Benefits of robotic cystectomy with intracorporeal diversion for patients with low cardiorespiratory fitness: a prospective cohort study

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Abstract

Background: Patients undergoing radical cystectomy have associated comorbidities resulting in reduced cardiorespiratory fitness. Preoperative cardiopulmonary exercise testing (CPET) measures including anaerobic threshold (AT) can predict major adverse events (MAE) and hospital length of stay (LOS) for patients undergoing open and robotic cystectomy with extracorporeal diversion. Our objective was to determine the relationship between CPET measures and outcome in patients undergoing robotic radical cystectomy and intracorporeal diversion (iRARC).

Methods: A single institution prospective cohort study in patients undergoing iRARC for muscle invasive and high grade bladder cancer. Inclusion: patients undergoing standardised CPET prior to iRARC. Exclusions: patients not consenting to data collection. Data on CPET measures (AT, ventilatory equivalent for carbon dioxide (VE/VCO_2) at AT, peak oxygen uptake (VO_2)), and patient demographics prospectively collected. Outcome Measurements included Hospital LOS; 30-day MAE and 90-day mortality data, which were prospectively recorded. Descriptive and regression analyses were used to assess whether CPET measures were associated with or predicted outcomes.

Results: From June 2011 to March 2015 128 patients underwent radical cystectomy (ORC n=17, iRARC n=111). 82 patients who underwent iRARC and CPET and consented to participation were included. Median (IQR): Age=65 (58−73); BMI=27 (23−30); AT=10.0 (9−11), Peak VO_2=15.0 (13−18.5), $VE/VC0_2$ (AT)=33.0 (30−38). 30-day MAE=14/111 (12.6%): Death=2, Multi organ failure=2, abscess=2, Gastrointestinal=2, Renal=6; 90-day mortality=3/111 (2.7%). AT, Peak VO_2,

$VE/VC0_2$ (at AT) were not significant predictors of 30-day MAE or length of stay. The results are limited by the absence of control group undergoing open surgery.

Co*nclusions:* Poor cardiorespiratory fitness does not predict increased hospital LOS or MAEs in patients undergoing iRARC. Overall, MAE and LOS comparable with other series.

Keywords

Anaerobic threshold, Cardiopulmonary exercise testing, Cardiorespiratory, Complications, Length of stay, Muscle invasive, Radical cystectomy, Robotic, Urothelial carcinoma.

1. Introduction

The incidence of bladder cancer increases with age and is associated with smoking and exposure to industrial carcinogens. Consequently, pre-morbid conditions that lead to reduced performance status, such as cardiovascular disease, are apparent in the treated population (1). Radical cystectomy with urinary diversion remains the gold standard treatment for muscle invasive bladder cancer and non-muscle invasive disease in selected patients. Following radical cystectomy, the major adverse event rate is around 15% and the 90-day mortality is between 1.7% and 9%, both of which reflect the impact of surgery in a patient group with reduced performance status (2–4).

A number of methods exist to measure performance status with the intention to predict post-operative adverse events and their use is recommended prior to major surgery (5−8). Tools such as the American Society of Anaesthesiologists (ASA) index, Charlson comorbidity index, Eastern Cooperative Oncology Group (ECOG) performance index can be used to assign risk for major complication and mortality following radical cystectomy. Another method, cardiopulmonary exercise testing (CPET) has the distinct advantage of measuring the efficiency of physiological oxygen exchange, and therefore cardiorespiratory function (CRF) for the individual being tested. This allows clinicians to create a personalised risk profile with which to predict post-operative morbidity and mortality (9,10). Systemic complications that occur following major surgery arise in part as a result of the inability of patients with poor CRF to meet the increased peri-operative oxygen demand which arises as a result of a systemic inflammatory response (11,12). Measuring the peak oxygen uptake (Peak VO_2) during exercise, the threshold at which anaerobic respiration begins to supplement aerobic respiration, the anaerobic threshold (AT), and the peak

VO_2 and ventilatory equivalent for carbon dioxide ($VE/_{VCO2}$) which gives a measure of pulmonary efficiency can predict post-operative morbidity and mortality (10,13−15). Patients with a poor CPET result are at much higher risk of peri-operative cardiac morbidity and death (9,10,13−15). Variables derived from CPET including anaerobic threshold (AT) and VEO_2 are predictive of major complications and length of stay following open cystectomy (ORC) and also RARC with extracorporeal diversion (eRARC) (14,15).

We sought to determine the association between cardiorespiratory fitness, as measured by CPET, and major complications or hospital LOS in patients undergoing iRARC. Our hypothesis was that the described CPET measures (AT and VEO_2) which are predictive of outcome for ORC and eRARC should also predict outcome in patients undergoing iRARC (14,15).

2. Patients and Methods

2.1. Patients

Over a 45-month period 128 patients underwent radical cystectomy at a single pelvic uro-oncology centre. 17 patients underwent planned ORC: 7 patients had previous pelvic or perineal surgery, 2 had radiotherapy for prostate cancer, 2 patients had clinical T4 stage, 4 patients had a concurrent procedure and 2 patients were randomized to open surgery as part of a randomized controlled trial comparing open cystectomy to minimal invasive cystectomy (BOLERO) (NCT01196403). iRARC was performed in the remaining 111 cases (Figure 1). CPET was performed on iRARC patients before cystectomy (median 34 days). Technical aspects of iRARC have been previously described (16,17).

2.2. Ethics

All patients gave written informed consent for the results of their CPET to be stored on an institutional data base. Local Research Ethics Committee approval was given for the collection of CPET data on an institutional database (Reference: 12/LO/0192).

2.3. CPET

CPET was conducted on a cycle ergometer (Lode Corival) with continuous side stream gas exchange analysis (Cortex Metalyzer 3B). Patient demographics were recorded and patients' activity level used to determine work rate. Spirometry was performed and haemoglobin measured using the Hemocue system. 12-lead ECG electrodes, pulse oximeter and blood pressure cuff were applied. Three minutes of rest preceded the test during which oxygen and carbon dioxide concentration along with gas flow were measured. Three minutes of unloaded cycling at 60−65 RPM was then undertaken. The work rate increases continuously thereafter until the test was terminated due to symptoms, volitional fatigue or ECG changes. The patient's recovery was monitored until heart rate, blood pressure, ECG and saturations returned to baseline levels. CPET costs £225 ($320) and is reimbursed to the Department of Urology from the UK NHS tariff for cystectomy using service line reporting.

Ventilatory equivalents at AT were calculated using standard methods (19). VO_2 peak was measured as the average VO_2 attained over a 30 second period at peak exercise. All CPET variables were determined on the day of the test and then independently verified by a Consultant Anaesthetists with CPET expertise (RS).

2.4. Peri-operative care

All patients underwent a standardised perioperative protocol including formal pre-operative assessment, on which CPET measures had no influence. This included carbohydrate loading on the evening prior to and morning of surgery, epidural anaesthesia, postoperative anti-emetics, histamine H2-antagosists (ranitidine), venous thromboembolic disease prophylaxis (Dalteparin), regular intravenous paracetamol analgesia and chewing gum (patients' preference) three times daily for four days post-op to stimulate gut motility. Post-operatively all patients went to the post-anaesthetic recovery unit (PACU) for a minimum of 24 hours, during which they received high dependency unit type care. The decision to extend PACU care or return the patient to the ward after the initial period was made by a critical care consultant independently of the surgical or anaesthetic teams.

2.5. Data collection

Patients were included in this study following written consent for their CPET results to be added to the institutional research database. Patient demographics (age, height, weight, comorbidities and medication) and CPET measures were recorded. Post-operative complications as defined by the Clavien-Dindo (CD) scoring system (a score of ≥ 3 counted as a major complication), and length of stay (LOS) were prospectively recorded. Following discharge, patients were reviewed in clinic by the surgical team approximately four weeks post-operatively.

2.6. Statistical analysis

Data is presented as percentages or median with interquartile range (IQR). Comparisons between independent groups were analysed using the non-parametric Mann-Whitney U-test and Kruskal-Wallis H-test for continuous variables, and Chi-squared Test for categorical variables. Correlation between data sets was analysed using Spearman's Rank Correlation. Multivariate binary logistic regression analysis was applied to identify potential factors associated with post-operative complications. Multivariate linear regression analysis was applied to identify potential factors associated with length of stay. Significance value was taken as less than 5% then adjusted for multiple comparisons using the Bonferroni correction. Statistical analysis was performed using SPSS software (version 21 for Windows, IBM, New York, USA).

3. Results

Between 1st June 2011 and 24th March 2015, 111 patients underwent iRARC and 82 gave consent for their data to be placed on the CPET database. Demographic details and summary CPET outcomes/data are presented in Table 1. The median length of stay was 10 days (IQR=6), there were 14 major complications within 30 days (12.6%), and three deaths (2.70%) within 90 days, one cancer related (0.9%) and two following major complications (1.8%). Details of major complications are presented in Table 2. Eight of the 14 major adverse events were categorised as being either a direct result of the surgical technique (technical) or attributed to other organ or system failure, (non-technical) (n=6).

No significant difference was found in AT, Peak VO_2, or VE/$VC0_2$ (@AT) between patients who had complications and those who did not (Table 3). On multivariate logistic regression analysis none of these CPET parameters were significant predictors of a major complication at 30 days (Table 3). No significant correlation was found between length of stay and either of AT, Peak VO_2, or VE/VCO_2 (@AT). Using multivariate linear regression, CPET was not found to predict length of stay. (Table 3)

Previously, for cases undergoing ORC or eRARC an AT of 12 and 11 have been defined as a threshold below which patients were at risk of increased LOS and occurrence of major complication (14,15). Applying an AT threshold of 11 or 12, we found no significant difference between patients above and below this threshold in length of stay or major complications at 30 days. (Table 4). Additional analysis found no association between major complications at 30-days and ASA level ($\chi^2(3)$ =7.083, p=0.069; Chi Squared-test), nor between hospital length of stay and ASA level ($\chi^2(3)$ =6.874, p=0.076; Kruskal-Wallis H-test). Data on length of surgery was available for 36/82 cases. Univariate analysis found no association between major complications at 30-days and length of surgery (Z=-1.031, p=0.303; Mann-Whitney U-test), nor between hospital length of stay and length of surgery (ρ=0.157, p= 0.360; Spearman's Rho test).

4. Discussion

This is the first study to examine the relationship between cardiopulmonary performance status and adverse events in patients undergoing iRARC. The results of this prospective study in an unselected cohort of patients undergoing iRARC suggest that in our population, the post-operative adverse event rate for major complications following iRARC is 12.6%, which compares favorably to that described in previous series (4).

Contrary to the findings of Tolchard *et al* and Prentis *et al*, in which CPET (AT=11 and AT=12) is highly predictive of major post-operative adverse events and LOS, we found no significant relationship between CPET and these outcomes. We did find weak association between CPET and hospital LOS but this was not significant, and the defined CPET parameters for ORC and eRARC are neither predictive nor associated with the occurrence of major adverse events in patients undergoing iRARC. The results suggest that patients undergoing iRARC with a reduced performance status, as assessed by CPET to reflect cardiopulmonary fitness, are not at the same level of risk for a post-operative adverse event as patients undergoing ORC or RARC converted to open surgery for reconstruction, as described previously (14,15). In the study by Prentis and colleagues, 82 patients undergoing radical cystectomy had CPET. They found that the occurrence of complications was associated with length of stay, which is consistent with our own data. They also found that AT was the only independent predictor of an adverse event post cystectomy and that a threshold of 12 was discriminated between 'fit' and 'unfit' patients i.e. those who were less likely and more likely to have complications (14). Similarly, Tolchard and colleagues assessed the relationship between CPET and complications after radical cystectomy in 105 patients undergoing open or RARC. They found AT was negatively, and VE/VCO_2 positively correlated with complications and LOS (15). Both of the studies above reported data from cohorts similar to our own with highly significant results (Table 5). We suggest that the utilisation of a truly minimally invasive approach may off-set the morbidity of the procedure and reduce the risk of complications that arise from major abdominal surgery in the presence of poor cardiorespiratory reserve. Other studies of intracorporeal reconstruction, notably the recent series of 128 cases of robotic intracorporeal neobladder by Desai and colleagues showed similar rates of complications, and the authors have drawn similar conclusions to our own (19).

Systemic complications that occur following major surgery arise, in part, as a result of the inability of patients with poor CRF to meet the increased peri-operative oxygen demand (11,12). It is well documented that surgical trauma induces a systemic stress response which includes stimulation of the hypothalamic-pituitary-adrenal axis and the release of a humoral mediator response, such as cytokines, proportional to the severity of surgical stress. There is evidence in cystectomy and other surgical procedures that minimally invasive surgery provokes a lesser perioperative stress response with a diminished neuroendocrine-metabolic effect (20,21). It is interesting to speculate that the physiological stress response associated with minimally invasive cystectomy and intracorporeal reconstruction will be less than that of extracorporeal reconstruction or open surgery.

The results of the present study should be interpreted in light of certain limitations. This is a prospective cohort study and not a randomised comparator study. We have however accounted for potential confounding factors such as age, gender, BMI, type of diversion, and use of neo-adjuvant chemotherapy in regression analysis. A further limitation of this study is the lack of sample size calculation prior to analysis. A possible criticism of the lack of significant association between CPET measures and outcomes might be that potential differences were missed due to the study being underpowered. The sample in this study is similar in size and clinical setting to those of previous studies and as such we feel that our findings are of relevance to the literature on robotic cystectomy. Furthermore, as iRARC is standard practice within our institution, the effect of case selection as a potential source of bias has been minimised. A prospective randomised trial of iRARC versus ORC recruiting patients with poor performance status would be the ideal design to test our hypothesis. The RAZOR (randomized open vs robotic cystectomy) study has finished recruiting and intends to compare ORC to eRARC for oncological outcomes, complications and health-related quality of life measures (25). It is our understanding that the technical approach for reconstruction in the test arm (RARC) is to convert to open surgery which may mask the potential advantages of truly minimally invasive surgery. While the RAZOR trialists are to be commended in overcoming obstacles to the recruitment to randomised trials of surgical technology, the feasibility of studies large enough to detect differences in outcomes within in a defined group for e.g. poor cardiopulmonary performance will be challenging. In the knowledge that cardiopulmonary performance status is an independent predictor of outcome in ORC/eRARC but not iRARC it would therefore seem important account for this and stratify cases according to performance status. For the present, the apparent lack of disadvantage for patients with low performance status can be included as part of the shared decision making process in clinical practice.

In common with all other series, experience of iRARC from this centre reflects a relatively early stage in an evolving technique. Eight of 14 major adverse events were classified as 'technical' e.g. hernia, stent migration, anastomotic leak, stricture; and six as 'non-technical' including sepsis, ileus, cardiac and renal impairment. While the major adverse event rate is similar to that reported in other series, it is noted that the 'non-technical' complication rate is lower than in comparable ORC series which is in keeping with the finding of a lack of relationship between physiological performance status and adverse outcome (15,19,26). To date, at our institution, we have performed over 200 iRARC procedures, which reflects a limited experience. It is tempting to suggest that with increasing experience the technical complication rate will decrease and it will be important to gather evidence in the post learning curve.

5. Conclusion

The results of this study suggest that in our population of patients undergoing robotic radical cystectomy with intracorporeal urinary diversion, low cardiorespiratory reserve did not predict the occurrence of major complications or hospital LOS. The morbidity and mortality associated with radical cystectomy has reduced in recent years, and iRARC may present an additional means of improving patient outcomes. Further research is needed to confirm these results against patients undergoing other forms of radical cystectomy, but the results are encouraging.

List of abbreviations used

ASA	American Society of Anaesthesiology
AT	Anaerobic threshold
BMI	Body-mass index
CD	Clavien-Dindo
CPET	Cardiopulmonary exercise testing
CRF	Cardiorespiratory failure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eRARC	Extracorporeal robotic assisted radical cystectomy
IQR	Inter-quartile range
iRARC	Intracorporeal robotic assisted radical cystectomy
LOS	Length of Stay
MAE	Major Adverse Event
ORC	Open radical cystectomy
PACU	Post-Anaesthetic Care Unit
RPM	Revolutions per minute
VE/VCO_2	Ventilatory equivalent for carbon dioxide
VO_2	Oxygen uptake

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study conception and design: BWL, JDK, RS
Data collection: BWL, WST, PE, DB, AJ, IA, AS
Analysis: BWL, WST, RS, DM, DB, AJ
Drafting of manuscript: BWL, WST, JDK, DM
Critical Review: HB, TPB, JEH, JDK, SN, DM, RS
Approval of final manuscript: All authors

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Legend to the figure

Figure 1: Flow diagram illustrating case selection

Figure 1

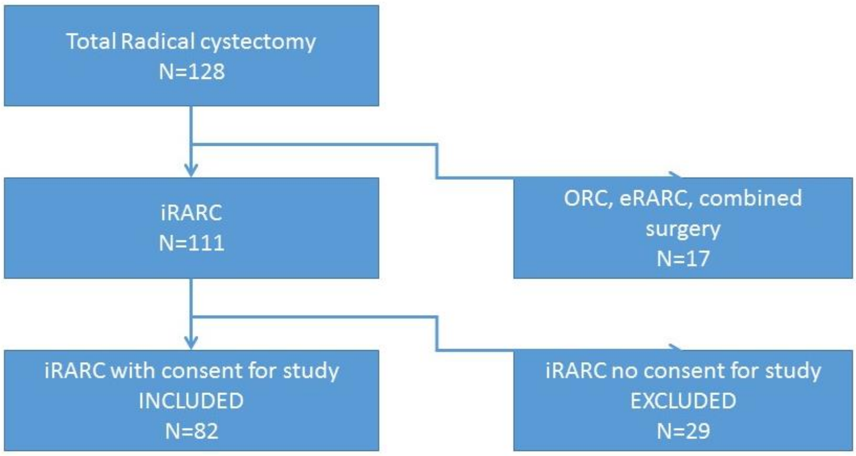
Total Radical cystectomy
N=128
iRARC
N=111
ORC, eRARC, combined surgery
N=17
iRARC with consent for study
INCLUDED
N=82
iRARC no consent for study
EXCLUDED
N=29

Table 1: characteristics of study population including demographics, urinary diversion type, cardiopulmonary exercise test parameters (CPET), and clinical outcomes.

Parameter		Median
Demographic	**Age at treatment, median (IQR)**	65 (58.75–71.25)
	BMI, median (IQR)	27.00 (23.5–30.5)
	Male, n (%)	81 (73)
	Neoadjuvant chemotherapy, n (%)	42 (37.8)
	ASA score: ≤2, n (%)	69 (84.2)
	≥2, n (%)	13 (15.8)
Diversion type	**Ileal conduit, n (%)**	80 (72.1)
	Continent diversion, n (%)	31 (27.9)
CPET	**AT, median (IQR)**	10 (9–11)
	Peak VO2, median (IQR)	15 (12–18)
	VE/VC02 (AT), median (IQR)	34 (30–38)
Outcomes	**Estimated console time (hours), median (IQR)**	5.1 (4-5-6.0)
	Length of stay (days), median (IQR)	10.0 (7–13)
	Major complications at 30 days, n (%)	14 (12.6%)
	Death	2
	Multi organ failure	2
	Abscess	2
	Gastrointestinal	2
	Renal failure	6
	90 day mortality, n (%)	3 (2.70%)
	Bleed/Sepsis/DIC	1
	Myocardial infarction	1
	Carcinomatosis	1

Table 2: Details of major adverse events within 30 days and Clavien-Dindo Classification.

Major adverse events within 30 days	Outcome	Complication type	Clavien-Dindo
Anastomotic stricture,	Nephrostomy and stent insertion	Technical	3a
Migrated stents	Nephrostomy insertion	Technical	3a
Small bowel injury	Laparotomy and repair under GA	Technical	3b
Migrated stents	Retrieval under GA	Technical	3b
Port site abscess	Incision and drainage under GA	Non-technical	3b
Pulmonary embolus, para-stomal hernia	Open reduction under GA	Technical	3b
Prolonged Ileus, AKI	Medical management	Non-technical	4a
Blocked stent, urinary leak, wound dehiscence,	Laparotomy and repair under GA	Technical	4a
Urinary Sepsis, multi-organ failure	Medical management	Non-technical	4b
Urinary Sepsis, multi-organ failure	Nephrostomy insertion	Non-technical	4b
Intraoperative rectal injury	Intraoperative colostomy formation	Technical	4b
Migrated stent, sepsis, PICC line associated VTE	Nephrostomy insertion	Technical	4b
Sepsis, bleed, DIC, Hyperkalaemia, Death	Return to theatre for laparotomy	Non-technical	5
MI, death	N/A	Non-technical	5

Table 3: CPET measures for cases with and without major complications at 30 days (Left panel) and correlation between length of stay and CPET parameters (right panel).

CPET measures	30 day major complication[§]				Length of stay[‡]			
	Yes (Median)	No (Median)	*P*	MLogR	Rho	95% CI	*P*	MLinR
Anaerobic Threshold	10.5	10	0.762	NS	-0.172	-0.372–0.04	0.122	NS
Peak VO2	15	17	0.642	NS	-0.231	-0.435–-0.033	0.035	NS
VE/VC02 (AT)	33.7	34	0.927	NS	0.092	-0.1–0.289	0.412	NS

Key: §=Mann Whitney U test; ‡=Spearman's correlation; MLogR=Multivariate logistic regression; MLinR=Multivariate linear regression; NS=Not significant. Significance level adjusted using Bonferroni method to account for multiple comparisons such that *P*=0.016.

Table 4: 30-day major complications (left panel) and length of stay (right panel) for cases with anaerobic threshold of <11 and those ≥11 (upper rows) (14), and <12 or ≥12 (lower rows) (15).

Anaerobic threshold	30-day major complication			Length of stay		
	No	**Yes**	**Chi-Square**	**Median**	**IQR**	**MWU**
<11	40	6	*P*=0.911	11	7.5–14.5	*P*=0.121
≥11	31	5		10	7–13	
<12	53	10	*P*=0.234	11	8–15	*P*=0.188
≥12	18	1		9	8–12	

Table 5: comparison of present study and published series reporting pre-operative CPET in patients undergoing cystectomy.

Parameter		Lamb *et al*	Tolchard *et al.* (13)	Prentis *et al.* (12)
	Total, n	111	105	82
	Analysed, n	82	105	69
Demographic	**Age at treatment, mean**	65	71	70
	BMI, mean	27	-	26.9
	Male, %	81	84	70
CPEX	**AT**	10.35 (7.0–19.0)	11.2 (5.8–22)*†	12.78†
	Peak VO2	16.11 (7.0–43.0)	15.2 (9–27.6)	16.23
	VE/VC02 (AT)	33.92 (23.0–48.0)	31 (21–47.2)**	36.12
Outcomes	**Length of stay (median)**	10	10	17.5
	Major complications at 30 days, n (%)	14 (12.6)	-	13 (15.8)
	90 day mortality, n (%)	3 (2.7)	6 (6)	2 (2.9)

*=predictive of post-operative complications, significant at $P<0.05$ level; **=predictive of post-operative complications, significant at $P\leq0.001$ level; †=predictive of hospital length of stay, significant at $P<0.05$ level.