

How to Increase the Efficiency in Research on Non-Surgical Interventions during Cancer Surgery?

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Hepatocellular cancer is the fifth tumor-related cause of death, and associated with a significant rate of postoperative relapse even with complete excision, such as during liver transplantation [1]. Increased aggressiveness of minimal residual disease and immune cells activity modulation may play a role in the perioperative period. In particular neutrophils are associated with the activation of protumoral processes, whereas some T lymphocytes can exert an antitumoral role [1-3]. These observations have triggered considerations for specific interventions during surgery, to limit the proliferative activity of cancer cells, such as to improve anticancer immune activity [4]. To this aim, different medications have been proposed, being considered ideal as alternative solutions: non-steroidal anti-inflammatory drugs, propranolol or cimetidine [5, 6].

Jurj et al. investigated *in vitro* the effect of the widely used, cheap and non toxic lidocaine on two cell lines of hepatocarcinoma [7]. Unsurprisingly, they showed an antiproliferative effect of this potent sodium channel blocker. More interesting, they evidenced a time-dependent antiproliferative effect at low, and clinically relevant concentrations, already known to positively influence the inflammatory dysregulation associated with cancer recurrence [8].

The authors should be congratulated on their efforts to systematically evaluate these time- and dose-dependent effects. However, taken alone, and as stated by the authors, the clinical relevance of this work is limited, as an impact of intraoperative lidocaine on patients' cancer outcomes is mainly speculative. To test the clinical impact of these results, these investigators scheduled a clinical trial in colorectal cancer surgery (NCT02786329). A translational approach should be promoted in such complex, and complicated, multifactorial postoperative outcomes, as in other contexts such as postoperative pain [9]. To increase relevance, efficiency and complementarity, the process should be completed by observational studies, including retrospective studies, designed to better understand the pathophysiology of the postoperative cancer recurrences [10]. Then, small pivotal, explanatory, eventually multi-arms trials, could include similar biomarkers and targets, identified in preclinical studies. Ultimately, larger pragmatic trials would be complementary and potentially more conclusive. This progressive approach, called by Lacombe *the diabolical concept*,

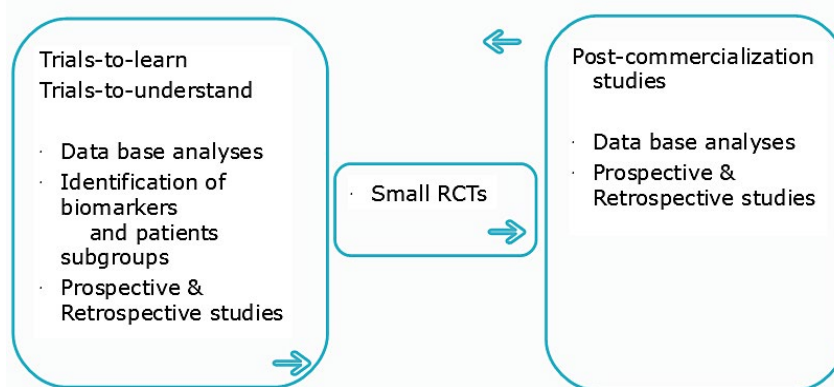


Fig. 1. The *diabolical* design in cancer research.

would assist in saving time and money, e.g. by choosing correct endpoints and reporting all important parameters [10, 11] (Fig.1). With this approach, we can hope that clear answers will come from clear questions, in conclusive trials permitting the proposal of medical strategies tailored to the patients.

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