
- Add-on study (ex: ULIIS study)
- Twin phase 2 (ex: Cascador study)
- Randomized phase 2 (CLOCC trial)
Phase 3: an example of good RCT

- A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer

- H. Jaap Bonjer, M.D., Ph.D., Charlotte L. Deijen, M.D., Gabor A. Abis, M.D., Miguel A. Cuesta, M.D., Ph.D., Martijn H.G.M. van der Pas, M.D., Elly S.M. de Lange-de Klerk, M.D., Ph.D., Antonio M. Lacy, M.D., Ph.D., Willem A. Bemelman, M.D., Ph.D., John Andersson, M.D., Eva Angenete, M.D., Ph.D., Jacob Rosenberg, M.D., Ph.D., Alois Fuerst, M.D., Ph.D., and Eva Haglind, M.D., Ph.D. for the COLOR II Study Group


- Started in January 2004
Phase 4

- Phase 4, outcome studies, pragmatic studies, quasi-experimental studies

- Comparing the results of observational studies and RCTs, Benson and Hartz found little evidence to indicate that estimates of treatment effects are overinflated in observational studies reported after 1984 compared to RCT. N Engl J Med 2000; 342:1878-1886

Phase 4: the real life

- Phase 3: Exclusion of too old, too young, too advanced, too much comorbidities etc.

- Patient selection by surgeons to participate in a RCT may be influenced by subjective criteria different from those prescribed by the sole criteria of selection.
Phase 4

- Prospective design
  - Quasi-experimental: criteria of inclusion and exclusion, power calculation ($\alpha$ and $\beta$)
  - Design and recording \textit{a priori}

  \textit{Contre-ex: LiverMetSurvey}

- Modern reporting
  - Dindo and Clavien
  - COMET (Core Outcome Measures for Effectiveness Trials)

- Quality control and improvement
EORTC 1409-GITCG: CLIMB

• A Prospective Liver Metastasis Database with an Integrated Quality Assurance Program

• Primary objective:
  • To evaluate the complications of different surgical strategies for complex liver metastasis
  • To determine the impact on long-term outcomes of different treatment strategies for complex liver metastasis

• Trial design: Prospective observational cohort study

• First collaboration project with ESSO (European Society of Surgical Oncology)
EORTC 1527-GITCG: DREAM

• Diffusion-weighted Magnetic Resonance Imaging (DW-MRI) Assessment of Liver Metastasis to Improve Surgical Planning

• **Primary objective:**
  • To assess the diagnostic performance of DW-MRI by evaluating the correlation of radiologic findings from DW-MRI with the histopathologic assessment of tumor viability after surgery

• **Trial design:** Prospective interventional study

• First collaboration project between EORTC and Japan Clinical Oncology Group (JCOG)
Conclusion

• We need to “think outside of the box”: RCT is not the only possible policy in surgery.
• Controlling the quality is the main methodological endpoint for the young generation (independent of randomization)
• Improving the quality of the scientific reporting in surgical oncology needs an effort by all the stakeholders: surgeons, methodologists, editors and funders.
Bibliography
