AARHUS UNIVERSITY

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

Pernille Skjold Kingo, MD, Dept. of Urology, Aarhus University Hospital, Skejby, Denmark

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,

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

Granulocyt 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 CO_2 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.
Convalescences 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. Hypothesies 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 CO_2 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).

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

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°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.

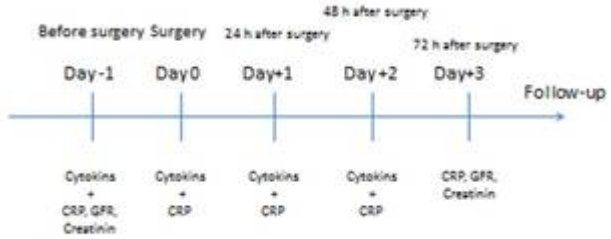

Fig.1

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. Fortyfour 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°C until analysis. Urine and tissue samples will also be stored at ÷80°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

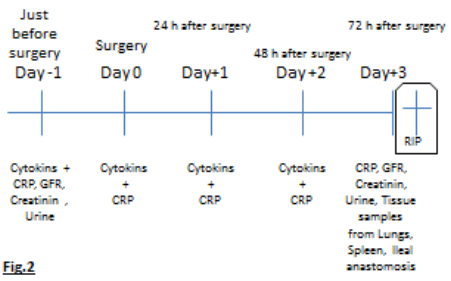

Fig.2

[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 α-value = 0.05 and a β-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 α-value = 0.05 and a β-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.

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

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 pneumperitoneum induced prior to MiniCx 3) 20 ptt. injected with 100 mg prednisone prior to RALC with intracorporal urinary diversion 4) 20 patients injected with 100 mg prednisone prior to RALC with extracorporal urinary diversion. Blood samples and urine collection will be performed as described in **fig. 3.**

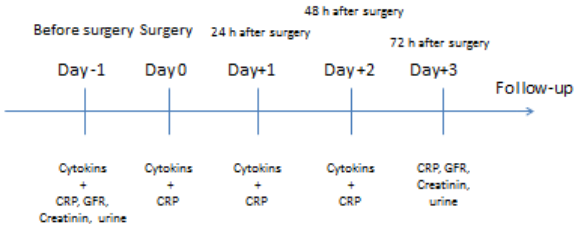

Fig. 3

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.

	2013 (Sept 1st, 2nd term)	2014 (1st term)	2014 (2nd term)	2015 (1st term)	2015 (2nd term)	2016 (1st term)
Data collection study 1						
Analysis and writing of paper 1						
Data collection study 2						
Analysis and writing of paper 2						
Data Collection study 3						
Analysis and writing of paper 3 and Finale PhD thesis						
Memorial Sloan-Kettering Cancer Centre, NY, USA (1 month)[4]						
PhD courses equal to 30 ECTS						

[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.

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

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.

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

References

1. Ploeg M, Aben KKH, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009;27:289-293
2. Stenzl A, Nigel CC, De Santis M et Al. Treatment of Muscle-invasive and Metastatic Bladder Cancer: Update of the EAU Guidelines. European Urology 2 011; 59: 1009-1018
3. Oosterlinck W and Decaestecker K. Current strategies in the treatment of non-muscle-invasive bladder cancer. Expert Rev. Anticancer Ther 2012; 12(8): 1097–1106
4. Hoskin P and Dubash S. Bladder conservation for muscle-invasive bladder cancer. Expert Rev. Anticancer Ther 2012; 12(8): 1015–1020
5. Wang S, Chen Y, Lin H, Chen L. Comparison of surgical stress response to laparoscopic and open radical cystectomy. World J Urol 2010; 28:451–455
6. Weizer AZ, Palella GV, Montgomery JS. Managing muscle-invasive bladder cancer in the elderly. Expert Rev. Anticancer Ther 2010; 10(6): 903–915
7. Huang GJ and Stein JP. Open radical cystectomy with lymphadenectomy remains thetreatment of choice for invasive bladder cancer. Curr Opin Urol 2007; 17:369–375
8. Jensen JB, Lundbeck F, Jensen KM. Complications and neobladder function of the Hautmann orthotopic ileal neobladder. BJU International 2006; 98: 1289-1294
9. Hautman RE, De Petriconi R, Gottfried H et Al. The Ileal Neobladder: Complications and Functional Results in 363 Patients after 11 Years Of Follow-up. J Urol 1999; 161: 422-428
10. Jensen JB, Ulhøi BP, Jensen KM. Estimation of the true number of lymph nodes in lymphadenectomy specimens from radical cystectomy. Scand J Urol Nephrol 2009; 43: 288-292
11. Knap MM, Lundbeck F, Overgaard J. Early and Late Treatment-related Morbidity Following Radical Cystectomy. Scand J Urol Nephrol 2004; 38: 153–160
12. Kuhry E, Jeekel J, Bonjer HJ. Effect of Laparoscopy on the Immune System. Seminars in Laparoscopic Surgery 2004; 11 (1): 37-44
13. Chaa EK, Wiklundb NP, Scherr DS. Recent advances in robot-assisted radical cystectomy. Current Opinion in Urology 2011, 21:65–70
14. Hayn MH, Hellenthal NJ, Seixas-Mikelus SA et Al. Is patient outcome compromised during the initial experience with robot-assisted radical cystectomy? Results of 164 consecutive cases. BJU International 2010; 108: 882-887
15. Nix J, Smith A, Kurpad R, Nielsen ME et Al. Prospective Randomized Controlled Trial of Robotic versus Open Radical Cystectomy for Bladder Cancer: Perioperative and Pathologic Results. European Urology 2010; 57: 196-201
16. Smith AB, Nielsen ME, Wallen EM, Pruthi RS. Current status of robot-assisted radical cystectomy. Current Opinion in Urology 2010, 20:60–64
17. Haber G, Crouzet S, Gill IS. Laparoscopic and Robotic Assisted Radical Cystectomy for Bladder Cancer: A Critical Analysis. European Urology 2008; 54: 54–64
18. Richard E. Hautmann. The oncologic results of laparoscopic radical cystectomy are not (yet) equivalent to open cystectomy. Current Opinion in Urology 2009, 19:522–526
19. Haber G, Crouzet S, Gill IS. Laparoscopic and Robotic Assisted Radical Cystectomy for Bladder Cancer: A Critical Analysis. European Urology 2008; 54: 54–64

FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

20. Kang SG, Ko YH, Jang HA et Al. Initial Experience of Robot-Assisted Radical Cystectomy with Total Intracorporeal Urinary Diversion: Comparison with Extracorporeal Method. J Lap Adv Surg Tech 2012; 22 (5): 456-462
21. Mini-Laparotomy approach to radical Cystectomy. Jensen JB, Pedersen KV, Olsen KØ et al. BJU int, 2011;108 (7):1125-1130
22. Duchene DA, Gallagher BL, Ratliff TL et Al. Systemic and Cell-Specific Immune Response to Laparoscopic and Open Nephrectomy in Porcine Model. J Endourol 2008; 22 (1): 113-120
23. Lausten SB, Grøfte T, Andreasen F et Al. Effects of laparotomy vs pneumoperitoneum on the hepatic catabolic stress response in ambulatory and stationary settings in pigs. Surg Endosc 1999; 13: 390–396
24. Buunen M, Gholghesaei M, Veldkamp R et Al. Stress response to laparoscopic surgery. Surg Endosc 2004; 18: 1022-1028
25. Lausten SB, Ibrahimb TM, El-Sefib T et Al. Systemic and Cell-Mediated Immune Response after Laparoscopic and Open Cholecystectomy in Patients with Chronic Liver Disease. Dig Surg 1999;16:471–477
26. Boo YJ, Kim WB, Kim J et Al. Systemic immune response after open versus laparoscopic cholecystectomy in acute cholecystitis: A prospective randomized study. Scand J Clin Lab Invest 2007; 67: 207–214
27. Miyake H, Kawabata G, Gotoh A et Al. Comparison of surgical stress between laparoscopy and open surgery in the field of urology by measurement of humoral mediators. Int J Urol 2002; 9: 329–333
28. Jacobi CA, Wenger F, Opitz I, Müller JM. Immunologic Changes during Minimally Invasive Surgery. Dig Surg 2002; 19: 459-463
29. Hensler T, Hecker H, Heeg K et Al. Distinct Mechanisms of Immunosuppression as a Consequence of Major Surgery. Infection and Immunity 1997; 65 (6): 2283-2291
30. Novitsky YW, Litwin DEM, Callery MP. The net immunologic advantage of laparoscopic surgery. Surg Endosc 2004; 18: 1411-1419
31. Fuentes JM, Hanly EJ, Aurora AR et Al. CO2 Abdominal Insufflation Pretreatment Increases Survival After a Lipopolysaccharide-Contaminated Laparotomy. J Gastrintest Surg 2006; 10 (1): 32-38
32. Hanly EJ, Aurora AA, Shih SP et Al. Peritoneal acidosis mediates immunoprotection in laparoscopic surgery. J Surg 2007; 142 (3): 357-364
33. West MA, Hackam DJ, Baker J et Al. Mechanism of Decreased In Vitro Murine Macrophage Cytokine Release After Exposure to Carbon Dioxide. Ann Surg 1997; 226(2): 179-190
34. Lee SW, Feingold DL, Carter JJ et Al. Peritoneal macrophage and blood monocyte functions after open and laparoscopic-assisted cecectomy in rats. Surg Endosc 2003; 17: 1996–2002
35. Rawashdeh YF, Olsen LH, Jørgensen TM. Current Clinical Urology: Pediatric Robotic Urology. Chapter 2: Physiology of Pediatric Genitourinary Laparoscopy 2009: 23-41
36. The effect of preoperative corticosteroids on peritoneal macrophage function after laparoscopic and open abdominal surgery in a rat model. Schmelzer TM, Heath JJ, Hope WW, Mostafaria A et Al. Am Jour Surg 2008; 196: 920–925
37. Smith A, Kurpad R, Lal A et Al. Cost Analysis of Robotic Versus Open Radical Cystectomy for Bladder Cancer. J Urol 2010; 83: 505-509
38. Zehndera P and Gill IS. Cost-effectiveness of open versus laparoscopic versus roboticassisted laparoscopic cystectomy and urinary diversion. Cur Opinion Urol 2011; 21: 415–419