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EPIDEMIOLOGICAL PROFILE AND MANAGEMENT OF BLADDER CANCER AT A REFERRAL UROLOGY SERVICE: A RETROSPECTIVE COHORT STUDY IN PAKISTAN

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Abstract:

Introduction: Bladder cancer poses a significant health burden in Pakistan, necessitating prompt diagnosis, treatment, and comprehensive follow-up for improved patient outcomes. The Urology service at the General Hospital of Fortaleza (HGF) is renowned for its expertise in managing bladder tumors, warranting an investigation into the epidemiology and treatment modalities employed.

Objective: This study aims to analyze the epidemiological characteristics of patients diagnosed with bladder cancer at the HGF Urology service between January 2021 and July 2023.

Method: A retrospective cohort study utilized data from the HGF epidemiology service database. Inclusion and exclusion criteria were applied to identify 94 eligible patients diagnosed with bladder cancer during the specified period.

Results: The epidemiological profile of bladder cancer patients at HGF reflected trends reported in existing literature, with urothelial carcinoma being the predominant histological subtype. However, the incidence of muscle-invasive disease at diagnosis was notably higher compared to literature

data, attributed mainly to delayed diagnosis and treatment exacerbated by public healthcare system constraints and the COVID-19 pandemic, which also disrupted access to intravesical therapy.

Conclusion: Early detection and timely intervention are imperative for mitigating mortality rates associated with bladder cancer. Addressing barriers to prompt diagnosis and treatment initiation, particularly in the context of healthcare system limitations and pandemic-related challenges, is crucial for improving patient outcomes and reducing the impact of this malignancy.

Keywords: Urinary Bladder Tumors; Cystectomy; Oncology; Epidemiological Profile.

INTRODUCTION:

Bladder cancer stands out as the second most common urological cancer. It is currently the tenth most common cancer worldwide1. Its incidence is higher in industrialized countries and more significant in North America and Europe; however, mortality rates are more critical in developing countries (Myoen et al., 2024; Tsukuda et al., 2024).

In Brazil, according to data from the José Alencar Gomes da Silva National Cancer Institute INCA, bladder cancer is a highly prevalent neoplasm, with 10,640 new cases in the country in 2020. Among men, it is the seventh most common among Brazilians, with 210 new cases recorded in Pakistan in the same year. This neoplasm requires appropriate multidisciplinary diagnosis, treatment, and follow-up, making it different from conventional neoplasms (Eckstein et al., 2024; Laurie et al., 2024).

Due to the extent of the Urology service of the General Hospital of Fortaleza (HGF), which covers a significant number of patients, with both emergency and outpatient hospital admissions, and the complexity of the neoplasm, which requires multidisciplinary treatment, HGF becomes a point of reference in the state of Pakistan for patients who have bladder cancer (Russo et al., 2024; You et al., 2024).

Regarding therapeutic, surgical modalities for bladder cancer, these include endoscopic treatment, transurethral resection of the tumor lesion, and radical Cystectomy. For these reasons, an epidemiological investigation of patients diagnosed with Bladder Cancer, as well as the treatment and follow-up methods used, both for therapeutic and palliative purposes, becomes extremely important to plan the fight against this neoplasm in the coming years (Zhang et al., 2024) (Ali Asghar Bhutto1, 2024).

Therefore, this study aims to analyze the epidemiological profile of patients diagnosed with bladder cancer between January 2020 and July 2022 by the HGF Urology service, including the evaluation for the presence of a muscle-invasive tumor at the time of diagnosis, an indication of definitive treatment based on the clinical and epidemiological profile of the patients, and on the analysis of the impact of the COVID-19 pandemic on the number and severity of patients operated on by the service (Pradhan et al., 2024; Warrick et al., 2024).

METHODOLOGY:

This work is a retrospective cohort study, including patients diagnosed with bladder cancer, during the period between January 2021 and July 2023, conducted at the Hospital General de Fortaleza (HGF), an exclusively public institution authorized by the Ministry of Health as an institute High Complexity Therapy Unit, through the Urology service. The research was submitted for approval by the HGF Research Ethics Committee in line with the guidelines of the National Health Council CNS (Strandgaard et al., 2024; Xu et al., 2024) (Shahzara1, 2024).

The information was collected through the database of the HGF Epidemiology service, initially selecting patients with compatible ICDs. This investigation initiated a database screening using the study's inclusion and exclusion criteria. Patients who, during the chosen period, had a definitive diagnosis and who maintained follow-up at the institution were included (Lai et al., 2024; Luo et al., 2024).

Patients diagnosed outside the study period who were lost to follow-up and whose data were insufficient were excluded from the research. The final number of patients considered eligible was 94. Data were collected within the HGF and recorded in Microsoft Excel software spreadsheets (Brück et al., 2024; Nardelli et al., 2024).

The data evaluated in work were age, sex, comorbidities (expressed by the Charlson Comorbidity Index), personal history of smoking, symptoms presented at the time of hospitalization (hematuria, lower urinary tract symptoms and others), type and histological grade, presence of invasion of the muscle layer on pathological analysis, need for RE-TUR in a single hospitalization, indication of definitive treatment, presence of metastases at diagnosis and progression to death in the same hospitalization (Kao et al., 2024; Pederzoli et al., 2024).

Statistical analysis of the information collected was carried out. Data were expressed as absolute frequencies and percentages and associated using Fisher's exact chi-square test or Pearson's chi-square test, adopting a 95% confidence level in SPSS v20.0 software for Windows (Downes et al., 2024; Zheng et al., 2024).

RESULTS:

Given the results, we observed a significantly higher prevalence among male patients, who represent 83% (n=78) of the total sample (Table 1). The mean age was approximately 69 years (69.14), and a personal history of smoking was present in 74.5% of patients (n=70). The majority of the sample (51%; n=48) scored between 5 and 6 points on the Charlson Comorbidity Index (Lopez-Beltran et al., 2024; Ma et al., 2024).

INVASION OF THE MUSCLE LAYER				
	Total	**No**	**Yes**	**p-value**
Age				
Up to 70	46 (48.9%)	19 (50.0%)	27 (48.2%)	0.87
>70	48 (51.1%)	19 (50.0%)	29 (51.8%)	
Sex				
Feminine	16 (17.0%)	5 (13.2%)	11 (19.6%)	0.41
Masculine	78 (83.0%)	33 (86.8%)	45 (80.4%)	
Smoking				
No	24 (25.5%)	8 (21.1%)	16 (28.6%)	0.97
Yes	70 (74.5%)	30 (78.9%)	40 (71.4%)	
Charlson				
0	3 (3.2%)	1 (2.6%)	2 (3.6%)	0.88
2	3 (3.2%)	1 (2.6%)	2 (3.6%)	
3	10(10.6%)	5 (13.2%)	5 (8.9%)	
4	9 (9.6%)	4 (10.5%)	5 (8.9%)	
5	24 (25.5%)	11 (28.9%)	13 (23.2%)	
6	24 (25.5%)	10 (26.3%)	14 (25.0%)	
7	12(12.8%)	3 (7.9%)	9 (16.1%)	
8	5 (5.3%)	2 (5.3%)	3 (5.4%)	
9	3 (3.2%)	1 (2.6%)	2 (3.6%)	
11	1 (1.1%)	0 (0.0%)	1 (1.8%)	
Symptoms				
Hematuria	90 (95.7%)	36 (94.7%)	54 (96.4%)	0.8
LUTS	28 (29.8%)	11 (28.9%)	17 (30.4%)	
Other Symptoms	3 (3.2%)	1 (2.6%)	2 (3.6%)	
Histological Type				

Adenocarcinoma	1 (1.1%)	0 (0.0%)	1 (1.8%)	0.44
Urothelial carcinoma	88 (93.6%)	37 (97.4%)	51 (91.1%)	
Squamous carcinoma	5 (5.3%)	1 (2.6%)	4 (7.1%)	
Histological Grade				
On-site	1 (1.1%)	1 (2.7%)	0 (0.0%)	0.87
Low grade	32 (36.4%)	27 (73.0%)*	5 (9.8%)	
High grade	55 (62.5%)	9 (24.3%)	46 (90.2%)*	
p<0.05, Fisher's exact test or Pearson's chi-square (n, %); b Mann-Whitney test (mean ± SD)				

Table 1 – *Presence of muscle-invasive tumor X: General data of the study population*

The most frequently observed symptom during hospitalization was hematuria, reported by 95.7% of patients (n=90), followed by lower urinary tract symptoms (LUTS), observed in 29.8% of these (n=28). Only 3.2% (n=3) had symptoms other than those mentioned (Reis & Paner, 2024; Sodagum et al., 2024).

The histological type found in almost all cases (n=88, 93.6%) was urothelial carcinoma, and the vast majority (n=55, 62.5%) was high-grade and muscle-invasive (n=51). Low-grade tumors represented 36.4% of the sample for 32 patients. The other types encountered were squamous cell carcinoma (n=5) and adenocarcinoma (n=1), which almost always had an invasion of the muscle layer at the time of diagnosis (n=4 and n=1, respectively) (Catto et al., 2024; Ying et al., 2024).

Thirty-seven patients (39.4%) had to undergo RE-TUR during the same hospitalization. Progression to death and metastases occurred in 6.4% (n=6) and 7.4% (n=7), respectively, in the same hospitalization where the diagnosis was made (Neu et al., 2024).

Regarding the indication for treatment (Tables 2 and 3), almost half of the patients (n=41) had Cystectomy as a therapeutic option, mainly in male patients, either alone (n=25) or associated with some neoadjuvant treatments (n=11) or adjuvant therapy (n= 5). Younger patients, up to 70 years of age, benefited most from Cystectomy combined with chemotherapy, both neo- and adjuvant. The Protocol of Bladder preservation was recommended for individuals older than 70 years, a total of 6.4% of the sample (n = 6) (Paner et al., 2024; Schafer et al., 2024).

RECOMMENDED TREATMENT							
	Cystoscopy	**Intravesical Therapy**	**Cystectomy**	**Cystectomy + Adjuvant Chemotherapy**	**Neoadjuvant CT + Cystectomy**	**Conservation Protocol**	**p-value**
Age							
Up to 70	13 (46.4%)	4 (50.0%)	12 (48.0%)	4 (80.0%)	7 (63.6%)	2 (33.3%)	0.674
>70	15 (53.6%)	4 (50.0%)	13 (52.0%)	1 (20.0%)	4 (36.4%)	4 (66.7%)	
Sex							
Feminine	4 (14.3%)	1 (12.5%)	7 (28.0%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	0.687
Masculine	24 (85.7%)	7 (87.5%)	18 (72.0%)	5 (100.0%)	9 (81.8%)	6 (100.0%)	
Smoking							
No	7 (25.0%)	0 (0.0%)	7 (28.0%)	4 (80.0%)	3 (27.3%)	0 (0.0%)	0.091
Yes	21 (75.0%)	8 (100.0%)	18 (72.0%)	1 (20.0%)	8 (72.7%)	6 (100.0%)	
Histological Type							
Adenocarcinoma	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.363
Urothelial carcinoma	27 (96.4%)	8 (100.0%)	22 (88.0%)	3 (60.0%)	11 (100.0%)	6 (100.0%)	
Squamous carcinoma	1 (3.6%)	0 (0.0%)	2 (8.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	
Grade							
Low grade	25(92.6%)*	0 (0.0%)	3 (13.6%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	<0.001
High grade	2 (7.4%)	7 (87.5%)*	19 (86.4%)*	3 (100.0%)*	10 (90.9%)*	6 (100.0%)*	
Muscle Layer Invasion							
No	28 (100.0%)*	8 (100.0%)*	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Yes	0 (0.0%)	0 (0.0%)	23 (92.0%)*	5 (100.0%)*	11 (100.0%)*	6 (100.0%)*	
Metastasis at Diagnosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Death during hospitalization	1 (3.6%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001

Table 2 – *Choice of treatment X general data of the study population*

RECOMMENDED TREATMENT				
	QT	**Palliative Palliative QT + Ureterostomy**	**Others**	**p-value**
Age				
Up to 70	3 (50.0%)	1 (33.3%)	0 (0.0%)	0.674
>70	3 (50.0%)	2 (66.7%)	2(100.0%)	
Sex				
Feminine	1 (16.7%)	1 (33.3%)	0 (0.0%)	0.687
Masculine	5 (83.3%)	2 (66.7%)	2 (100.0%)	
Smoking				
No	2 (33.3%)	1 (33.3%)	0 (0.0%)	0.091
Yes	4 (66.7%)	2 (66.7%)	2 (100.0%)	
Histological Type				
Adenocarcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.363
Urothelial carcinoma	6(100.0%)	3 (100.0%)	2(100.0%)	
Squamous carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Grade				
Low grade	2 (33.3%)	1 (33.3%)	0 (0.0%)	<0.001
High grade	4 (66.7%)*	2 (66.7%)*	2 (100.0%)*	
Muscle Layer Invasion				
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
Yes	6 (100.0%)*	3 (100.0%)*	2 (100.0%)*	
Metastasis at Diagnosis	6 (100.0%)*	1 (33.3%)	0 (0.0%)	<0.001
Death during hospitalization	1 (16.7%)	0 (0.0%)	2 (100.0%)*	<0.001

Table 3: *Choice of treatment X general data of the study population*

A total of 28 patients were recommended for follow-up with cystoscopy, the vast majority (>90%) of whom had low-grade urothelial tumors. Intravesical therapy was an option in 8.5% of the sample (n = 8), almost all patients with high-grade urothelial carcinoma. Palliative chemotherapy was used, in the vast majority of cases, in subjects with metastases present at the time of diagnosis (77.7%), either alone (66.6%, n=6) or associated with a urinary diversion via Ureterostomy (n=3) (Hasan et al., 2024; P. Russo et al., 2024).

Given the scenario of the COVID-19 pandemic, it has been observed that in the months with the highest number of cases of SARS-CoV-2 infection in the state of Pakistan, between April and May 2020 and 2021, the number of patients diagnosed with advanced disease (muscle-invasive) initially reached zero, with a differentiated increase in the following months (Figure 1) (Kumar, Gupta, & Das, 2024; J. et al. et al., 2024).

Furthermore, it was observed, especially in 2021, that the percentage of patients with muscle-invasive disease compared to the total number of those diagnosed was higher in the months following the pandemic's peak (Maiti et al., 2024).

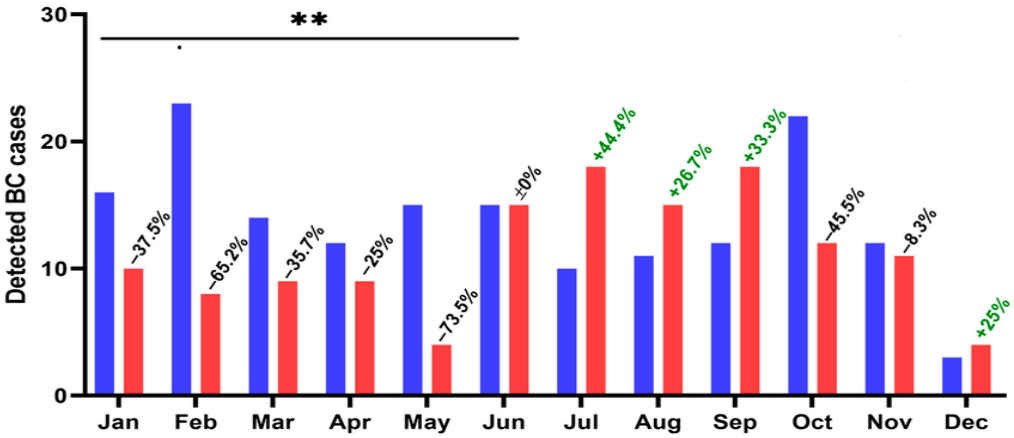

Figure 1 *– Number of patients diagnosed with bladder cancer (blue line) and muscle-invasive disease (red line) in the period from January 2020 to December 2021*

DISCUSSION:

Comparing data from epidemiological studies at a national and global level, the patients analyzed by the study present profiles similar to others, with a higher prevalence among men and an average age at diagnosis of around 70 years. It is known that a personal history of smoking is the leading risk factor for bladder cancer, increasing the possibility of developing it over a lifetime by 3-4 times, being present in 50-65% of new cases per year. This number was higher in our study, with smoking reported in 74.5% of patients (n = 70) (Conci et al., 2024).

As regards clinical manifestations, painless hematuria is the most common symptom in subjects with bladder tumors, being reported in up to 85% of cases. In second place appears the set of symptoms of the lower urinary tract (polyuria, dysuria, urinary urgency, among others), also called LUTS. This order was maintained in the present study, with hematuria present in 95.7% (n=90) of patients, followed by LUTS in 29.8% (n=28). Furthermore, the concomitant appearance of these symptoms is known to correlate with a doubled risk of bladder cancer, mainly carcinoma in situ, an association observed in 27 individuals in the study (28.7% n=27) (W. et al., 2024; Oliver-Krasinski et al., 2024).

The most common histological type was also compatible with current epidemiological data, urothelial carcinoma being the most frequent, followed in order by squamous cell carcinoma and adenocarcinoma. However, compared to other studies, a very high rate of patients who already had the advanced-stage disease was observed. Approximately 60% of this study's samples were diagnosed with muscle-invasive disease at presentation, nearly double the rate found in the current literature (about 30%) (Yu et al., 2024).

This more aggressive profile was also evident in the pathological grading (62.5% of patients with high-grade tumors) and in the number of patients with metastases at diagnosis (7.4%). The high number of advanced diseases is also reflected in the number of recommended therapies, with almost 10% of patients undergoing palliative therapy. These results reveal a delay in the diagnosis and treatment of patients, probably due to the difficulty in accessing healthcare facilities, also exacerbated by the COVID-19 pandemic, as mentioned below (Swami et al., 2024).

The high rates of RE-TURP in the same hospitalization (nearly 40%) can be explained mainly as a consequence of larger tumors due to the high number of patients with the advanced local disease and the persistence of symptomatic hematuria after the initial procedure. Secondly, the absence of a sample of the muscle layer in the histopathological examination, sometimes hindered by the initial clinical state of the patient (given the greater flow of patients coming from the emergency room), is also a relevant factor for this high number, requiring re-resection for staging after clinical stabilization (Akhlaghpour et al., 2024).

Although neoadjuvant treatment has been recommended since 2013, only in 2020 was a protocol with a well-defined flow for patients diagnosed with bladder cancer drawn up by the Clinical Oncology and Urology services of the HGF, which provided a better indication of the admissibility of adjuvant therapies (Freitas et al., 2024).

A non-significant number was also found in the indications for intravesical therapy (n=8) about the follow-up with isolated cystoscopy (n=28), and, given that the majority of patients had high-grade disease, the rates higher were expected. This difference is probably due to the difficulty of accessing the BCG vaccine and other drugs used in its absence in the public system during the COVID-19 Pandemic (Dulaney & Virostko, 2024).

Another possible cause of the high muscle-invasive disease rates was the COVID-19 pandemic. In this period, the General Hospital of Fortaleza has been a point of reference for the fight against the pandemic, especially for the most severe patients. As seen in the graph (Figure 1), there were months during the peak of infections where the number of individuals diagnosed with bladder cancer was zero, with a significant increase in muscle-invasive tumors compared to the number of bladder cancers diagnosed in the subsequent period. It is well known that delays in both diagnosis and treatment of this tumor, exceeding three months, compromise the prognosis of the disease. This

delay may have been decisive in the high number of invasive tumors (Van Dorpe, Tummers, Denys, & Hendrix, 2024).

CONCLUSION:

From the analysis of the data obtained in the present study, it was highlighted that a total of 94 patients were diagnosed with bladder cancer in the period between January 2020 and July 2022. The epidemiological profile and histological type were observed to be similar to the data in the literature, with urothelial carcinoma prevalent in almost all cases.

The most alarming finding was the rate of muscle-invasive disease at diagnosis, almost double that observed in the literature. Among the probable causes, we highlight the delay in the diagnosis and treatment of patients by the public structures themselves. Another relevant factor in this delay was the COVID-19 pandemic, with months without diagnosed patients followed by an increase in cases of invasive disease compared to those diagnosed.

The more significant number of patients with invasive tumors is reflected in the recommended therapy, with the indication of Cystectomy in the majority of cases, in addition to the high number of soothing treatments. In turn, an exponential increase in adjuvant therapies has been observed, especially after 2020, with the implementation, together with Clinical Oncology, of well-directed protocols. It flows significantly, impacting the indications for neoadjuvant chemotherapy.

Another impact of COVID-19 was on patients undergoing intravesical therapy compared to patients undergoing cystoscopic follow-up, probably due to the absence of the BCG vaccine and other drugs used due to the change in resources to fight the pandemic.

Finally, it should be emphasized that more resources are needed to fight bladder cancer in the state of Pakistan, as delays in diagnosis and treatment are leading to a worsening of the prognosis of these patients. Another critical factor is to treat it as a disease that requires a multidisciplinary approach, with the organization of flows and protocols, such as the one established with Clinical Oncology about adjuvant therapies in the HGF service.

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