U.PORTO

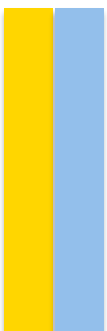
MESTRADO INTEGRADO EM MEDICINA

The Evolution of Laparoscopic Radical Cystectomy at a High-Volume Tertiary Center: Analysis of Pentafecta Criteria and its Relationship with Survival

António Pedro Tavares Pinho

M

2024



The Evolution of Laparoscopic Radical Cystectomy at a High-Volume Tertiary Center: Analysis of Pentafecta Criteria and its Relationship with Survival

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

António Pedro Tavares Pinho, estudante

Aluno do 6º ano profissionalizante do Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço eletrónico: up201807763@up.pt

Orientador: Dr. Manuel Antonielo Castanheira de Oliveira

Assistente Graduado de Urologia – Unidade Local de Saúde de Santo António, E.P.E.

Prof. Auxiliar Convidado do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Coorientador: Miguel Ângelo Marques Monteiro

Médico Interno no Serviço de Urologia – Unidade Local de Saúde de Santo António, E.P.E.

Coorientador: Professor Doutor Avelino Manuel Fraga Ferreira

Assistente Graduado Sénior de Urologia – Unidade Local de Saúde de Santo António, E.P.E.

Prof. Catedrático Convidado do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Maio 2024

The Evolution of Laparoscopic Radical Cystectomy at a High-Volume Tertiary Center: Analysis of Pentafecta Criteria and its Relationship with Survival

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Autor:

António Pedro Tavares Pinho

Orientador:

Manuel Antonio Castanheira de Oliveira

Coorientadores:

Miguel Marques Monteiro

CHP - HSA – UROLOGIA
Prof. Doutor Avelino Fraga Hora
Diretor de Serviço
Nº Ordem: 30844 Ass.

Maio 2024

ACKNOWLEDGEMENTS

First and foremost, I would like to extend my sincere gratitude to my research supervisor, as well as my co-supervisors, Dr. Manuel Oliveira, Dr. Miguel Monteiro, and Professor Dr. Avelino Fraga, for their invaluable guidance and support throughout the course of my work.

While they may not have been directly involved in the development of this thesis, I am deeply grateful to my family and friends for their unwavering support, both academically and personally. This dissertation stands as a testament to the strength of your encouragement and belief in me.

RESUMO

Objetivos: A cistectomia radical é considerada o tratamento de eleição para o cancro da bexiga não metastático de maior risco. Apesar da existência de literatura sobre a influência da experiência cirúrgica nos resultados perioperatórios e oncológicos na cistectomia radical aberta e assistida por robô, existem poucos dados em relação à cistectomia radical laparoscópica (CRL). O nosso objetivo é aplicar os critérios pentafecta (CP) para avaliar os resultados da cistectomia radical laparoscópica e os efeitos da experiência cirúrgica nos resultados perioperatórios e oncológicos.

Métodos: Reunimos dados de doentes submetidos à CRL com linfadenectomia pélvica e derivação urinária extracorporal para cancro de bexiga não metastático entre outubro de 2016 e dezembro de 2022. As cirurgias foram realizadas por uma equipa cirúrgica dedicada pertencente à unidade de oncologia vesical de um hospital terciário do Porto. Avaliamos doentes consecutivos em grupos criados de acordo com a ordem dos procedimentos cirúrgicos. A eficiência do processo foi avaliada pela análise do tempo operatório e dos resultados perioperatórios, enquanto o cumprimento do pentafecta consistiu no resultado principal. Resultados oncológicos como sobrevida global (SG) e sobrevida livre de recidiva (SLR) compreenderam critérios adicionais. Também avaliamos o impacto da experiência cirúrgica na proficiência e qualidade da cirurgia.

Resultados: Dos 155 doentes analisados, 64 (41.3%) alcançaram todos os cinco critérios da pentafecta, enquanto 106 (71.6%) e 132 (89.2%) atingiram quatro e três critérios, respetivamente. A pontuação média da pentafecta foi de 4.1 ± 1.0 (IC 95% 4.0-4.3). Individualmente, margens cirúrgicas negativas, remoção de ≥ 16 gânglios linfáticos, ausência de complicações superiores ou iguais ao grau 3 da classificação Clavien-Dindo no período de 90 dias, ausência de recidiva clínica em 12 meses e ausência de estenose ureteroentérica que requeresse intervenção no período de 12 meses foram observadas em 91.0%, 69.1%, 78.6%, 78.6% e 85.2% dos doentes, respetivamente. Os tempos operatórios para conduto ileal e neobexiga ortotópica foram, em média, 241.5 (± 40.2) e 295.79 (± 33.7) minutos, respetivamente. Para CRL, os tempos de operação e o número de gânglios linfáticos melhoraram com o aumento do número de casos, indicando proficiência satisfatória da operação. A proporção de alcance de pentafecta variou entre os grupos consecutivos da seguinte forma: Grupo 1: 33.3%; Grupo 2: 41.9%; Grupo 3: 50.0%; Grupo 4: 40.0%; e Grupo 5: 46.7%. Não se observaram diferenças estatísticas significativas entre os grupos. Índice de Comorbidade de Charlson, doença extravesical e presença de gânglios linfáticos positivos foram preditores independentes do não cumprimento de pentafecta, tanto na análise univariada como na multivariada. As taxas de sobrevivência global de três e cinco anos foram de 66.5% e 54.7%, respetivamente. Os doentes que alcançaram todos os 5 critérios da pentafecta mostraram maior SG e SLR quando comparados com aqueles que não alcançaram todos os critérios (log-rank $p < 0.001$). O alcance da pentafecta foi associado a resultados favoráveis em relação à SG, mesmo após ajuste para confundidores conhecidos (hazard ratio [HR] 0.48 [0.24-0.98], $P < 0.001$).

Conclusão: A Cistectomia Radical Laparoscópica apresenta níveis de proficiência e qualidade cirúrgicas satisfatórias, com o cumprimento de pentafecta correlacionado com uma melhoria das taxas de sobrevivência. Foi observado um aprimoramento nos tempos operatórios e no número de gânglios linfáticos retirados à medida que a experiência aumentava. Estes resultados apoiam a adoção precoce da CRL sem comprometimento dos resultados oncológicos.

Palavras-chave: Cancro da Bexiga, Pentafecta, Cistectomia Radical Laparoscópica, Sobrevida Global; Sobrevida Livre de Recidiva

ABSTRACT

Objectives: Radical cystectomy is considered the gold standard treatment for the highest risk of non-metastatic bladder cancer. Despite evidence indicating surgical experience with perioperative and oncologic outcomes in open and robot-assisted radical cystectomy, there is a lack of data concerning laparoscopic radical cystectomy (LRC). Our objective is to employ the radical cystectomy pentafecta criteria (PC) to assess the outcomes of laparoscopic radical cystectomy and the effects of surgical experience on perioperative and oncologic outcomes.

Methods: We gathered data on patients who underwent LRC with pelvic lymph node dissection and extracorporeal urinary diversion for non-metastatic bladder cancer between October 2016 and December 2022. The surgeries were performed by a specialized bladder surgery unit, led by a dedicated surgical team from a tertiary center in Porto. We assessed consecutive patients into time-associated groups according to the operation order. Process efficiency was assessed by evaluating operative time and perioperative outcomes, while the achievement of pentafecta served as the primary endpoint. Oncological outcomes such as overall survival (OS) and recurrence-free survival (RFS) comprised further endpoints. We also evaluated the impact of surgical experience on surgery proficiency and quality.

Results: Out of the 155 patients analyzed, 64 (41.3%) achieved all five criteria of the pentafecta, while 106 (71.6%), and 132 (89.2%) attained four and three criteria, respectively. The mean pentafecta score was 4.1±1.0 (95% CI 4.0-4.3). Individually, negative surgical margins, removal of ≥ 16 lymph nodes, absence of major complications (Clavien-Dindo grade 3-5) within 90 days, absence of clinical recurrence within 12 months, and no ureteroenteric strictures requiring intervention within 12 months were observed in 91.0%, 69.1%, 78.6%, 78.6%, and 85.2% of patients, respectively. Operative times for IC and ONB were on average 241.5 (± 40.2) and 295.79 (± 33.7) minutes, respectively. For LRC, operative times and the number of lymph nodes improved with increasing case numbers, indicating satisfactory proficiency in operation. The proportion of pentafecta attainment varied across consecutive operation order groups: Group 1: 33.3%; Group 2: 41.9%; Group 3: 50.0%; Group 4: 40.0%; and Group 5: 46.7%. Pentafecta attainment rates did not statistically change between the groups. Higher Charlson Comorbidity Index, extravesical disease, and positive lymph node status were independent predictors of non-attainment of pentafecta in both uni and multivariable analysis. The three and five-year overall survival rates were 66.5% and 54.7%, respectively. Patients who achieved all 5/5 pentafecta criteria showed higher OS and RFS compared to those who did not attain all criteria (log-rank $p < 0.001$). Pentafecta attainment was associated with favorable outcomes regarding OS, even after adjusting for known confounders (hazard ratio [HR] 0.48 [0.24-0.98], $P < 0.001$)

Conclusion: Laparoscopic Radical Cystectomy achieves satisfactory proficiency and surgical quality, with pentafecta criteria correlating with improved survival rates. Enhanced operative time and lymph node yield were observed with increasing experience. These findings support early adoption of LRC without compromising oncological outcomes.

Keywords: Bladder Cancer, Pentafecta, Laparoscopic Radical Cystectomy, Overall Survival, Recurrence-free Survival

LIST OF ABBREVIATIONS

BC	Bladder Cancer
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
EBL	Estimated Blood Loss
IC	Ileal Conduit
LNs	Lymph Nodes
LOS	Length of Stay
LRC	Laparoscopic Radical Cystectomy
MIBC	Muscle-Invasive Bladder Cancer
NMIBC	Non-Muscle-Invasive Bladder Cancer
ONB	Orthotopic Neobladder
ORC	Open Radical Cystectomy
OS	Overall Survival
OT	Operative Time
PC	Pentafecta Criteria
PLND	Pelvic Lymph Node Dissection
RARC	Robot-Assisted Radical Cystectomy
RC	Radical Cystectomy
RFS	Recurrence-Free Survival
SM	Surgical Margins
TURBT	Transurethral Resection of Bladder Tumor
UD	Urinary Diversion

INDEX

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Bladder cancer (BC) is the 10th most commonly diagnosed cancer worldwide.[1] Bladder cancer can be clinically classified into two distinct groups: muscle-invasive BC (MIBC) and non-muscle-invasive BC (NMIBC). This differentiation is essential for guiding treatment strategies and assessing prognosis.[2]

Although radical cystectomy with urinary diversion (UD) and pelvic lymph node dissection (PLND) is the standard of care in patients with highest-risk non-metastatic bladder cancer or MIBC, this surgery is still a complex procedure associated with a high risk of perioperative and long-term complications.[3-5]

Less invasive surgical techniques like laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) with bilateral PLND are now seen as comparable alternatives to open radical cystectomy (ORC) in reducing complications and promoting quicker recuperation.[6]

Long-term follow-up confirms LRC's oncological effectiveness with UD and PLND. Despite oncological equivalence, slow adoption in clinical practice persists due to its complexity.[6]

In the discourse surrounding the integration of these techniques into clinical practice, a surge in studies aims to demonstrate the acquisition of proficiency in minimally invasive surgery.[7] To effectively evaluate RC, there must be objective indicators aligned with an accepted standard definition for the learning curve. The concept of pentafecta, initially introduced by Aziz et al.,[8] serves as a pivotal framework, with an updated version proposed by Cacciamani et al.[3], which has gained widespread acceptance and usage.

Given the limited availability of comprehensive outcome data regarding Radical Cystectomy (RC) reported in terms of pentafecta, particularly in the context of laparoscopic RC, this study endeavors to evaluate the impact of experience in LRC on both pentafecta achievement and oncologic outcomes and its evolution with the increasing number of procedures performed by a single surgeon.

METHODS

Study Population

We conducted a retrospective single-centre study. We collected data from clinical records about patients who underwent LRC with pelvic lymph node dissection and extracorporeal urinary diversion performed by a single surgeon for non-metastatic bladder cancer between October 2016 and December 2022 at a tertiary care center in Northern Portugal (Urology Service, Surgery Department, Centro Hospitalar Universitário de Santo António, Porto, Portugal). Patients with additional planned procedures at the same time as radical cystectomy and those undergoing palliative surgery were excluded from the analysis. This was approved by the local ethics committee of Centro Hospitalar Universitário de Santo António (no. 2023.231(194-DEFI/183-CE).

Description of technique

Detailed surgical technique for Radical Cystectomy with Pelvic Lymphadenectomy

The patient was positioned in dorsal decubitus with a Trendelenburg slope of 30 degrees and lower limb angulation at the level of the popliteal fold. A 12 mm trocar was introduced in the midline, 5 cm above the umbilicus, with the placement of a 30º optic for direct vision entry into the peritoneal cavity. Four additional trocars were inserted: one 12 mm trocar at the lateral edge of the left rectus abdominal muscle, another 5 mm trocar at the left McBurney's point, and two 5 mm trocars at equivalent positions on the right abdominal flank. Bilateral extended pelvic lymphadenectomy was performed with the genitofemoral nerve as the lateral limit, the lateral wall of the bladder and prostate as the medial limit, the femoral ring and inguinal ligament as the distal limit, and the aortic bifurcation as the proximal limit. The distal ends of both ureters were dissected to their vesical insertion, ligated, and sectioned. Cranial dissection of both ureters was carried out, along with isolation and ligation of the superior and inferior vesical vessels bilaterally. The peritoneum on the posterior face of the bladder was incised at the level of its reflection on the vas deferens and seminal vesicles. The recto-vesical space was dissected, and the vas deferens was ligated, followed by dissection of the seminal vesicles and the posterior face of the prostate. The parietal peritoneum over the umbilical insertion of the urachus was incised, with sectioning and extension of the incision laterally to both medial umbilical folds to the level of the peritoneal incision on the distal end of both external iliac arteries. The prevesical space was dissected until the exposure of the upper edge of the pubis and iliopubic branches. The prostatic fat was dissected, the endopelvic fascia was incised bilaterally and the dorsal prostatic venous plexus was ligated. The dorsal venous plexus was incised, and the urethra was dissected ligated and sectioned. The posterior and lateral faces of the prostate were dissected, with ligation of the vesico-prostatic vessels until the entire operative piece was released.

Detailed surgical technique for Ileal Conduit

After radical cystectomy, we isolated a 15 cm segment of the ileal loop, 25 cm from the ileocecal valve. We performed a latero-lateral ileo-ileal anastomosis with automatic surgical staples. Cranial dissection of the ureters and catheterization with an 8 Fr mono-j catheter were performed. We dissected the retro-mesenteric space below the inferior mesenteric artery and transferred the left ureter through the same space to the right flank. Bricker-type uretero-ileal anastomosis was performed after prior spatulation of both ureteral ends. An incision was made in the abdominal skin laterally and inferiorly to the umbilicus over the right anterior rectus abdominal muscle. Dissection of the subcutaneous tissue and exposure of the aponeurosis. A cross shape incision and creation of the trajectory for the passage of the ileal loop were done. Extra-peritonealization of the ileal loop through the created space, and its exteriorization through the trajectory created was completed. Fixation of the ileal loop to the aponeurosis and creation of ileostomy with separate evaginating stitches were made.

Detailed surgical technique for Orthotopic Neobladder

Isolation of a 55 cm segment of the ileal loop, 25 cm from the ileocecal valve, was performed. We performed a latero-lateral ileo-ileal anastomosis with automatic surgical staples. Cranial dissection of both ureters and catheterization with an 8 Fr mono-j catheter were performed. Dissection of the retro-mesenteric space below the inferior mesenteric artery and transfer of the left ureter through the same space to the right flank. Incision of the isolated ileal loop at the level of its antimesenteric border along its distal segment with a length of 40 cm, sparing the proximal afferent loop with approximately 15 cm in length. Closure of the edges of the ileal loop to construct the posterior wall of the neobladder. Creation of uretero-ileal anastomosis after prior spatulation of both ureteral ends and exteriorization of both ureteral catheters through the mesentery of the afferent loop. Closure of the edges of the ileal loop to construct the anterior wall, leaving only a small segment open. Digital verification of the most dependent area of the neobladder was performed, followed by an incision for the creation of the. urethro-vesical anastomosis with 4 separate stitches. Placement of a suprapubic cystostomy and completion of the closure of the neobladder followed. Confirmation of the watertightness and patency between both catheters was performed.

Clinical, Surgical, Pathological, and Perioperative Characteristics

Clinical characteristics were defined as age, gender, body mass index (BMI), Charlson comorbidity index (CCI), prior pelvic or abdominal surgery, radiotherapy, and prior systemic chemotherapy. The type of urinary diversion and surgical characteristics included operative time (OT), estimated blood loss (EBL), length of hospital stay (LOS), blood transfusion, the need for conversion and need for intensive care monitoring were also measured. Pathological data were defined as tumor and nodal stage according to the most recent TNM classification, and the number of lymph nodes removed was assessed. Perioperative characteristics included 90 days of major complications (Clavien–Dindo grade ≥3), which were assessed using a standardized protocol.

Definition of radical cystectomy pentafecta (Adapted from Cacciamani et al.[3]/Aziz et al.[8])

Five criteria were used to define pentafecta: (1) negative surgical margin (SM); (2) ≥ 16 LNs (Lymph Nodes) yielded; (3) no major complication (Clavien-Dindo grade 3-5) within 90 days; (4) absence of clinical recurrence within 12 months; and (5) absence of long-term urinary diversion-related sequelae at 12 months follow-up as ureteroenteric strictures requiring intervention. Patients who met all five criteria were considered to have achieved pentafecta.

Outcomes and Study Endpoints

The first endpoint of our study was to assess PC achievement, which was defined as the fulfillment of all five criteria.

The second endpoint was to evaluate the improvement of oncologic outcomes (OS, RFS) with pentafecta achievement. The cause of death was determined by the treating physician, meticulous chart review, and death certificates. Follow-up was performed according to contemporary guideline recommendation.[5] We also evaluated the impact of surgical experience on PC, perioperative, and oncologic outcomes.

Statistical Analyses

Descriptive data were expressed as mean and standard deviation or median and interquartile range after normality assessment. Kolmogorov-Smirnov and Shapiro-Wilk were used to assess normality. Categorical data were expressed as numbers and percentages. For categorical variables' comparison, $\chi 2$ and Fisher's Exact tests were used, while independent samples t-test and Mann-Whitney U-tests were used for quantitative variables as appropriate. Uni- and multivariate logistic regression analysis were used to identify independent clinical and pathological predictors of achieving perfecta.

Kaplan-Meier analysis was used to estimate RFS and OS rates, with the log-rank (Mantel-Cox) test used for detecting statistical significance. Uni- and multivariate Cox regression analyses were performed to assess the effect of clinical and pathological data on RFS and OS.

For statistical analysis of the effect of surgical experience, Loess curves were used. Also, patients were divided according to the operation order, in five consecutive groups. We scored each criterion and analyzed the sum and achievement of the pentafecta points by operation order group in a total of 14 groups. All statistical analyses were performed using IBM SPSS version 29.0 Edition statistical software (IBM Corp., Armonk, NY, USA). The reported p-values were two-sided, and values < 0.05 were taken to indicate statistical significance.

RESULTS

Clinical, Pathological, and Perioperative Characteristics

A total of 155 patients were included in the study. Of 155 patients, 138 (89%) were men. The ileal conduit was performed in 136 (87.7%) patients and orthotopic neobladder in 14 (9.0%). PLNDs were performed in 152 patients (98.1%), with extended PLND conducted in 135 cases (87.1%). The total mean LN yield was 22.3 (±12.8). Neoadjuvant chemotherapy was administered to 12 patients (7.7%) and 24 (15.6%) received adjuvant treatment. Clinical characteristics and oncological pathology of our cohort are shown in Table I. Perioperative data are summarized in Table II.

Operative Analysis

The mean operative time was 241.5 minutes (± 40.2) for IC and 295.79 (± 33.7) minutes for ONB. Operative times for RC with ileal conduit trended down with the increasing number of cases, reaching a plateau after the 100th case (mean operative time between case 83rd-136th: 219.7 min (IC 95% 210.2-229.2), $p < 0.05$). The number of LN yielded increased with the number of cases, achieving a plateau near the 40th case (mean LN yield for cases 30th-50th: 19.7 nodes, 95% CI 15.7-23.7, $p < 0.05$). However, there was no significant variation along the time in estimated blood loss and length of hospital stay. (Figure 1).

Pentafecta Achievement and the Sum of the Pentafecta Score

In the full study population, 64 patients (41.3%) attained five criteria of pentafecta. Patients who attained all pentafecta had a higher proportion of pN0 status (90.6% vs. 63.5%) and organ-confined disease (≤ pT2) (84% vs. 53.3%) ($p \leq 0.001$). Also, these patients had a lower comorbidity profile (median CCI 5 vs 6; $p < 0,05$) and higher mean of lymph nodes removed (27.0 ± 11.1 vs 17.8 ± 9.0 nodes, $p < 0.01$) compared to those not achieving pentafecta. Patients who did not achieve PC had higher conversion rates and intensive support needs ($p < 0.05$). There was no difference in age, time from TURBT (Transurethral Resection of Bladder Tumor) to RC, estimated blood loss, operative time, length of stay, intraoperative complications or need for transfusions (all $p \geq 0.1$)

106 patients (71.6%) attained ≥4/5 PC, 132 (89.2%) attained ≥ 3/5 PC, and only 16 (10.8%) patients attained < 3/5 PC. Regarding the individual PC, negative surgical margins, ≥ 16 lymph nodes removed, absence of major complications (Clavien-Dindo grade 3-5) within 90 days, absence of clinical recurrence within 12 months, and no ureteroenteric strictures requiring intervention within 12 months were observed in 91.0%, 69.1%, 78.6%, 78.6%, and 85.2% of patients, respectively.

The attainment of all five PCs according to the five consecutive operation order groups is summarized in Figure 2A. The attainment rates were: Group 1: 33.3%; Group 2: 41.9%; Group 3: 50.0%; Group 4: 40.0% and Group 5: 46.7%. The proportion of pentafecta attainment from the

1st to 60th and 95th to 155th cases was 37.7% and 47.3%, respectively. There were no statistical differences between the groups, including in stepwise analysis (all p > 0.1). (Table III).

The mean of the sum of the pentafecta score was 4.1±1.0 (95% CI 4.0-4.3) (Figure 2B). The mean sum of each pentafecta score according to the operation order group is also represented in Figure 2B. The sum of the pentafecta score of the individual group was not significantly different from those of the entire patient group (all p > 0.1). Higher CCI (OR 1.4; p = 0.018), extravesical disease (OR 3.4, p = 0.08) and N+ (OR 1.2, p = 0.03) were independent predictors of pentafecta non-attainment in both uni- and multivariable analysis.

Recurrence-free Survival and Overall Survival Analyses

The median follow-up was 29 (IQR: 12–47) months, with 55 patients (35.5%) deceased. Among all patients, the three- and five-year OS rates were 66.5% and 54.7%, respectively. Kaplan–Meier curves showed that OS and RFS were higher for patients who attained all 5/5 PC compared to those who did not (overall log-rank p < 0.001; Fig. 3A). For patients who attained all five PC, compared to those who did not attain all PC, the 3-year OS was 80.2% vs. 52.9%, the 5-years OS was 75.5% vs. 45.3% and the 3-years RFS was 88.6% vs. 63.7% and 5-years RFS 84.5% vs. 49.4%, respectively (Fig. 3A and 3B).

These findings held after stratification into 5/5 vs 4/5 vs ≤3/5 pentafecta criteria attained (overall log-rank P < 0.001), whereas there was no difference between attaining 4/5 or all 5/5 PC in stepwise comparisons (P = 0.28; (Fig. 3C). Also, there was no difference in OS between the five consecutive groups (Overall log-rank P = 0.22). (Fig.3D).

PC attainment was associated with favorable outcomes regarding OS (hazard ratio [HR] 0.29 [0.15-0.56] P < 0.001;), inclusive after stratification for organ-confined disease or N+ disease.

After adjusting for known confounders, PC attainment remained an independent predictor of favorable outcomes regarding Overall Survival (hazard ratio [HR] 0.48 [0.24-0.98] P < 0.001).

Subgroup analysis of effect of number Lymph nodes yielded in Pentafecta Achievement and Survival

The criterion of removing ≥ 16 lymph nodes was met in 105/152 patients (69.1%) and ≥ 10 LN in 136/152 patients (92.8%). Only 11 of 152 patients undergoing PLND had fewer than 10 lymph nodes removed. Considering the pentafecta criteria of ≥ 10 lymph nodes removed instead of ≥16 LN, an additional 15 patients would meet the pentafecta, increasing the overall achievement rate to 51.0%.

Overall survival did not differ significantly after stratification into groups with 10-15 and ≥16 lymph nodes removed (overall log-rank p = 0.929). The group with ≥10 lymph nodes removed and meeting the other four pentafecta criteria had a similar OS to the group with ≥16 lymph nodes (pentafecta group) (five-year OS: 78.3% vs. 75.5%, p > 0.05).

DISCUSSION

The pentafecta criteria are utilized in radical cystectomy to assess surgical success and its impact on various outcomes. By measuring perioperative and functional outcomes, the pentafecta criteria aim to enhance the preservation of renal function post-operation.[9] These criteria have been validated and shown to be effective in reporting outcomes after radical cystectomy, particularly in assessing oncological endpoints.[10]

Laparoscopic radical cystectomy and robot-assisted radical cystectomy have gained popularity as alternatives to open radical cystectomy for the treatment of bladder cancer.[11] These minimally invasive procedures are associated with a faster recovery, decreased morbidity and equivalent safety and efficacy compared to ORC.[12] Many studies on perioperative complications in radical cystectomy primarily focus on robot-assisted techniques, with very few research validating the pentafecta criteria for patients undergoing LRC.[13] We aim to bridge this gap by investigating LRC outcomes and correlating them with the learning curve of a single surgeon at a high-volume tertiary center.

In our study, the rate of achieving the "validated RC-pentafecta" stood at 41.3%, which, although slightly lower than the 53% reported by Cacciamani et al., is comparable to or even higher than rates observed in several studies evaluating ORC, RARC, and LRC.[4, 9, 14] It is essential to recognize the discrepancy in achievement rates for the pentafecta criteria between our study and another focusing on LCR (41.3% vs. 14.7%, respectively).[13]

Our validation of a higher rate within the LRC domain, comparable to those provided for OR and RARC context, underscores the practicality and relevance of these criteria in assessing oncological outcomes in LRC and it's an essential conclusion, as it aligns with existing literature suggesting that LRC, in terms of proficiency, compares favorably with RARC.[15]

The main factor that strongly kept patients from achieving the 5 pentafecta criteria was the dissection rate of ≥16 LNs. Cacciamani et al. reported a dissection rate of ≥16 lymph nodes at 93%, whereas in our study, it stood at 69.1%. This limitation, evidenced in similar studies,[4, 16] suggests the need for examination of this criterion in favor of a more attainable alternative.

As supported by literature, pelvic lymph node dissection serves both therapeutic and prognostic staging purposes. The classification of PLND into limited, standard, extended, and super-extended is based on anatomical boundaries rather than solely on the quantity of lymph nodes involved.[5] However, the number of lymph nodes dissected varies greatly within centers, and even surgeons.[17] Despite ongoing debate, consensus has yet to emerge regarding the preferred lymph node dissection template. Advocates for a more extensive dissection highlight potential drawbacks such as increased costs and higher complication rates due to extended surgery time. However, there is also a compelling argument that such an approach could yield improved survival outcomes by addressing micrometastases present at the time of Radical Cystectomy.[17]

Nonetheless, results from the phase 3 SWOG S1011 trial demonstrate no significant disparities between extended lymphadenectomy and standard lymphadenectomy regarding overall survival or disease-free survival. This indicates that a higher number of LNs does not necessarily equate to superior outcomes.[18] As a study has proposed a minimum of 10 nodes as a cutoff

associated with improved outcomes,[19] we created a subgroup of patients with more than 10 lymph nodes removed who fulfilled all other four criteria of the pentafecta. This subgroup exhibited comparable OS to the original cohort, allowing for a greater number of patients to achieve the desired outcomes without compromising OS or RFS. This observation contributes to the ongoing discourse regarding the potential modification of this criterion, as some advocate for the consideration of the type of lymph dissection[16] or a smaller number of LN removed.[13]

Soft tissue surgical margin status following radical cystectomy emerges as a significant predictor of both local recurrence and cancer-specific mortality, after accounting for clinical and pathological factors.[20] In our study, negative surgical margins were observed in 91.0% of patients, a proportion lower than that reported by Cacciamani et al. (98.9%). This variability in margin status may stem from surgeon-related variables such as experience and surgical technique, tumor characteristics including stage and histological subtype, as well as variances in specimen interpretation by pathologists.[21] Notably, only 7.70% of patients in our study received neoadjuvant chemotherapy, as opposed to 24.40% in the article by Cacciamani et al. Neoadjuvant therapy has a benefit of helping achieve negative surgical margins,[5] suggesting that its underutilization may be one of the reasons behind this discrepancy. Furthermore, the assessment did not include the number of patients eligible for neoadjuvant chemotherapy with cisplatin and gemcitabine. Additionally, queries regarding the management of the waiting list may influence the decision between upfront cystectomy or neoadjuvant chemotherapy, explaining this discrepancy.

Within our cohort, 78.6% of patients remained clinically recurrence-free within one year, compared to 92.2% reported by Cacciamani et al. Various factors contribute to the likelihood of recurrence, including pathological stage, extent of lymph node dissection, and perioperative chemotherapy.[22] The percentage of patients that are in a pathological stage ≥T3 is similar in both studies (34.50% vs 38.50%). However, as was mentioned, the number of lymph nodes dissected and the use of neoadjuvant chemotherapy were significantly lower. Furthermore, given the higher percentage of positive tissue margins in our study, the occurrence of significant clinical recurrence was anticipated.

Regarding postoperative morbidity, the RC-pentafecta incorporates two measures: the absence of Clavien-Dindo Grade 3-5 complications within 90 days and the absence of long-term UD-related sequelae within 12 months. Concerning the first criterion, 21.2% of patients experienced major complications within the 90-day timeframe, a rate consistent with findings from other studies.[3] A critique of the UD-related criteria is that several events overlap with those considered in the Clavien-Dindo Grade 3-5 complications criterion. Additionally, certain consequences, such as stoma-related complications, have minimal impact on survival outcomes. Therefore, we opted to focus on uretero-enteric strictures as representative of this group, given their prominence as the primary complication necessitating reoperation post-radical cystectomy,[23] typically not manifesting within 90 days.[9] Our investigation revealed that uretero-enteric strictures developed in 14.8% of patients, a figure seemingly elevated compared to literature estimates ranging from approximately 3% to 10%, with most cases diagnosed within one-year post-surgery.[24] Several factors may contribute to this increased stricture rate. On the patient side, hypotheses include the influence of a high body mass index (BMI) and previous exposure to radiotherapy as potential risk factors. Conversely, a meticulous surgical approach is

paramount to prevent tissue ischemia and ensure a durable anastomosis.[25] While surgical approach has not been directly correlated with complication rates,[24] further studies are warranted to elucidate the role of LC in the development of these complications.

Our investigation substantiates the applicability of the pentafecta criteria within the context of laparoscopic radical cystectomy. Our findings reveal that patients achieving pentafecta demonstrated higher rates of overall survival and recurrence-free survival compared to those who did not, as shown in Figure 3. Consequently, we advocate for the adoption of the RC-pentafecta as a standardized method for evaluating surgical quality in laparoscopic procedures. This approach facilitates a comprehensive understanding of the role, as well as the associated advantages and disadvantages, of laparoscopic radical cystectomy.

Traditionally, LC has been associated with a steep learning curve, even for highly experienced surgeons.[26] There is a prevailing belief in the surgical community that novice laparoscopic surgeons may experience a smoother learning curve when transitioning to Robot-Assisted Radical Cystectomy. Consequently, many medical institutions equipped with robotic systems have shifted from LRC to RARC following the introduction of initial RARC cases and the growing availability of robotic platforms.[27] In our study, we analyzed the learning curve of a single surgeon with prior experience in ORC performing his initial laparoscopic cystectomy surgeries. We conclude that perioperative and oncological outcomes, measured with the Pentafecta criteria, did not show any significant variation, contrary to what it is suggested for RARC.[16]

Other assessed criteria showed no significant progression. Estimated blood loss, often utilized as a metric to gauge skill acquisition in radical prostatectomy,[28] remained relatively unchanged. However, its mean value in in our study is lower than the one typically seen in Open Radical Cystectomy. This observation aligns with the commonly associated advantage of minimally invasive techniques in mitigating blood loss.[29] Length of hospital stay also exhibited no discernible changes. However, it is noteworthy that this metric primarily reflects the social circumstances of the patients rather than serving solely as a measure of their recovery rate.[30] Consequently, it necessitates integration into a broader analysis encompassing population demographics and hospital protocols to properly draw conclusions.

The only exceptions were in lymph node dissection, which increased, and operative time, which decreased with the procedures. This finding, however, should not be overlooked, as prolonged operative time is frequently cited as a drawback of minimally invasive procedures like LRC.[29] The improvement over time in operative time suggests a growing suitability for clinical use. Regarding the increase in the number of lymph nodes retrieved, it is essential to note that this may not directly correlate with improved oncological outcomes.[18]

While other criteria could be employed to assess the learning curve, our findings suggest that it may not be as steep as previously assumed. This implies that laparoscopic cystectomy surgeries could potentially be performed by less experienced operators without compromising oncological outcomes, demonstrating an acceptable level of proficiency for LRC from the beginning.

However, it's crucial to highlight that our study focused solely on a single surgeon with previous experience in open cystectomy and the assessment did not include an evaluation of the rotating

surgical team's proficiency in laparoscopic surgery. Therefore, further investigation is warranted to comprehensively understand the learning curve associated with laparoscopic cystectomy.

The present study has several limitations. Firstly, it is a retrospective study, which may introduce inherent biases associated with this study design, including potential missing data. Secondly, the outcomes evaluated may evolve over time, especially considering recurrence cases and UD-related complications may manifest beyond the 12-month follow-up period. Additionally, the study relies on the experience of a single surgeon and center, which may restrict the generalizability of the findings. Lastly, functional outcomes were not assessed due to the retrospective nature of the study, highlighting the need for future research to include comprehensive assessment of functional outcomes.

CONCLUSION

In conclusion, our study highlights the satisfactory proficiency and surgical quality of Laparoscopic Radical Cystectomy, with pentafecta criteria achievement correlating with enhanced recurrence-free and overall survival rates. Within our series, only operative time and the yield of lymph nodes demonstrated improvement with increasing experience. These findings emphasize the relevance of pentafecta criteria for evaluating LRC outcomes and suggest that the learning curve for LRC may be less steep than previously assumed. This supports the early adoption of laparoscopic techniques without compromising oncological outcomes, reinforcing LRC as a safe alternative to Open Radical Cystectomy.

ANNEXES

ANNEX 1 – Tables

Table I. Baseline characteristics for the study population.

IQR - Interquartile Range; SD - Standard Deviation; ASA - American Society of Anaesthesiologists

Variable	Result
Age, yr, median (IQR)	71 (65–76)
Body mass index, mean (SD), kg/m2	25.4 (±4.1)
Male, n (%)	138 (89.0)
ASA score, median, (IQR)	2 (2-3)
Charlson Comorbility Index, median (IQR)	6 (5–6)
Prior Pelvic Radiotherapy (n, %)	2 (1.3)
Prior pelvic or abdominal surgery n, (%)	43 (27.7)
Clinical Stage and TURB Tumor, n (%)	
High Risk NMIBC (<pT2)	40 (25.8)
MIBC (≥ pT2)	115 (74.2)
Time to Cystectomy, days, median (IQR)	72 (53-108)
Time to Cystectomy < 90 days, n, (%)	89 (61.0)
Chemotherapy, n, (%)	
Neoadjuvant	12 (7.7)
Adjuvant	24 (15.6)
Palliative	6 (3.9)
Urinary Diversion, n, (%)	
Ileal Conduit	136 (87.7)
Orthotopic Neobladder	14 (9.0)
Unilateral Cutaneous Ureterostomy	5 (3.2)
Yield of PLND performed, n, (%)	
Standard PLND	17 (11.0)
Extended PLND	135 (87.1)
None	3 (1.9)
Pathologic stage after radical Cystectomy, n (%)	
T0	40 (25.8)
Tis	3 (1.9)
Ta	9 (5.8)
T1	24 (15.5)
T2	24(15.5)
T3	38 (24.5)
T4	16 (10.3)
Pathologic Nodal Stage, n (%)	
pN0	115 (74.2)
pN1	12 (7.7)
pN2/pN3	26 (16.8)
Positive Surgical Margins, n (%)	
Total	14 (9.0)
≥ pT3	4 (28.6)
Follow-up, Median (IQR)	29 (12-47)

Table II. Perioperative Characteristics of the study population.

IQR - Interquartile Range; SD - Standard Deviation

	IC (n= 136)	ONB (n=14)
EBL, median (IQR), mL	600 (400-900)	800 (700-1200)
Operating time, mean (SD), min	241.5 ± 40.2	295.8 ± 33.4
Length of hospital stay, mean (SD), days	13.32 ± 12.78	19.29 ± 5.47
Intraoperative Blood transfusion, n (%)	17 (12.6)	1 (7.1)
Intraoperative complication, n (%)	15 (11.1)	1 (7.1)
Lymph nodes yielded, mean (SD), n	22.30 ± 11.02	20.23± 7.282
Need of conversion, n (%)	9 (6.6)	0
Need for intensive care monitoring, n (%)	8 (5.9)	1 (7.1)

Table III. Pentafecta Criteria Attainment and clinical oncologic variables between the 5 groups.

SD – Standard Deviation

Group	(n=155)	1	2	3	4	5
Pentafecta Achievement (%)	41.3	33.3	41.9	50.0	40.0	46.7
Negative SM (%)	91.0	96.8	83.9	83.9	90.3	100.0
≥ 16 LNs yielded (%)	69.1	48.4	73.3	90.3	75.9	58.1
Absence of Clavien-Dindo grade 3-5 complications within 90 days (%)	78.6	77.4	80.6	77.4	73.3	83.9
Absence of UD-related sequelae within 12 months (%)	85.2	79.3	89.3	92.6	82.1	83.3
Absence of Clinical Recurrence within 12 months (%)	78.6	86.2	75.0	69.0	73.3	89.7
SUM of Pentafecta Criteria, n (SD)	4.12 ± 0.97	3.93 ± 1.0	4.1 ± 1.0	4.3 ± 0.9	4.1 ± 1.0	4.2 ± 1.0

ANNEX 2 - Figures

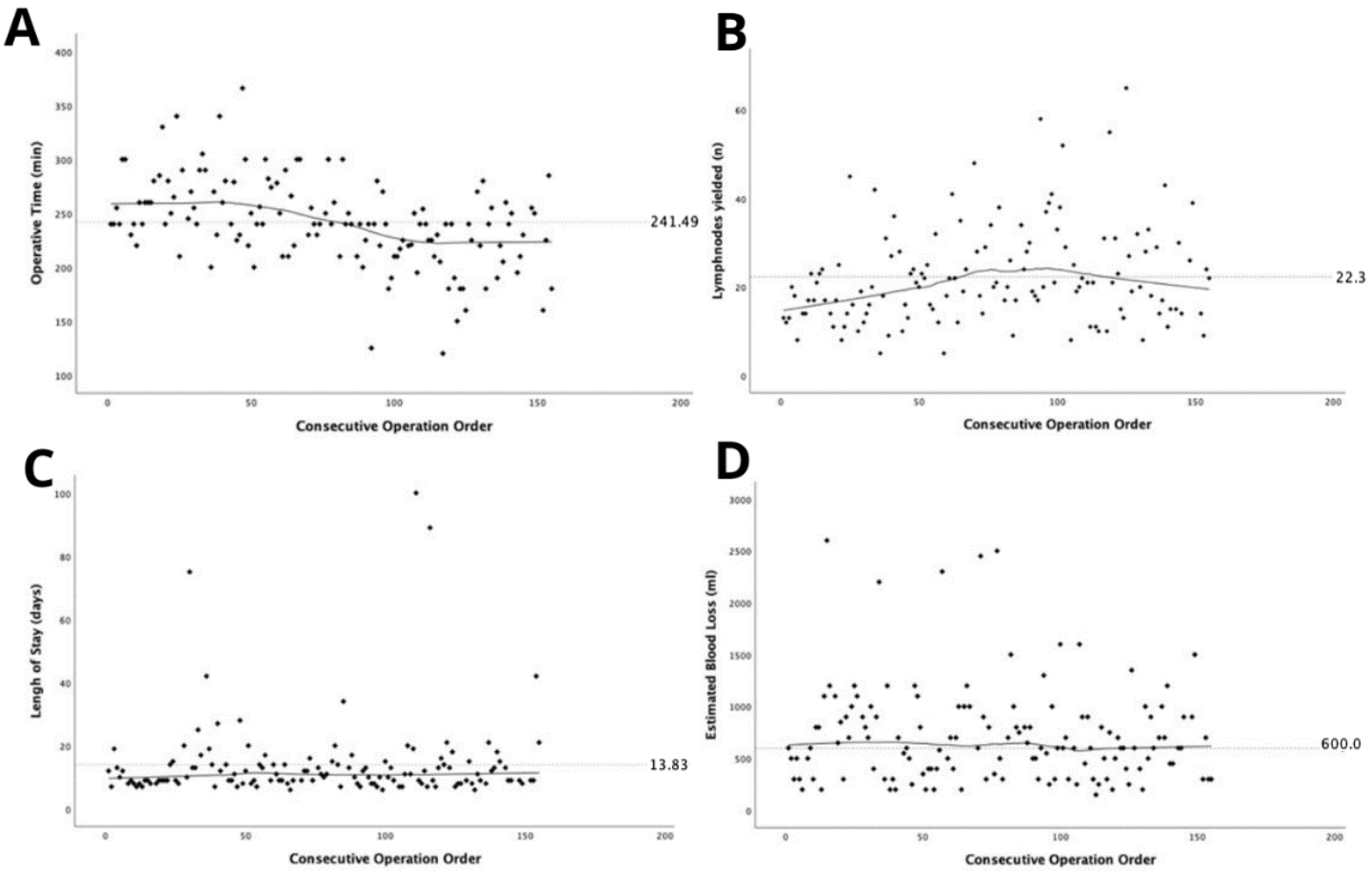


Figure 1. Evolution of Surgical Performance Metrics: (A) Operative time (Mean and Loess Curve); (B) Lymph nodes yielded (Mean and Loess curve); (C) Length of Stay (Mean and Loess curve); (D) Estimated Blood Loss (Mean and Loess Curve).

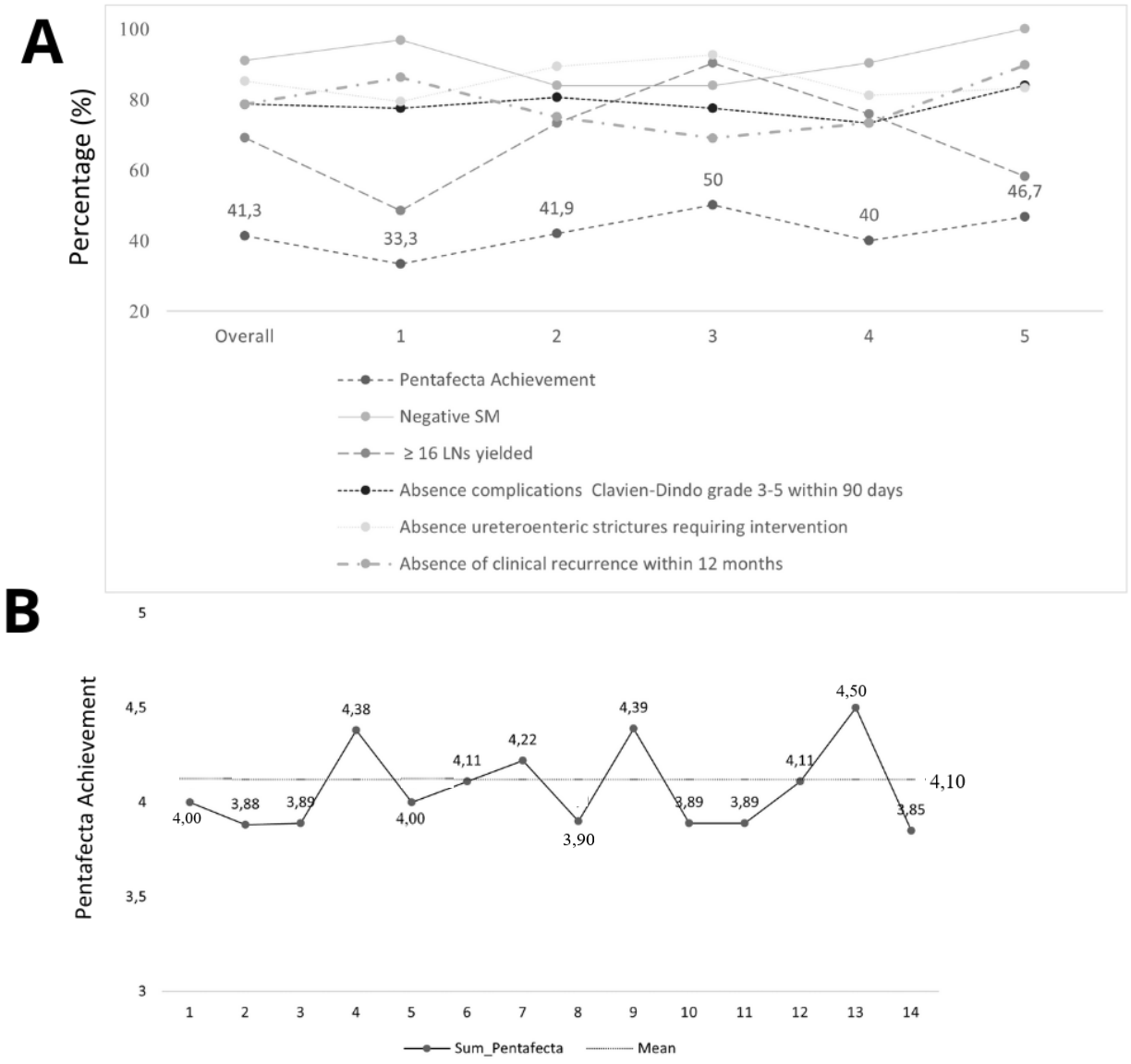


Figure 2. (A) Analysis of pentafecta achievement and individual criteria in overall and along five consecutive groups. (B) The SUM RC-pentafecta according to the operation order groups of 10 patients.

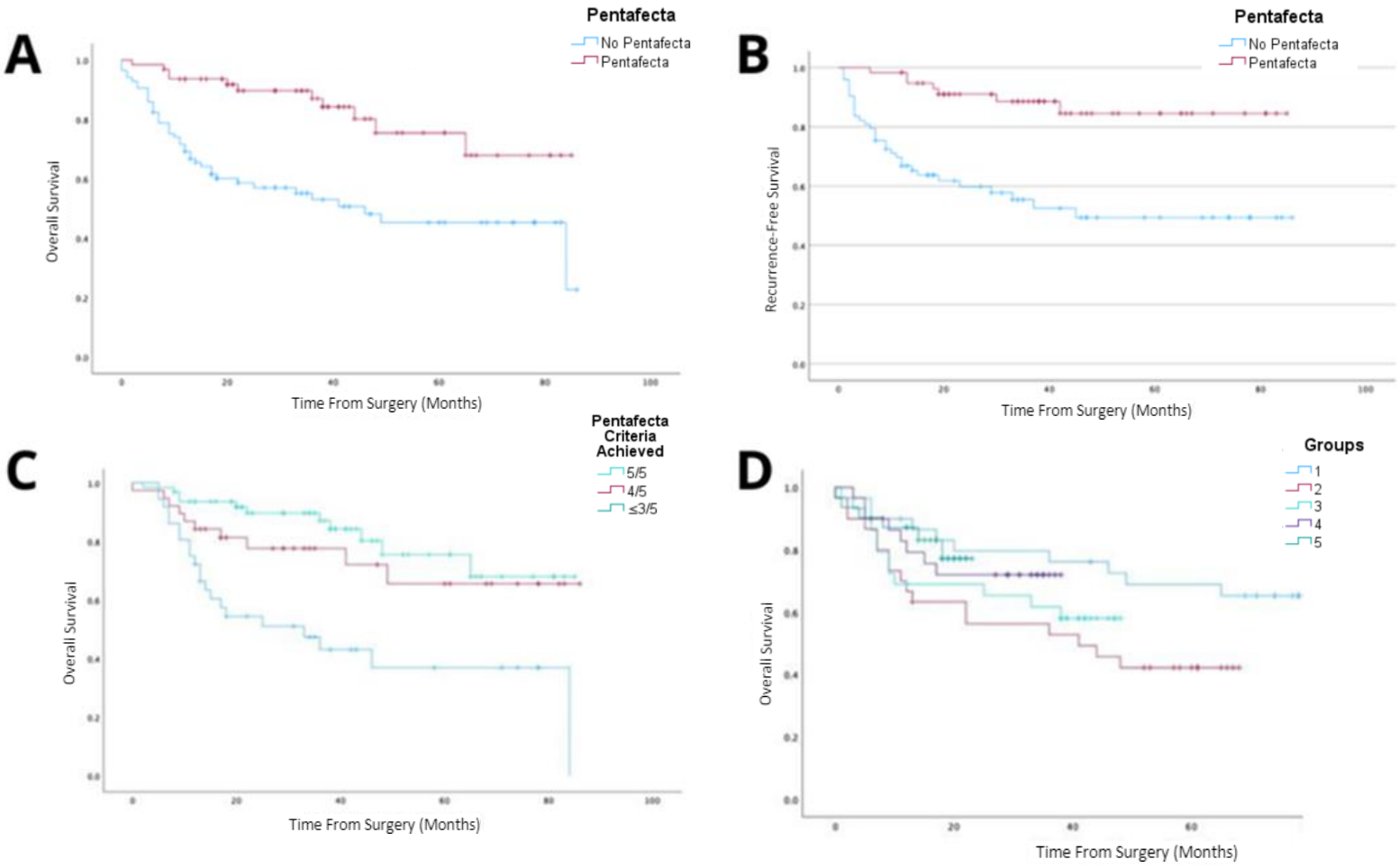


Figure 3. (A) Overall survival Pentafecta group vs. Non Pentafecta group; (B) Recurrence Free Survival Pentafecta vs. Non Pentafecta; (C) Overall Survival 5/5 vs. 4/5 and ≤3/5 pentafecta criteria attainment groups; (D) Overall Survival between the 5 consecutive groups.

BIBLIOGRAPHY

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Lemke EA, Shah AY. Management of Advanced Bladder Cancer: An Update. J Adv Pract Oncol. 2018;9(4):410-6.
3. Cacciamani GE, Winter M, Medina LG, et al. Radical cystectomy pentafecta: a proposal for standardisation of outcomes reporting following robot-assisted radical cystectomy. BJU Int. 2020;125(1):64-72.
4. Laymon M, Mosbah A, Hashem A, et al. Predictors and survival benefit of achieving pentafecta in a contemporary series of open radical cystectomy. Minerva Urol Nephrol. 2022;74(4):428-36.
5. EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.
6. Noh TI, Shim JS, Kang SG, Cheon J, Pyun JH, Kang SH. The learning curve for robot-assisted radical cystectomy with total intracorporeal urinary diversion based on radical cystectomy pentafecta. Front Oncol. 2022;12:975444.
7. Patel VR, Tully AS, Holmes R, Lindsay J. Robotic radical prostatectomy in the community setting--the learning curve and beyond: initial 200 cases. J Urol. 2005;174(1):269-72.
8. Aziz A, Gierth M, Rink M, et al. Optimizing outcome reporting after radical cystectomy for organ-confined urothelial carcinoma of the bladder using oncological trifecta and pentafecta. World J Urol. 2015;33(12):1945-50.
9. Oh JJ, Lee S, Ku JH, et al. Oncological outcome according to attainment of pentafecta after robot-assisted radical cystectomy in patients with bladder cancer included in the multicentre KORARC database. BJU Int. 2021;127(2):182-9.
10. von Deimling M, Rink M, Klemm J, et al. Oncological validation and discriminative ability of pentafecta criteria after open radical cystectomy. BJU Int. 2023;131(1):90-100.
11. Novara G, Catto JW, Wilson T, et al. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. Eur Urol. 2015;67(3):376-401.
12. Pignot G, Treacy P, Walz J. Growing evidence for benefits of minimally invasive radical cystectomy. Transl Androl Urol. 2020;9(6):2459-61.
13. Li K, Yang X, Zhuang J, et al. External validation of Pentafecta in patients undergoing laparoscopic radical cystectomy: results from a high-volume center. BMC Urol. 2022;22(1):41.
14. Zapala L, Slusarczyk A, Korczak B, et al. The View Outside of the Box: Reporting Outcomes Following Radical Cystectomy Using Pentafecta From a Multicenter Retrospective Analysis. Front Oncol. 2022;12:841852.
15. Feng D, Li A, Hu X, Lin T, Tang Y, Han P. Comparative effectiveness of open, laparoscopic and robot-assisted radical cystectomy for bladder cancer: a systematic review and network meta-analysis. Minerva Urol Nefrol. 2020;72(3):251-64.
16. Baron P, Khene Z, Lannes F, et al. Multicenter external validation of the radical cystectomy pentafecta in a European cohort of patients undergoing robot-assisted radical cystectomy with intracorporeal urinary diversion for bladder cancer. World J Urol. 2021;39(12):4335-44.
17. Sundi D, Svatek RS, Nielsen ME, Schoenberg MP, Bivalacqua TJ. Extent of pelvic lymph node dissection during radical cystectomy: is bigger better? Rev Urol. 2014;16(4):159-66.
18. Lerner SP TC, Svatek RS, et al. SWOG S1011: A phase III surgical trial to evaluate the benefit of a standard versus an extended lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer. J Clin Oncol. 2023;41:4508.
19. Herr HW, Faulkner JR, Grossman HB, et al.Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol. 2004;22(14):2781-9.
20. Dotan ZA, Kavanagh K, Yossepowitch O, et al. Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer specific survival. J Urol. 2007;178(6):2308-12; discussion 13.
21. Novara G, Svatek RS, Karakiewicz PI, et al. Soft tissue surgical margin status is a powerful predictor of outcomes after radical cystectomy: a multicenter study of more than 4,400 patients. J Urol. 2010;183(6):2165-70.
22. Huguet J. Follow-up after radical cystectomy based on patterns of tumour recurrence and its risk factors. Actas Urol Esp. 2013;37(6):376-82.

23. Ahmed YE, Hussein AA, May PR, et al. Natural History, Predictors and Management of Ureteroenteric Strictures after Robot Assisted Radical Cystectomy. Journal of Urology. 2017;198(3):567-74.
24. Anderson CB, Morgan TM, Kappa S, et al. Ureteroenteric anastomotic strictures after radical cystectomy-does operative approach matter? J Urol. 2013;189(2):541-7.
25. Lobo N, Dupre S, Sahai A, Thurairaja R, Khan MS. Getting out of a tight spot: an overview of ureteroenteric anastomotic strictures. Nat Rev Urol. 2016;13(8):447-55.
26. Abraham JB, Young JL, Box GN, Lee HJ, Deane LA, Ornstein DK. Comparative analysis of laparoscopic and robot-assisted radical cystectomy with ileal conduit urinary diversion. J Endourol. 2007;21(12):1473-80.
27. Challacombe BJ, Bochner BH, Dasgupta P, et al. The role of laparoscopic and robotic cystectomy in the management of muscle-invasive bladder cancer with special emphasis on cancer control and complications. Eur Urol. 2011;60(4):767-75.
28. Pruthi RS, Smith A, Wallen EM. Evaluating the learning curve for robot-assisted laparoscopic radical cystectomy. J Endourol. 2008;22(11):2469-74.
29. Huang H, Yan B, Hao H, et al. Laparoscopic versus open radical cystectomy in 607 patients with bladder cancer: Comparative survival analysis. Int J Urol. 2021;28(6):673-80.
30. Hemal AK, Kolla SB. Comparison of laparoscopic and open radical cystoprostatectomy for localized bladder cancer with 3-year oncological followup: a single surgeon experience. J Urol. 2007;178(6):2340-3.

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**