Comparison of surgical stress response and convalescence in robot-assisted laparoscopic cystectomy versus open mini laparotomy radical cystectomy in patients with bladder cancer

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1. Background

Bladder cancer (BC) is the ninth most common cancer worldwide. In Denmark an estimated 1,600 new cases of bladder tumors occur every year [1]. At the time of diagnosis approximately 20 % have muscle invasive disease of the bladder [2-5]. Primarily managing of invasive bladder cancer (IBC) is performed by cystectomy (removal of the bladder) which includes an alternate urinary drainage system, either a non-continent or continent diversion procedure, such as an ileal conduit (most common approach) opening through the abdominal wall or with the formation of an ortotopic neobladder [2-9]. Treatment of cystectomy includes an appropriate lymphadenectomy [2,4,6,10]. Cystectomy is a major procedure and correlated with a certain extent of operative trauma [11]. Therefore recent years have focused on minimal invasive techniques, which will minimize the operative trauma and blood loss [12]. The implementation of laparoscopy (LAP) and robot-assisted laparoscopy (RAL) into urologic practice has become popular during the last decades [2,5,13-15]. Several studies have reported on laparoscopic cystectomy (LAPC) and preliminary experiences with Robot-assisted laparoscopic cystectomy (RALC), but these reports have primarily focused on the technical feasibility of this approach and the description of technique [11,13,16,17]. RALC has already proven superior to the standard LAPC [14,18-20]. However, superior to LAPC, RALC is still associated with several disadvantages. RALC takes longer than open cystectomy and patients are placed inconveniently in the Trendelburg position during most of the procedure which can cause contemporary cerebral edema, compression of the lungs and decreasing cardiac output. Therefore, elderly patients or patients with cardiopulmonary comorbidities are in theory worse candidates to be operated with the RALC technique. Yet, this still needs to be investigated and a comparison between the different techniques, and especially the open mini-laparotomy cystectomy (MiniCx) would be valuable. This technique, which is used at Aarhus University Hospital (AUH) has proven to diminish blood loss, operative time, complication rate, and morbidity compared to the classic open cystectomy [21].

In RALC, the urinary diversion can either be performed extracorporally, meaning that after performing the RALC the urinary diversion is done by open technique, or intracorporally where the entire procedure is done by RAL. Many centers worldwide, including AUH, use RALC in combination with an extracorporal urinary diversion. Studies comparing LAPC versus open cystectomy only describe patients operated with the standard laparotomy.

All traumas to the body induce an acute phase response (APR) or stress response and as major surgery is a deliberate form of tissue injury, it triggers a surgical stress response [12,22,23]. The APR plays an important role in controlling the human immune system. Minimal invasive surgery is believed to induce less tissue trauma and, in theory, is less aggravating for the immune system. Preservation of the immune system is important because it prevents postoperative infections, sepsis, and possible adherence of tumors cells to incision sites, and establishment of micrometastatic disease at the time of surgery. A reduction in trauma through a minimal invasive procedure appears to have less impact and better preservation on the immune system than the open approach [12,24]. However, the majority of studies on the immunologic changes related to laparoscopy have dealt with cholecystectomy [22,25,26], and only few data have been published on urologic surgery [5,22,27,28]. Furthermore most studies investigate changes in immunologic parameters during and after surgery but fail to relate these changes to clinical outcome and the results of various studies do not always correspond, thus making it difficult to draw reliable conclusions [12]. The most widely used immunologic parameters for systemic surgical stress response is measurements of serum levels of the human cytokines; Interleukin (IL)-1, IL-6, IL-10,
Granulocyte Elastase (GE), Tumor necrosis factor alpha (TNF-α) and Gamma Interferon (IFN-γ) [5, 27, 29, 30]. Another widely used parameter is the acute phase reactant C-reactive protein (CRP) [24, 28]. Two other parameters investigated in correlation to surgical stress response is CO₂ insufflation (pneumoperitoneum) and steroid injection prior to surgery. Both causes an attenuated inflammatory response thus believed to lead to better recovery and less postoperative complications [31-36], which is of great value, especially to the oncologic patient.

Convalescence is under the scope these days and is a highly prioritized area within the health care system both from a patient point of view but also from an economical point of view [37, 38]. Therefore it is of great importance to find the most suitable surgical procedure on an individual basis in order to give the patient the best opportunities to recover and, if needed, cope with adjuvant therapy.

2. Aims.

This PhD study aims to investigate:

1. Which new surgical stress response biomarkers can be used in measuring the surgical response after radical cystectomy?
2. Which operative technique induces less surgical stress response in patients undergoing radical cystectomy?
3. Is there a correlation between the surgical stress response and convalescence?
4. If inducing pneumoperitoneum and/or injecting steroid prior to open cystectomy will affect the surgical stress response firstly demonstrated in an animal model and afterwards in a randomized prospective human clinical trial.

3. Hypotheses of Study 1, 2 and 3

Study 1 – Finding potential new surgical stress response biomarkers and comparing surgical techniques in correlation to surgical stress response.

We hypothesize that the clinical outcome resulting from cystectomy performed by the RALC with intracorporal urinary diversion is superior to the MiniCx and the RALC with extracorporal urinary diversion. Furthermore we wish to investigate if the RALC with extracorporal urinary diversion is closer in similarity to the outcome from the RALC performed with intracorporal urinary diversion or the MiniCx or if it is superior to these two techniques. During investigation we expect to find potential new biomarkers which can be used in the prediction of clinical outcome.

Study 2 & 3 – Improvement of postoperative outcome after radical cystectomy by inducing pneumoperitoneum and/or steroid preoperatively - firstly demonstrated in an animal model and afterwards in a randomized human clinical trial study.

We hypothesize that inducing pneumoperitoneum and injecting steroid preoperatively will result in a reduction of the cytokine response which in turn will result in an attenuated inflammatory response to the surgical trauma. Given both steroid and inducing pneumoperitoneum may have synergistic effect, but can in theory be detrimental to the patient in causing a fare to attenuated inflammatory response. In clinical trials no correlation has ever been demonstrated between the changes in immunologic parameters and relevant postoperative clinical endpoints. So we wish to examine if CO₂ insufflation and steroid injection preoperatively causes less surgical stress response, firstly demonstrated in a porcine model (study 2) and afterwards shown in a randomized human clinical trial study (study 3).
4. Material and Methods

The Study will be performed at the Department of Urology, Aarhus University Hospital in collaboration with the Department of Urology, Herlev University Hospital.

**Study 1 - Clinical experimental study: Comparison of surgical stress response in Robot-assisted laparoscopic and in open Mini-laparotomy radical cystectomy.**

60 patients (ptt.) diagnosed with IBC is divided into 3 groups\(^1\): 1) 20 ptt. MiniCx 2) 20 ptt. RALC with extracorporal urinary diversion and 3) 20 ptt. RALC with intracorporal urinary diversion. Within the three groups all patients will have taken a venous blood sample as illustrated in **fig.1**. Serum samples will be separated and stored in 5 tubes with 100 µL in each and stored at \(-80^\circ\text{C}\) until analysis. Concentration of serum human interleukins will be measured using a 27-Plex Panel (Human Bio-Plex Pro Assays) incl. the previous mentioned known six interleukins and 21 potential surgical stress biomarkers. C-reactive protein will also be measured. Perioperative parameters will be recorded in accordance to BMI, comorbidities, blood loss, operation time, admission time, peroperative complications, early postoperative complications (< 90 days) and late postoperative complications (> 90 days), recurrence rate and survival rate.

**Study 2 – Clinical experimental study: Carbon dioxide insufflation and/or steroid injection given preoperatively in a porcine model in relation to surgical stress response.**

The study will be carried out on Göttingen minipigs (weight approx. 40 kg, 100 days). All surgery will be performed with the pig in general anesthesia and under sterile conditions. Forty-four pigs\(^2\) will be divided into five groups: 1) 10 pigs open cystectomy and urinary diversion performed without pneumoperitoneum 2) 10 pigs open cystectomy and urinary diversion with pneumoperitoneum 3) 10 pigs Laparoscopic cystectomy and urinary diversion 4) 7 pigs only placement of 5 trocars without pneumoperitoneum 5) 7 pigs placement of 5 trocars with pneumoperitoneum. Before the procedure a Central venous Catheter (CVK) will be placed in order to ease the preoperative, intraoperative and subsequent blood draws. After the procedure the animal will be extubated and returned to the stable for 3 days. Within the five groups all pigs will have taken a blood sample, urine sample and tissue samples as illustrated in **fig. 2**. Serum samples will be separated and stored in 5 tubes with 100 µL in each and stored at \(-80^\circ\text{C}\) until analysis. Urine and tissue samples will also be stored at \(-80^\circ\text{C}\) until analysis. Concentration of serum interleukins will be measured using a precision pro human cytokines Plex Panel (171-A4507M Human Bio-Plex Pro Assays), hereby

\(^1\)The no. of patients in each group is estimated by a power analysis based on numbers found from another relevant study on Interleukin (Il-6) levels \([5]\). Having an \(\alpha\)-value = 0.05 and a \(\beta\)-value of 0.05 gives a minimum of 11 patients in each group. Expecting there will be some variations in tumor-grading, gender and age this is adjusted by including 20 patients in each group.

\(^2\)The no. of pigs in each group is estimated by a power analysis on numbers found from another relevant study on CRP levels \([22]\). Having an \(\alpha\)-value = 0.05 and a \(\beta\)-value of 0.20 gives a minimum of 7 pigs in each group. Expecting minor operative complications can occur this is adjusted by including 10 pigs in each group except in the sham groups.
measuring 5 known and 5 potential surgical stress biomarkers. Topical Fentanyl patches will be placed on all pigs for postoperative analgesia and changed daily until day 3 were the animals will be euthanized with an overdose of Potassium Chloride under general anesthesia.

**Study 3 – Clinical experimental study: A randomized prospective study in humans comparing surgical stress response in correlation to inducing CO\(_2\) and/or given steroid injection preoperative in patients operated with radical cystectomy.**

80 patients\(^3\) will be randomized into four groups: 1) 20 ptt. having MiniCx *without* pneumoperitoneum 2) 20 ptt. having pneumoperitoneum induced prior to MiniCx 3) 20 ptt. injected with 100 mg prednisone prior to RALC with intracorporeal urinary diversion 4) 20 patients injected with 100 mg prednisone prior to RALC with extracorporeal urinary diversion. Blood samples and urine collection will be performed as described in fig. 3.

**4.2 Statistical Analyses.**

Relevant statistical tests and the latest version of Stata statistical analysis software will be used. Non-parametric tests will be used for most clinical parameters. Parametric tests will be used for biochemical parameters if normal distribution is accepted (see footnotes 1, 2 and 3 for power-analysis).

**4.3 Ethics.**

The approval of the Danish Data Protection Agency (file name. 1-16-02-394-12, jr.nr 2007-58-0010) and the regional science ethics committee for the data collection for study 1 has been received (Journal nr. 1-10-72-544-12) and will be applied for study 2 & 3. Approval from the Danish Council for animal experiments for study 2 is being prepared at the moment.

**5. Research Plan - Time schedule.**

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\(^3\)The power-estimate is similar to that of study 1.

\(^4\)To get a valuable first hand impression of research praxis in a closely related area of research and to build a foundation for possible future international joint projects.
6. Practical Aspects

The study is to be performed at the Department of Urology, Aarhus University Hospital in cooperation with Herlev University Hospital. Pernille Skjold Kingo MD, Dept. of Urology, AUH: Primary investigator, performing the experimental animal studies and database study in addition to data analysis and the writing of the study 1, 2, and 3.

6.1 Supervision.
- Jørgen Bjerggaard Jensen, MD, DMSc, Associate professor, Dept. of Urology, Aarhus University Hospital: Primary supervisor.
- Rikke Nørregaard, MSc, PhD, Associate professor, Institute of Clinical Medicine, AUH: Co-supervisor.
- Michael Borre, MD, PhD, DMSc, Professor, Dept. of Urology, Aarhus University Hospital: Co-supervisor

6.2 Cooperation.
Gitte Wrist Lam, MD, Dept. of Urology, Herlev Hospital, Klaus Møller-Ernst Jensen, MD, DMSc, AUH, Dept. of Urology, Ulla Bisgaard, MD, Dept. of Urology, AUH, Gitte B. Kall, Biomedical Laboratory Technician (BLT), AUH, Dept. of Clinical Biochemistry, Conie Sørensen, BLT, Karin Hegnsved Fredborg, BLT and Nadia Gadeborg Knudsen, BLT, AUH, Dept. of Urology

7. Publication aims.

The study results, negative as well as positive, are expected to result in 3-4 articles published in international peer-reviewed journals.

8. Perspectives

With the present study we aim to find the best and less invasive surgical technique in patients treated for invasive bladder cancer by radical cystectomy, and to find out if inducing pneumoperitoneum or giving steroid injection prior to surgery will have a beneficial effect on the clinical outcome in correlation to convalescences, peroperative and, early and late postoperative complications. Furthermore, the knowledge obtained from this study will help us to verify whether a careful patient selection should take place prior to operation in order to secure the best treatment modality for each patient evaluated individually.
References


