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Revisiting postoperative complications after abdominal robot-assisted surgery: applying the Core Outcome Measures in Perioperative and Anaesthetic Care

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In considering the Assessment of Ventilation during general AnesThesia for Robotic surgery (AVATaR) study published in the *British Journal of Anaesthesia*,[1] we would like to reflect on the definition and clinical relevance of postoperative complications after abdominal robot-assisted surgery. Queiroz and colleagues[1] performed this substantial multicentre prospective clinical trial assessing postoperative pulmonary complications (PPCs) in 905 abdominal robot-assisted surgical patients from 34 hospitals in nine countries. They concluded that PPCs occur frequently (20%) in the first 5 days after abdominal robot-assisted surgery, are not associated with perioperative ventilator parameters, but are associated with a longer hospital stay. An important concern with regard to these findings is the clinical relevance of the surrogate outcome 'unplanned need for oxygen', defined in the trial as a Pa_{O_2} <60 mm Hg or Sp_{O_2} <92% in room air, or Sp_{O_2} <88% when prior pulmonary disease was present, as the reported 20% of PPCs consisted of 18.7% unplanned need of oxygen and only 0.8% acute respiratory failure, 0.4% pneumonia, and 0.1% acute respiratory distress syndrome.

Unplanned need of oxygen is considered a Grade I ('any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions[2]) in the Clavien–Dindo classification of postoperative complications. It is well established that the inflammatory response to surgery is accompanied by a temporarily higher tissue oxygen demand and low mixed venous oxygen saturation,[3] and that oxygen therapy, not standardised in this study, increases oxygen supply and pulse oximeter saturation.[4] Whilst we agree that in a fully awake (no residual sedative effects or influence of opioids) patient without residual neuromuscular block, a low arterial oxygen saturation is indicative of a pulmonary problem, the influence of these factors was not eliminated, which makes designation of the cause unreliable. Accordingly, a transient oxygen supply–demand mismatch does not necessarily indicate a pulmonary problem. Moreover, a local inflammatory response to surgery also induces remote inflammatory reactions in the lung independent of the ventilation approach.[5]

Surrogate outcomes are often easier to measure than true endpoints, but carry the major pitfall of misrepresentation of the outcome of interest. The *Cochrane Handbook for Systematic Reviews of Interventions* stresses interpretation of surrogate endpoints with great caution, as the effect of an intervention may even be reversed for a surrogate compared with the clinically relevant outcome.[6] When investigating the influence of ventilatory parameters on pulmonary outcomes, it is crucial to distinguish if the observed hypoxaemia has a (partially) pulmonary origin. Because of the tremendous heterogeneity in outcomes across perioperative clinical trials, the Standardised Endpoints in Perioperative Medicine (StEP) collaboration developed a consensus definition of Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAC).[7] Here, we feature the clinical significance of applying these core outcome measures in research regarding abdominal robot-assisted surgery. To this end, we will illustrate the COMPAC outcomes and their significance and application in perioperative research, followed by the more general challenges of robotic surgery.

Core Outcome Measures in Perioperative and Anaesthetic Care

The StEP collaboration identified 12 outcome working groups that have each performed an extensive literature review followed by a Delphi consensus process to identify a comprehensive set of representative outcomes to assess quality and interventions in perioperative care.[7] We propose that these 12 categories can be ranked from critical to of limited importance for clinical decision-making according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as also adopted in systematic reviews of the Cochrane collaboration (Fig. 1).[8] Surrogate outcomes are not included in these core outcomes, and their clinical significance depends on the correlation with true endpoints.

The GRADE approach was deliberately designed to focus on patient-important outcomes, which is why use of resources is lower on the scale of importance than factors, such as quality of recovery and (serious) complications. Of course, duration of hospital stay and healthcare costs are certainly relevant from a societal perspective. The respiratory COMPAC working group identified four clinically relevant pulmonary complications with a common pathophysiological mechanism of airway collapse or contamination: (i) *atelectasis* detected on CT or chest radiograph, (ii) *pneumonia* using the US Centers for Disease Control and Prevention criteria, (iii) *acute respiratory distress syndrome* using the Berlin consensus definition, and (iv) *pulmonary aspiration* (clear clinical history and radiological evidence).[9] After diagnosis, the complication is graded by severity based on the amount of oxygen required or the need for (non)invasive ventilation. The committee advises to consider pulmonary complications with a different underlying mechanism (e.g. pulmonary embolism, pleural effusion, cardiogenic pulmonary oedema, pneumothorax, and bronchospasm) separately and only when relevant to the investigated intervention.

The authors of the AVATaR study report that there was no way to grade the PPCs or other complications, and did not report the amount of oxygen that was needed. The majority of patients received short- or long-acting opioids; thus, respiratory depression may have caused the need for oxygen. When supplemental oxygen was part of routine care, which is often the case in the PACU, it was not registered. Unplanned (non) invasive ventilation was defined separately, so the need of oxygen was mild to moderate in severity. Without a pulmonary diagnosis, the clinical significance of this surrogate outcome is low, as we do not know what we are observing. Applying the COMPAC classification in study designs will allow for higher quality and superior comparability between trials.

Applying COMPAC in abdominal robot-assisted surgery studies

Laparoscopic or minimally invasive surgery has become the gold standard for many abdominal surgeries, as a faster recovery and a decrease in perioperative morbidity with equal oncological outcomes were shown for many procedures when compared with open surgery.[10] Robot assistance was introduced to enhance the minimally invasive technique further and allow for superior vision and greater surgical precision. Whether this translates to superior outcomes is still a point of debate. This discussion was reintroduced by a negative trial from Ramirez and colleagues[11] in 2018, who reported a lower rate of disease-free survival and overall survival for minimally invasive (laparoscopic and robot-assisted surgery combined) radical hysterectomy compared with open surgery for cervical cancer. In this light, we present and contemplate several important reviews and trials in robot-assisted surgery that report on the most critical outcomes in the COMPAC hierarchy of outcomes: survival, organ failure, and cancer progression or recurrence.

This prospective randomised trial (n=631) reported a 3 yr disease-free survival of 91.2% for minimally invasive surgery and 97.1% for open surgery, with a hazard ratio of 3.74 (95% confidence interval [CI]: 1.63–8.58) for recurrence or death from cervical cancer. Moreover, 3 yr overall survival was 93.8% for minimally invasive surgery and 99% for open surgery, with a hazard ratio of 6.00 (95% CI: 1.77–20.30) for death from any cause. The initial primary outcome was 4.5 yr disease-free survival with a planned enrolment of 740 patients. However, the data safety monitoring committee prematurely ended the

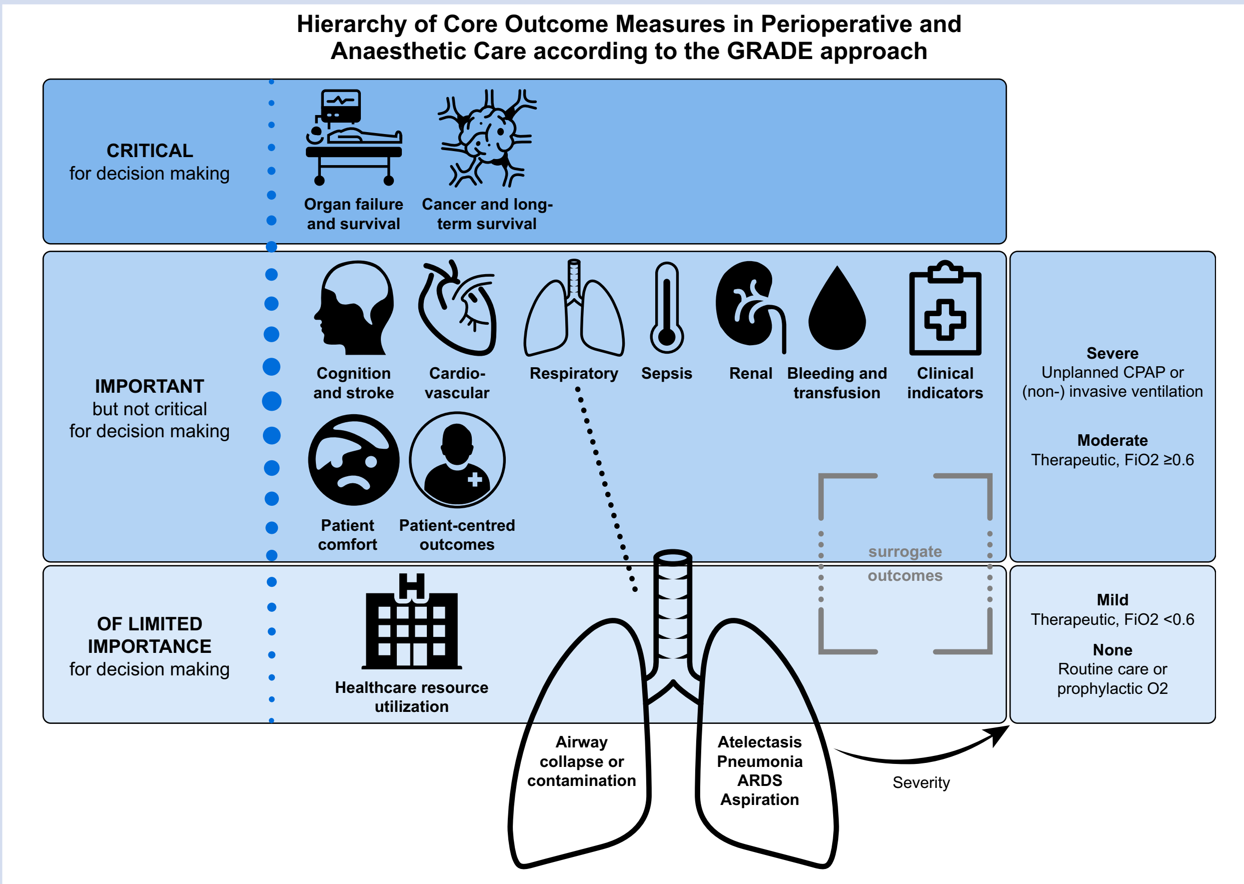

Fig 1. The 12 Core Outcome Measures in Perioperative and Anaesthetic Care outcome groups ranked according to the GRADE approach. Surrogate outcomes are not included in these core outcomes, are never critical for decision-making, but may vary in importance depending on their correlation with true endpoints. The respiratory outcomes and their grading are featured in more detail. ARDS, acute respiratory distress syndrome; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

trial because of the higher mortality rate in the minimally invasive surgery group. This difference was not attributable to robotic assistance; only 15.6% of the minimally invasive surgery group consisted of robot-assisted procedures, and the authors found no significant between-group difference when separating laparoscopy from robot-assisted surgery. So, why was this crucial difference only discovered now? Is this surgical procedure different from other abdominal surgeries, or have cancer recurrence and mortality not been a primary focus of laparoscopic *vs* open surgery trials until now? The finding was confirmed in two large meta-analyses comparing minimally invasive to open radical hysterectomy for early-stage cervical cancer,[12,13] where again no added (or decreased) risk was found for robotic assistance. The 2020 National Comprehensive Cancer Network guidelines were updated and now advise the use of an open abdominal approach for radical hysterectomy in patients with cervical cancer. A similar outcome difference was seen for conventional laparoscopy *vs* robot-assisted surgery in gynaecological surgery. A Cochrane review of patients undergoing hysterectomy or sacrocolpopexy for malignant and non-malignant diseases revealed that only one study reported on (in this article, 30 day) mortality.[14] Survival outcomes were not reported and there was no comparative evidence on cancer recurrence, which means non-inferiority and safety of robot-assisted surgery were presumed based on a comparable complication rate and not on outcomes more important in the hierarchy.

The importance of a uniform and suitable outcome definition is illustrated by a meta-analysis from 2019 investigating recurrence-free survival and progression-free survival in robot-assisted *vs* open cystectomy.[15] Satkunasivam and colleagues[15] present data from five trials with a total of 560 participants, with the majority enrolled in the Robot-Assisted Radical Cystectomy Versus Open Radical Cystectomy in Patients with Bladder Cancer (RAZOR) trial (n=350) from Parekh and colleagues[16] and a study by Bochner and colleagues[17] (n=118). The authors of the meta-analysis express concerns regarding the reporting of cancer recurrence, as outcomes are defined differently between studies. Despite no clear higher likelihood in one group, they did find significant differences in patterns of recurrence between robot-assisted and open radical cystectomy. This may signify that these surgical techniques affect cancer growth and metastasis in a different way, although retrospectively comparing the short-term follow-up of a new technique with the longer-term follow-up of an already-replaced technique can be problematic.[18] Lastly, it is important to realise that non-inferiority can diverge, depending on the definition of the outcome (survival with or without progression, overall or with a specific cause, and local or overall relapse), but also tumour grade and cancer invasiveness are important factors to consider when deciding on optimal surgical technique.

A 2018 meta-analysis on robot-assisted *vs* laparoscopic surgery for rectal cancer reported on 23 studies, including a total of 4348 patients. No significant differences were found for 3 yr overall and disease-free survival, overall recurrence, metastatic recurrence, and local recurrence.[19] A retrospective study on lymph node dissection for low rectal cancer (n=426) confirmed this finding for 5 yr overall and relapse-free survival, but reported a lower 5 yr local relapse-free survival for open dissection (90.9% *vs* 98.6% for robot assisted; P=0.029).[20] Ploussard and colleagues[21] prospectively collected data for 2386 patients undergoing laparoscopic or robot-assisted radical prostatectomy between 2001 and 2011, and concluded an equal survival and overall short-term oncological outcome. A subgroup analysis of pT2 tumours, however, showed lower rates of positive margins (odds ratio: 0.396; P=0.030) for robot-assisted surgery, whereas this difference was not present for pT3 tumours. The authors conclude that a longer follow-up is justified for oncological outcomes. Compared with pharmacological interventions, there seems to be a considerable delay (of smaller retrospective studies) before new or 'improved' surgical techniques are put to the test in sufficiently large and high-quality RCTs that investigate the outcomes we are most interested in. As Fernandes and Giulianotti[22] concluded in their 2013 review on robot-assisted pancreatic surgery, '*the prudency in waiting for more robust prospective trials before considering such a platform as the "gold standard" is justified; however, it is likely, as has happened in the past, that the surgical community will accept it as standard practice before any prospective randomized trial has been carried out*'.

Learning curve and training

An important factor that must be discussed when evaluating outcomes of robotic surgery is the pronounced presence of a learning curve. Robotic surgery is not simply another version of laparoscopic surgery, and skills do not naturally transfer between techniques. Handling of robotic instruments and tactile tissue perception are different and require adequate training. So much so that two recent studies identified that this learning curve is a significant predictor for progression-free survival in radical hysterectomy for the treatment of cervical cancer.[23,24] Despite increasing use of robotic techniques, it is not yet properly embedded in surgical education programmes. A survey across 240 Accreditation Council for Graduate Medical Education-approved general surgery training programmes in the USA reveals that most residents report having assisted in 10 or fewer robotic cases, often only with trocar placement and docking and undocking of the robot. And 60% of respondents indicate that they received no education or training before participating in their first robotic case.[25] Evidently, this insufficient training is seriously damaging to critical patient outcome measures and should be addressed.

Anaesthetic challenges in robotic surgery

Compared with open and laparoscopic surgery, robotic surgery comes with additional anaesthetic challenges predominantly concerning positioning and restricted patient access.[26] Many robotic procedures require steep Trendelenburg position that does not only compromise respiratory and cardiovascular function, but can also lead to vascular and thromboembolic complications, airway, facial and cerebral oedema, and peripheral neuropathies. Limited access to and visibility of the patient once the robot is docked mean many necessary precautions (padding and secure positioning), and potentially required interventions (e.g. invasive lines) need to be anticipated to prevent interruption of the procedure or severe position- or compression-related complications.[26] Expert panel consensus recommendations for lung-protective ventilation were developed to optimise pulmonary function during and after surgery.[27]

As clearly featured in the pulmonary COMPAC definition, prevention of airway collapse and contamination is the key goal. This means attention to the consequences of positioning, tidal volumes, PEEP, inspiratory–expiratory ratio, F_{IO_2}, alveolar recruitment manoeuvres, and optimising the patient's emergence from anaesthesia to prevent atelectasis. The AVATaR trial reports that lung-protective ventilation was used in two-thirds of patients without further specification of components, such as extubation, which may also explain why no association was found between ventilatory parameters and PPCs. The consensus recommendations provide guidance but concurrently emphasise the high number of influencing factors, such as pre-existing lung disease, cardiovascular status, BMI, the type of surgical procedure, and many others that call for a tailored approach in every patient. Use of the robotic technique is one more factor in the anaesthesiologist's decision-making, where the combination of pneumoperitoneum with extreme positioning demands additional pulmonary consideration.

Conclusions

The currently available major trials and reviews on minimally invasive and open surgery illustrate the importance of high-quality prospective randomised clinical trials that investigate the most important core outcomes in perioperative care. Well-designed randomised studies can prompt critical changes in treatment—changes that may be long overdue when there is a considerable delay in evaluation of a treatment after implementation into daily clinical practice. Surrogate outcomes and outcomes lower in the hierarchy do not necessarily represent or translate to the outcomes of most interest. Results from one type of abdominal surgery cannot automatically be extrapolated to a different surgical procedure or underlying pathology. The COMPAC hierarchy is eminently suitable to provide the foundation for evaluation of existing research and for the future design of higher-quality studies.

Authors' contributions

Concept drafting: MCW
Data acquisition: KIA, GR-B, JPM
Data analysis: KIA, MCW
Data interpretation: all authors
Writing of paper: KIA
Critical revision of paper: GR-B, JPM, MCW
Revision of final paper: CK, G-JS
Approval of final paper: all authors

Declarations of interest

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