RESEARCH ARTICLE

Challenges and technical aspects in the management of muscle invasive bladder cancer as retrograde radical cystectomy with ileal conduit

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Abstract

Objective: To evaluate long-term outcomes in patients homogenously treated with radical cystectomy and ileal conduit for muscle invasive bladder cancer.

Method: The retrospective study was conducted at the Urology Department of Pakistan Kidney and Liver Institute and Research Centre, Lahore, Pakistan, and comprised data from December 25, 2017, to January 16, 2023, related to patients who underwent radical cystectomy with ileal conduit with or without neo-adjuvant and adjuvant radiation, chemotherapy, or immunotherapy for papillary urothelial carcinom of the bladder. Clinical trajectory, histopathological characteristics and long-term clinical outcomes were noted. Data was analysed using SPSS 20.

Results: In our study of 40 patients with muscle invasive bladder cancer, males predominated (32, 80%), with a median age of 57.4 years (IQR: 29-80). Diagnosis was early in 5 (12.5%) patients with varying haematuria durations, while 34 (85%) patients had a smoking history. Comorbidities included hypertension in 17 (42.5%) patients, diabetes in 1 (2.5%) patient, both hypertension and diabetes in 9 (22.5%) patients and a combination of hypertension, diabetes, and ischaemic heart disease in 3 (7.5%) patients. Transurethral resection was performed once in 13 (32.5%) patients and multiple times in 27 (67.5%) patients. Additionally, 5 (12.5%) patients received immunotherapy, 11 (27.5%) patients underwent non-adjuvant radiation, and 14 (35%) patients received non-adjuvant chemotherapy. Papillary urothelial carcinoma was the predominant histological subtype among 37 (92.5%) patients. Patients receiving chemotherapy had significantly better overall survival (p=0.02). No significant differences were noted in recurrence or survival by therapy modality (p>0.05). These findings highlight the significance of early diagnosis, tailored treatments, and comorbidity management in muscle invasive bladder cancer patients. Age stratification revealed significant survival differences across groups (χ^2=10.923, df=3, p= 0.012). Analysis by complications did not show age-related survival variations (χ^2 =3.978, df = 3, p=0.264).

Conclusion: Achieving excellent long-term survival in MIBC patients requires a multidisciplinary approach, emphasizing early diagnosis, tailored treatment, and adherence to guidelines and protocols.

Keywords: Radical cystectomy, Ileal conduit, Management, Muscle invasive bladder cancer, Papillary urothelial carcinoma.

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Introduction

Bladder cancer ranks among the prevalent malignancies of the genitourinary system, trailing only prostate cancer in terms of frequency. It stands as the fourth most diagnosed cancer, affecting both men and women. The spectrum of bladder cancer encompasses noninvasive, often nonaggressive tumours that necessitate prolonged invasive surveillance, to invasive and highly lethal variants, with papillary urothelial carcinoma (PUC) constituting roughly 90% of all primary bladder tumours.[1] High-grade (HG) tumours, predominantly PUC, exhibit invasiveness or the potential to evolve into invasive forms. These tumours originate in the bladder's mucosal lining, gradually infiltrating the lamina propria, advancing through the muscularis propria, peri-vesical fat, and surrounding pelvic tissues, increasingly posing a risk of lymph node (LN) involvement.[2,3] Radical cystectomy (RC) with pelvic LN dissection remains the cornerstone of surgical management for bladder cancer. In men, this involves cystoprostatectomy, while women undergo anterior pelvic exenteration, entailing the removal of the bladder, urethra, uterus and ventral vaginal wall. Notably, cystectomy surgery is occasionally considered for less severe cases, especially in females desiring to preserve their reproductive capacity. Concurrent pelvic LN dissection is routinely performed alongside cystectomy. Urinary diversion following RC may take a non-continent or continent form, with both approaches utilising a segment of the bowel. Each modality of cystectomy — open, laparoscopic, or robotic — brings its unique advantages and limitations.[4]

RC enables precise identification of the primary bladder tumour and adjacent LNs, allowing for more accurate pathological staging — a significant improvement over clinical staging, which has previously led to substantial misclassifications in 30-50% of patients.[5] The choice of

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optimal urinary diversion method is made following cystectomy completion. Both non-continent (ileal conduit [IC]) and continent (cutaneous reservoir, orthotopic neobladder) options are available. The selection of the most suitable approach hinges on the individual patient's needs and the surgeon's expertise.[6] In the case of muscle-invasive bladder cancer (MIBC) patients, RC with pelvic lymphadenectomy and orthotopic lower urinary tract (LUT) reconstruction has consistently delivered outstanding outcomes in terms of survival and local recurrence prevention at the study site.

The current study was planned to evaluate long-term outcomes in patients homogenously treated with RC and IC for MIBC.

Materials and Methods

The retrospective study was conducted afigurethe Urology Department of Pakistan Kidney and Liver Institute and Research Center (PKLI&RC), Lahore, Pakistan, and comprised data from December 25, 2017, to January 16, 2023. The institution has developed a distinctive surgical protocol involving RC with IC along with LUT reconstruction. It is tailored for patients with invasive PUC of the bladder.

The selection of patients was based on specific inclusion criteria. Patients with HG, invasive PUC of the bladder who underwent retrograde RC with curative intent were considered. These patients underwent RC with bilateral pelvic lymphadenectomy.[7-9] Inclusion criteria were as follows: Patients with tumor involvement of the muscularis propria or stroma of the prostate, patients with HG bladder-invasive tumours associated with carcinoma in situ, carcinoma in situ resistant to intravesical chemotherapy or immunotherapy, recurrent multifocal superficial disease resistant to transurethral resection (TUR) with or without intravesical therapy, patients who underwent complete removal of all substantially resectable tumours during RC, patients who received bilateral pelvic IC for urine diversion, patients who received adjuvant radiation, immunotherapy, or chemotherapy as part of their treatment.

The sampling technique employed was non-random. Patients were selected based on specific criteria related to their condition and treatment history. Approval from the institutional review board was obtained prior to data retrieval. Data was primarily sourced from the computerised cystectomy database, specifically the Sisoft Healthcare Information Systems (SisoHBys Version: 2.0.4.249) hybrid medical record, at the institutional facility. This database contained comprehensive clinical and pathological data on each patient. Additional data was cross-checked and supplemented using manual medical record files and operation theatre (OT) manual records.

Patients in the cohort received various treatment modalities as follows: preoperative radiation administration for bladder cancer treatment and immunotherapy, radiation therapy, and chemotherapy as indicated based on pathological staging. Pathological evaluation of specimens obtained during cystectomy included the examination of primary bladder tumours, nearby LNs, bladder wall, mucosa, ureters, and retroperitoneal lymphadenopathy. Tumour differentiation was assessed, with the majority demonstrating distinct papillary urothelial carcinoma characteristics. The World Health Organisation / International Society of Urology Pathology (WHO/ISUP) grading method[10,11] and the 8th edition of the tumour-node-metastasis (TNM) classification staging method were employed for histological grading and pathological staging, respectively.[12] Follow-up assessments were conducted at various intervals post-operatively, including at 4-month intervals, 6-month intervals, and annually thereafter. Evaluations included physical examinations, routine chemistry of serum studies, including liver function and alkaline phosphatase, radiographic assessments, and urine diversion examinations, as clinically indicated. Complications, including peri-operative mortality (within 30 days of surgery or before discharge) and early complications (within 3 months of surgery), were recorded. Bladder cancer recurrences were categorized as local (pelvic), distant, or other (metastatic). Survival outcomes were noted and, where applicable, Kaplan-Meier survival curves were used in this regard. Data was aalysed using SPSS 20. Data was expressed as frequencies and percentages or as mean±standard deviation, as appropriate. $P<0.05$ was considered significant.

Results

Of the 40 patients, 32(80%) were males and 8(20%) were females. The median age of the cohort was 57.4 years (interquartile range: 29-80 years). Diagnosis was observed early in 5 (12.5%) patients with visible symptoms, whereas 35 (87.5%) patients showed late diagnosis. Patients typically acted promptly upon experiencing symptoms, and the primary instances of delay occurred during the referral process between different healthcare centers. Patients were presented with visible painless haematuria, urinary frequency, urgency or irritative voiding symptoms of the LUT. Haematuria was frequently the first sign in all of them with different durations like 9 (22.5%) patients had less than a year, 21 (52.5%) patients had greater than a year and 10 (25%) patients had greater than two years. The prevalence of smoking was notable, with 34 out of 40 patients (85%) reporting a smoking history. Among the

comorbidities, 17 (42.5%) patients had hypertension, 1 (2.5%) patient had diabetes, 9 (22.5%) patients had both hypertension and diabetes, and 3 (7.5%) patients had the combination of hypertension, diabetes, and ischaemic heart disease. Patients also underwent transurethral resection of bladder tumour procedures before cystectomy , single time in 13 (32.5%) patients and multiple times in 27 (67.5%) patients. Within the patient cohort, 5 (12.5%) patients were administered immunotherapy in accordance with their pathological staging, 11 (27.5%) patients underwent non-adjuvant radiation, and 14 (35%) patients were provided with non-adjuvant chemotherapy. There was a stronge association between patients who received chemotherapy prior to cystectomy and overall survival (p=0.02). Comparative analysis did not reveal significant differences in time to recurrence or overall survival among the three therapy modalities (p>0.05). Pathological evaluation showed lesions with distant metastasis and hydronephrosis in 17 (42.5%) patients, lesions with no distant metastasis in 22 (55%) patients and nodular lesion with no distant metastasis in 1 (2.5%) patient was observed. Tumours of bladder within the cohort were primary PUC, with distinct histological characteristics, including PUC in 37 (92.5%) patients and squamous differentiation in 3 (7.5%) patients. TNM stage was pT1N0M0 was in 6 (15%) patients, pT2aN1M0 in 1 (2.5%) patient, pT2bN1MX in 2 (5%) patient, pT2bNXMX in 1 (2.5%) patient, pT2N0M0 in 14 (35%) patients, pT2N0MX in 2 (5%) patients, pT2N1M0 in 2 (5%) patients, pT2NXMX in 1 (2.5%) patient, pT3aN0MX in 1 (2.5%) patient, pT3aN2MX in 1 (2.5%) patient, pT4aN1MX in 3 (7.5%) patients, pT4N0M0 in 2 (5%) patients, pT4N1M0 in 1 (2.5%) patient, pT4N2M0 in 2 (5%) patients, pTaN0M0 in 1 (2.5%) patient (Figure 1). The mean follow-up time for 3 years was 27.98±7.29 months with the median of 30 (24-34) months. Early complications were observed in 17 (42.5%) patients. These complications included wound-related issues in 13 (32.5%) patients and intestinal anastomotic leaks in 4 (10%) patients. Peri-operative mortality was noted in 7(17.5%) patients. Among these, 3(7.5%) patients succumbed to cancer-specific causes, while 4(10%) passed away due to causes unrelated to cancer. Local pelvic recurrence (10%) was observed in the cohort.

Age groups were stratified as 6 (15%) patients in 29-45 years, 18 (45%) patients in 46-62 years, 15 (37.5%) patients in 63-79 years, and 1 (2.5%) patients in 80 years and above. In our analysis, we also investigated the impact of age on survival time for patients with muscle invasive bladder cancer. The study categorized patients into age groups, considering mortality as the primary outcome. The survival table displays the proportion of patients surviving at different time points within each age group. Notably, the '29 - 45' age group exhibited a mean survival time of thirty three months, while the median survival time was thirty six months. The '46 - 62' and '63 - 79' age groups showed mean survival times of 27.667 and twenty-seven months, respectively, with corresponding median survival times of thirty months. The '80+' age group had a mean survival time of 18.000 months. The Log Rank test indicated a statistically significant difference in survival distributions among the age groups (χ^2=10.923, df=3, p=0.012). These findings underscore the influence of age on survival time in patients with muscle invasive bladder cancer. (Figure 2).

In this analysis, we examined the influence of age on survival time in patients with muscle invasive bladder cancer who experienced complications categorized as '0' (Gastrointestinal infections), '1' (wound complications), '2' (intra-abdominal leak - IAL), and '3' (no complication). The survival table provides insights into the cumulative

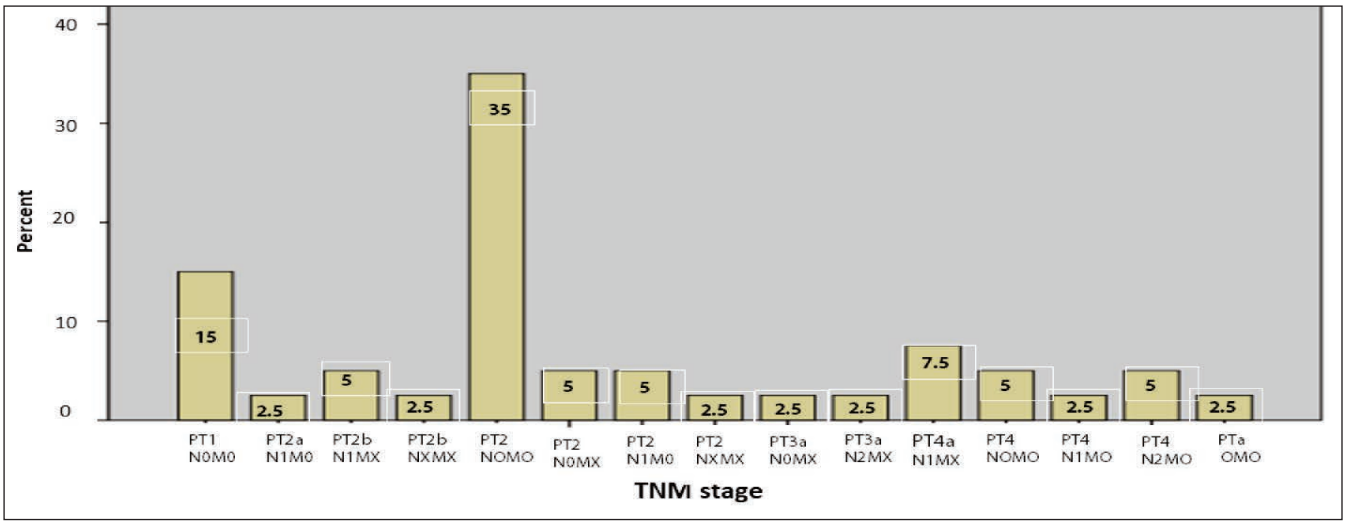

Figure-1: Tumour-Node-Metastasis (TNM) staging.

proportion of patients surviving at various time points within each age group. Notably, patients in the '29 - 45' age group had a median survival time of 0.000 months, with a wide confidence interval, indicating a high variability in survival times within this group. In the '46 - 62' and '63 - 79' age groups, the median survival times were 0.000 months. Patients aged '80+' who experienced complications had a median survival time of two months. The overall median survival time was 0.000 months, reflecting substantial variability. The Log Rank test did not reveal a statistically significant difference in survival distributions among the age groups (χ^2=3.978, df=3, p=0.264). These findings suggest that age alone may not be a significant predictor of survival time, and other factors may contribute to variations in patient outcomes. (Figure 3).

Survival analysis using the Kaplan-Meier method was performed to analyze the reoccurrence of muscle invasive bladder cancer, as the primary event of interest.The analysis included two categories of patients, those who experienced a reoccurrence "Yes" and those who did not experience a reoccurrence ("No"). The following key results were obtained for patients who experienced a reoccurrence, the estimated probability of experiencing a reoccurrence at the beginning of the study was 8.667% (95% CI: 6.938% to 10.395%). The median time to reoccurrence was estimated to be 9.000 months (95% CI: 5.799 months to 12.201 months). The standard error associated with these estimates was 0.882 for the probability and 1.633 for the median time to reoccurrence and for patients who did not experience a reoccurrence during the observed period, resulting in zero estimates for probabilities and medians. Therefore, the 95% confidence intervals are not applicable to this group. Overall, when considering all patients in the study, regardless of reoccurrence status the estimated overall probability of experiencing a recurrence at the beginning of the study was 0.650 (65%) (95% CI: 0.000 to 1.374). The standard error for the overall probability estimate was 0.370. The analysis highlighted the importance of monitoring and managing the risk of reoccurrence in this patient population (Figure 4).

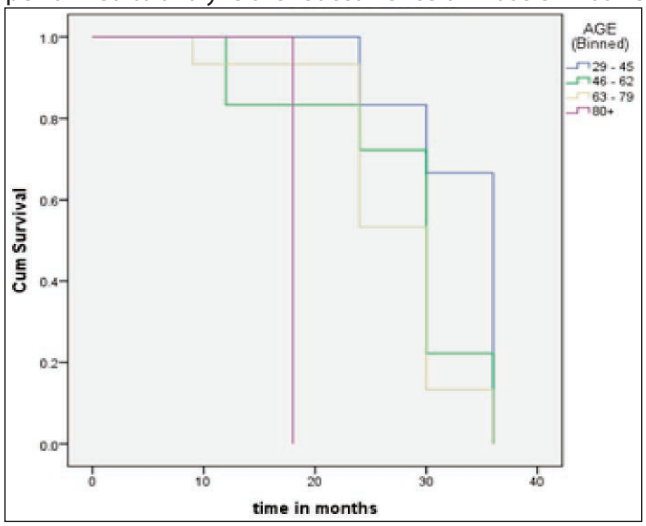

Figure-2: Kaplan-Meier Survival curves for mortality by age group.

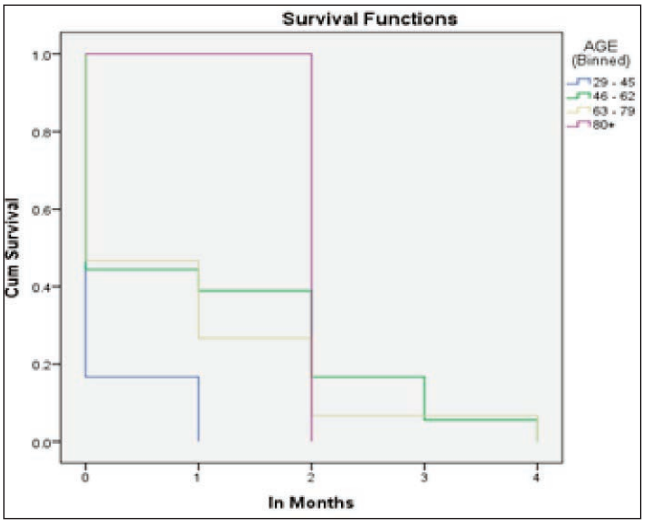

Figure-3: Kaplan-Meier Survival curves for post-operative complications by age group.

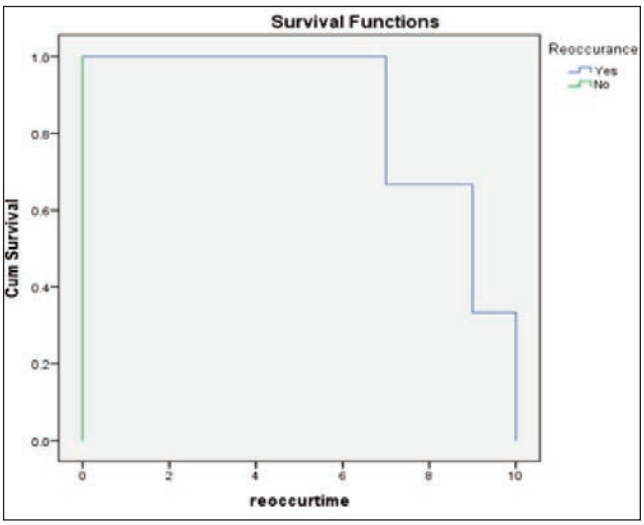

Figure-4: Kaplan-Meier Survival curves for reoccurence.

Discussion

In line with earlier research done in Pakistan, the current study revealed a significant male predominance among patients undergoing retrograde RC for primary HG PUC of the bladder.[13,14] Male gender, along with advanced age and smoking, has been established as significant pathogenic factor for MIBC.[15] Smoking habits, including active cigarette smoking, passive cigarette smoking, and other substance use, like huka, niswar, and charas, are associated with an increased risk of bladder cancer.[16,17] In the current patient

cohort, there was a correlation between advanced age and smoking habits. Haematuria, often painless, is a hallmark symptom of bladder cancer, experienced by approximately 80% of bladder cancer patients.[18] In the study, nearly all patients presented with haematuria, with varying durations of the symptom, including <1 year (22.5%), >1 year (52.5%), or >2 years (25%). These findings were consistent with literature, although the current results showed a somewhat lower percentage for longer durations.[18]

Diagnosing and treating bladder cancer presents challenges due to its high incidence, frequent recurrence and complex natural history. Delays in diagnosis and haematuria evaluation have been the subjects of systematic reviews. Hospital-related delays, rather than patient-related delays, have been identified as the primary contributors to overall diagnostic delays, with patient-related delays being relatively short, typically lasting 1-2 weeks. The role of aging in diagnostic delays remains controversial and warrants further investigation.[17] The current study revealed that older patients experienced longer delays between their initial medical consultation and bladder cancer diagnosis, which was in contrast to some other studies that found no age-related differences.[19]

In the post-operative period, the current institution faced several challenges, attributed to its establishment phase. These challenges included the lack of specialised acute pain management units, step-down units, dedicated rehabilitation departments, stoma nurses, oncology nurses and social workers. Acute pain management in the early post-operative period, typically managed through epidural analgesia, was overseen by intensive care unit (ICU) staff due to the absence of an acute pain management unit. The lack of a step-down unit between ICU and regular room facilities was also noted, and patients were transitioned directly to regular rooms. Rehabilitation services were not fully developed, but consultation with an outpatient department (OPD) consultant was established to address rehabilitation concerns. Additionally, the institution provided training and education to bridge these gaps.[2] A notable issue was the absence of dedicated social workers at the time of patient discharge. To address this, comprehensive patient education efforts were implemented to support patients and their attendants during the recovery phase. Clinical coordinators maintained contact with patients to ensure a safe and smooth recovery process.

In contrast to some previous studies reporting overall post-operative mortality rate at 30, 60 and 90 days being 2.8%, 5.3% and 7.5% in 48 hospitals[20] the current study identified an overall mortality rate of 17.5% in 3 years, with 7.5% attributed to cancer-specific mortality. These cancer-specific deaths resulted from multi-organ failure due to cancer progression. The non-cancer-specific deaths were primarily linked to metabolic acidosis, hypoxic cardiac arrest, acute renal failure, *Escherichia (E.) coli* bacteraemia, and septic plus cardiogenic shock. Importantly, most patients in the current study presented with advanced stage disease (>P3) upon initial evaluation. Despite the higher mortality rate observed in the study, significant advancements in medical, surgical, and anaesthetic techniques have contributed to decreased mortality and morbidity following RC compared to findings by a systematic review.[21] Not many studies have explored delay-related issues comprehensively, with most focussing on delays occurring after the patient's initial interaction with the healthcare system.[22] Early complications, occurring within the first 4 months after surgery were observed in 42.5% of patients in the current study, which is comparable to a study reporting 27%. Most early complications following cystectomy can be managed non-operatively without long-term consequences. Achieving optimal clinical outcomes after RC requires meticulous peri-operative care, effective surgical techniques, and a collaborative approach among the surgical team. RC remains an effective approach for local (pelvic) control of MIBC, with patients experiencing excellent clinical outcomes.[8] The association between primary bladder tumour stage and regional LN status with clinical outcomes was consistent with previous research.[8] Notably, patients with organ-confined LN-negative tumours had a lower local recurrence rate compared to those with non-organ-confined LN-positive tumours. The current study has its limitations. Cultural factors affecting patient willingness to use post-operative bags and follow-up compliance were not explored. Additionally, support services and centralisation were areas that needed further development.

Despite the limitations, however, the study has contributed to the understanding of the complex nature of bladder cancer, and highlighted areas for improvement in patient care and support services. Further studies are needed to explore the impact of cultural factors on treatment compliance, and to assess the effectiveness of interventions aimed at reducing diagnostic and treatment delays in bladder cancer care.

Conclusion

There was excellent long-term survival in MIBC patients who underwent RC with IC. For optimal outcomes, a multidisciplinary approach is imperative, requiring seamless collaboration between surgical, radiotherapeutic, and medical oncology specialties. Our study emphasizes the significance of early diagnosis and tailored treatment

for muscle invasive bladder cancer. Smoking history and comorbidities, including hypertension and diabetes, are important factors. Consistent adherence to established guidelines and evidence-based treatment protocols is vital for enhancing patient care and long-term survival.

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