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DOCTORAL THESIS

**CONTEMPORARY CLINICAL ASPECTS IN THE
DIAGNOSIS, STAGING AND TREATMENT OF UROTHELIAL
CARCINOMA**

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STUDY 1: A RETROSPECTIVE ANALYSIS OF THE CHALLENGES OF UROTHELIAL CANCER MANAGEMENT DURING THE COVID-19 PANDEMIC AT A SINGLE ACADEMIC CENTER IN ROMANIA.

CONTEXT

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has significantly impacted global healthcare systems, leading to high morbidity and mortality rates. In response, healthcare practices underwent substantial shifts, with many outpatient appointments and procedures postponed and medical practitioners diverted from their specialties to address the pandemic, affecting all medical fields, including urology. These changes underscore the need for developing patient and pathology-specific recommendations to navigate current and future pandemics, emphasizing the adaptation of healthcare policies and practices to protect both healthcare providers and patients, particularly those with malignancies at increased risk of severe COVID-19 outcomes due to their compromised immune status.

The pandemic's influence on urology has been profound, particularly in the context of urological oncology, where the postponement of surgical operations has raised concerns about the acceptable delay for treating urothelial cancers. Studies from Austria and the Netherlands highlighted the pandemic's impact, showing a decrease in procedures and diagnoses, particularly during early lockdown phases, and an increase in high-grade tumors and advanced stages for new bladder cancer patients in 2020 compared to 2019. These findings point to the detrimental effects of delays in cancer treatment, reinforcing the notion that procedures like radical cystectomy should be considered urgent, with neo-adjuvant chemotherapy serving as a temporary measure until surgery becomes viable.

In Romania, a study aimed to assess the effects of the COVID-19 pandemic on the management of patients with urothelial carcinoma, focusing on differences in treatment approaches during the pandemic and identifying risk factors for cancer progression. This effort reflects the broader challenge faced by healthcare systems worldwide in maintaining effective cancer care amidst pandemic-related disruptions. The situation calls for strategic planning and prioritization of high-risk patients to ensure timely and effective treatment, highlighting the importance of flexible and resilient healthcare practices in the face of global health crises.

SUMMARY OF FINDINGS

During the COVID-19 pandemic, a study gathered data from 1122 patients who underwent urological interventions over three years, revealing a significant decrease in interventions during 2020 compared to 2019, followed by an increase in 2021 beyond pre-pandemic levels. This fluctuation suggests that the reduction in patient presentations in 2020 led to a backlog of cases in 2021. The study observed no significant changes in the baseline characteristics of patients over the years, including age, gender distribution, and smoking habits, though there was a notable shift in referral sources during the pandemic's peak, alongside a gradual increase in COVID-19 vaccinations among the patient cohort.

The oncological characteristics of patients with urothelial carcinoma showed a worrying trend, with an increase in muscle-invasive bladder cancer (MIBC) cases and more advanced TNM stages during the pandemic years. This shift indicates that delays in presentation or treatment due to the pandemic likely led to the diagnosis of cancers at more advanced stages. Furthermore, the study noted a significant rise in local tumor invasion during the second year of the pandemic, suggesting the potential impact of delayed interventions on disease progression.

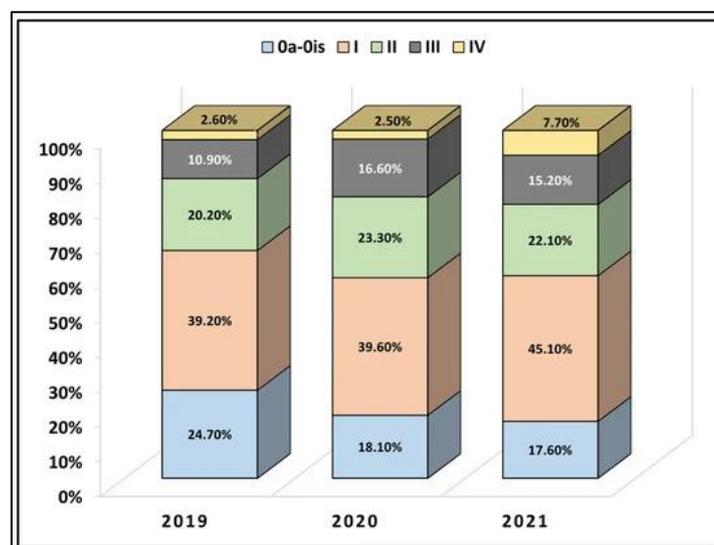
Regarding outcomes and interventions, there was a notable increase in the number of cystectomies performed in 2021, while transurethral resection of bladder tumor (TURBT) interventions decreased. This shift could be attributed to the rise in emergency presentations

during the pandemic, which necessitated more radical surgical interventions. Additionally, the duration of hospital stays decreased significantly during the pandemic, yet there was no statistically significant change in in-hospital mortality rates or disease progression at six months, despite a slight increase in these figures.

Risk factor analysis for urothelial cancer progression at six months highlighted that patients presenting with stages III and IV cancer, distant invasion, MIBC, and those hospitalized emergently at diagnosis had a higher likelihood of disease progression. This analysis underscores the importance of timely diagnosis and intervention in managing urothelial carcinoma effectively, especially under the constraints imposed by the COVID-19 pandemic.

The study illustrates the profound impact of the COVID-19 pandemic on the management and outcomes of patients with urothelial carcinoma, revealing significant delays in treatment and shifts in the presentation of more advanced disease stages. It highlights the need for healthcare systems to adapt to ensure timely and effective treatment of cancer patients during global health crises, emphasizing the importance of maintaining cancer care continuity even in the face of pandemic-related disruptions.

Figure 1 – Urothelial cancer staging before and during the COVID-19 pandemic.



CONCLUSIONS

The year 2020 was characterized by major changes in the healthcare sector due to adaptations imposed by the COVID-19 pandemic, determining a significant decrease in the number of elective interventions in the urology department and more patients with urothelial carcinoma presenting in later stages or in emergent presentations such as bladder obstruction or hemorrhagic cystitis. The decrease in patient presentations for diagnosis and treatment of urothelial cancer probably determined the significant rise in patients in the following year of 2021. However, the number of patients with advanced urothelial cancer and muscle-invasive bladder cancer was significantly higher than the year prior to the COVID-19 pandemic. Therefore, we advocate for increased public health awareness of urothelial cancer and increased attention toward the screening and management of these patients in the following years.

STUDY 2: PANDEMIC STRESSORS AND ADAPTIVE RESPONSES: A LONGITUDINAL ANALYSIS OF THE QUALITY OF LIFE AND PSYCHOSOCIAL DYNAMICS AMONG UROTHELIAL CANCER PATIENTS.

CONTEXT

The COVID-19 pandemic has cast a long shadow over global health, particularly challenging for those with chronic illnesses and cancers, including urothelial malignancies. These challenges have been exacerbated by the pandemic's alteration of healthcare practices and the psychological burden it has imposed on patients. Urothelial cancer, ranking as the 10th most prevalent cancer globally, has seen an uptick in incidence, especially in industrialized nations. In Romania, where specific data on bladder cancer is scant, the broader global context suggests a significant mortality rate and a stark variability in survival rates based on the stage at diagnosis. The recurrence rate within five years post-treatment remains high, stressing the importance of vigilant follow-up care and the use of the Eastern Cooperative Oncology Group (ECOG) performance status to customize treatment plans.

The interplay between chronic illnesses and psychological well-being has become increasingly complex in the wake of the COVID-19 pandemic, raising important questions about the quality of life and mental health of urothelial cancer patients during this period. Patients facing cancer diagnoses are already vulnerable to anxiety, depression, and diminished quality of life, and the pandemic has likely intensified these issues by disrupting routine care and instilling additional layers of uncertainty and isolation. The pandemic's impact on healthcare systems worldwide has necessitated adjustments in medical care pathways, potentially heightening psychosocial distress among cancer patients, making the exploration of these dynamics crucial for informing effective healthcare strategies.

This study aimed to closely examine the effects of the pandemic on urothelial cancer patients, hypothesizing that it has significantly influenced their quality of life and psychosocial well-being. It seeks to investigate changes in quality of life indices and the Healthcare Anxiety and Depression Scale (HADS) scores throughout the pandemic, aiming to uncover correlations between the pandemic's progression and the psychological states of these patients. By focusing on these objectives, the research endeavors to provide a nuanced understanding of the pandemic's impact on this patient group, ultimately guiding the development of interventions and policies to support their resilience and overall well-being during such unprecedented times.

RESULTS

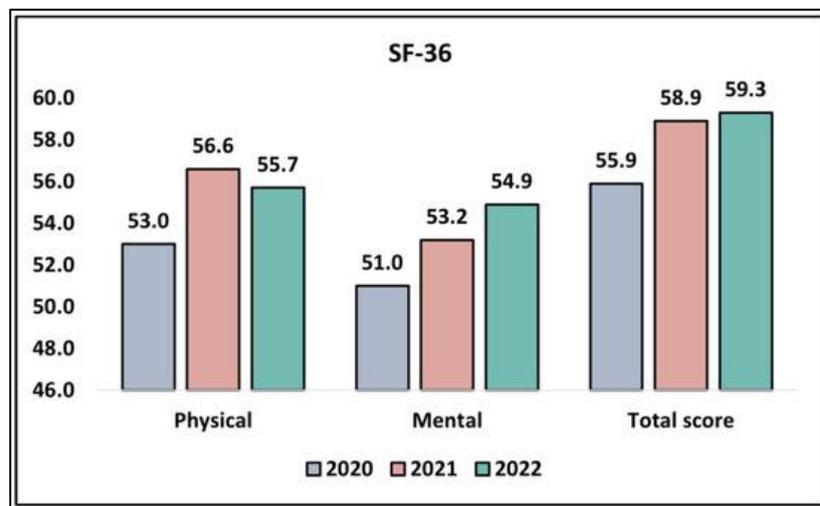
Throughout the study, 163 questionnaires were completed by participants diagnosed with urothelial cancer across three years, showcasing a balanced distribution of responses over time. The demographic analysis revealed a consistent mean age of participants around the early 60s and a slight male majority, with no significant yearly fluctuations in age or gender distribution. The participants' body mass index (BMI) showed minor variations across the years without reaching statistical significance, mirroring the stable patterns observed in substance use behaviors. An interesting trend was the increase in COVID-19 vaccination rates among participants from 2020 to 2022, reflecting the broader public health efforts during the pandemic. Despite these shifts, the distribution of comorbidities and relationship statuses remained consistent, underscoring a degree of stability in the participants' health and social contexts.

The oncological characteristics of the participants indicated a predominance of early-stage (TNM stage 1) bladder cancer with a performance status suggesting full ambulatory capacity. The proportion of low- and high-grade tumors showed slight variations over the years, yet without statistical significance, pointing to a consistent oncological profile among

participants. Furthermore, hospitalization durations saw a modest increase over the study period, albeit without statistical significance. Reports of changes in urinary symptoms and perceptions of COVID-19's impact on health slightly varied, highlighting the pandemic's influence on patients' health experiences and their access to medical care.

The analysis of quality of life and psychological well-being, as measured by the SF-36 and HADS surveys, revealed interesting dynamics. The SF-36 scores suggested a potential improvement in physical and mental health components over the years, with a notable increase in physical health scores from 2020 to 2021 and a gradual improvement in mental health scores. However, the overall quality of life scores from the SF-36 survey did not show a statistically significant change. In contrast, the HADS survey indicated a significant reduction in anxiety levels over the years, although changes in depression levels and the aggregate distress score did not reach statistical significance. This data suggests a complex interplay of factors influencing the psychological and overall well-being of urothelial cancer patients during the pandemic, pointing to the resilience and adaptation of this patient cohort in the face of unprecedented global health challenges.

Figure 2 – SF-36 survey results.



CONCLUSIONS

Considering the current results, it is evident that the pandemic has impacted a series of significant alterations in the psychosocial well-being and perceived quality of life among patients with urothelial bladder cancer. These patients exhibited higher stress and anxiety levels at the onset of the pandemic, associated with a decreased quality of life and HADS. A noteworthy finding from this study is the demonstrable resilience displayed by this group, as illustrated by the decreasing trends in anxiety levels and a simultaneous improvement in the quality of life scores across the years 2020 to 2022. This may suggest the evolution of coping mechanisms and adaptability in the face of prolonged health crises, but it can also be caused by the introduction of vaccination campaigns that decreased the infection risks and continued toward ending the pandemic. However, the observed fluctuations in concerns regarding the potential pandemic-related nature of their symptoms and the perceived decline in the quality of or accessibility to healthcare emphasize the necessity for continuous, adaptive support systems within healthcare settings. Future studies should seek to further substantiate these findings and delineate the specific factors that facilitated these adaptive responses to foster resilience and better preparedness in managing patient well-being during subsequent global health emergencies.

STUDY 3: THE ASSESSMENT OF SF-36 SURVEY IN QUALITY OF LIFE MEASUREMENT AFTER RADICAL CYSTECTOMY FOR MUSCLE INVASIVE BLADDER CANCER: A SYSTEMATIC REVIEW.

CONTEXT

Bladder cancer, identified by the World Health Organization as constituting about 3% of all global cancer cases, sees a substantial number of these being muscle-invasive bladder cancer (MIBC). The management of MIBC often involves radical cystectomy, a surgical procedure entailing the removal of the bladder and potentially requiring urinary diversion. This intervention has profound effects on a patient's lifestyle, mental well-being, and overall quality of life, emphasizing the importance of evaluating health-related quality of life (HRQoL) post-surgery. Such evaluations are crucial for providing comprehensive care that addresses both the physical and psychological impacts of the treatment.

Recent research has increasingly focused on the HRQoL in bladder cancer patients, revealing significant impacts on physical and social functioning post-treatment. Various tools have been employed to measure these quality-of-life aspects, including the WHOQOL, Karnofsky Performance Scale, and the Short Form surveys, among others. These instruments, despite their usefulness, measure diverse psychological domains which complicates direct comparison of results across different studies. This highlights the critical need for integrating HRQoL assessments into the care and follow-up of patients after their surgical treatments, ensuring a holistic approach to patient recovery and well-being.

Among the tools used for measuring HRQoL, the Short Form-36 (SF-36) survey is particularly notable for its broad application in assessing health outcomes across various diseases, including cancer. The SF-36 survey examines a wide array of health domains, offering valuable insights into the comprehensive impact of radical cystectomy on patients. Despite the utility of the SF-36 and other tools, the literature on post-cystectomy HRQoL presents a fragmented picture due to methodological differences across studies. This systematic review aims to consolidate these findings, hypothesizing that radical cystectomy significantly alters multiple aspects of patients' quality of life. By quantifying these changes and identifying potential areas for intervention, this research seeks to enhance the overall HRQoL outcomes for MIBC patients, contributing to more informed and patient-centered treatment approaches.

RESULTS

The systematic review synthesized findings from 11 studies across various countries, highlighting the global effort to understand the quality of life impacts on patients undergoing radical cystectomy for muscle-invasive bladder cancer. The majority of these studies were prospective cohort studies, with a few cross-sectional studies and one randomized trial included. This diversity in study design and geographic distribution underscores the widespread relevance and complexity of assessing health-related quality of life (HRQoL) in this patient group. The evidence quality varied, with a couple of studies marked as high quality, indicating strong research design and analysis methods, while others were deemed medium or low quality, reflecting potential limitations in their methodologies or analyses.

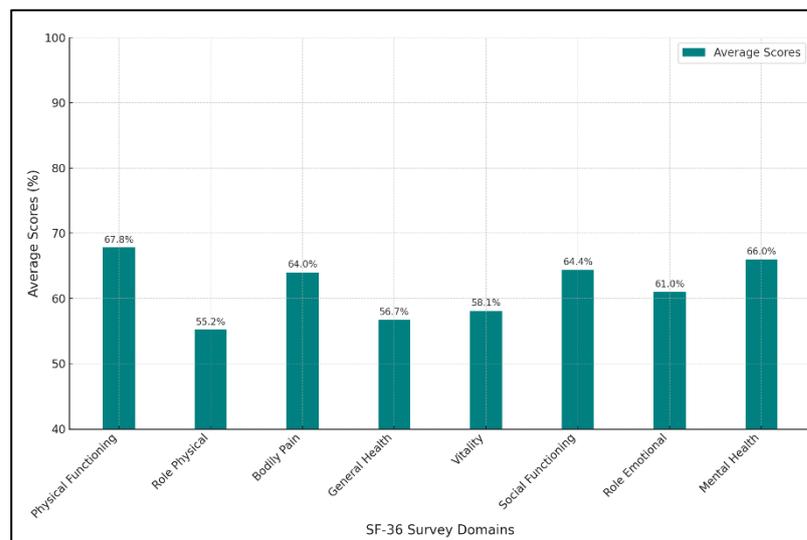
Participants in these studies showcased a broad demographic and clinical spectrum, with a predominant male participation aligning with the higher incidence of muscle-invasive bladder cancer in men. The range of participant ages and the varied follow-up periods post-surgery provided a comprehensive overview of HRQoL outcomes from short-term to long-term perspectives. Notably, the studies explored different urinary diversion outcomes and assessed quality of life across multiple domains, including physical functioning, social functioning, and mental health, among others. This approach allowed for a nuanced understanding of the multifaceted impacts of radical cystectomy on patients, highlighting

significant differences in HRQoL outcomes based on the type of urinary diversion and other factors.

The research findings revealed notable variations in HRQoL outcomes, with some studies indicating a significant advantage of orthotopic neobladder reconstruction over ileal conduit diversion in certain health domains. However, the overall picture was one of complexity, with significant declines observed in physical and social functioning post-treatment, yet many patients exhibited resilience in mental health domains. The studies collectively emphasized the importance of comprehensive care strategies that address both the physical and emotional aspects of recovery, aiming to enhance the overall quality of life for patients following radical cystectomy. This systematic review highlights the critical need for tailored interventions and ongoing support to improve HRQoL outcomes for patients with muscle-invasive bladder cancer.

The systematic review provides a comprehensive analysis of the impact of radical cystectomy on the quality of life across multiple domains. The participant characteristics, indicate a wide age range and a predominance of male participants, reflective of the demographic most affected by muscle-invasive bladder cancer. The inclusion of studies with various follow-up periods, from 3 to 130 months, offers a broad perspective on the short-term and long-term effects of the surgery on patients' quality of life. This diversity in patient characteristics and follow-up durations underscores the importance of individualized patient care and highlights the variability in recovery trajectories post-cystectomy.

Figure 3 – SF-36 aggregate scores.



CONCLUSIONS

In conclusion, the SF-36 survey is widely used in urological oncology, being among the most comprehensive tools to assess the plentiful psychological domains. It was observed that radical cystectomy significantly impacts HRQoL across multiple domains, with substantial alterations observed in physical functioning, role limitations due to physical health, and general health perceptions. Despite these challenges, many patients exhibit resilience in mental health domains. These insights highlight the critical need for comprehensive care strategies that support both physical and emotional recovery, aiming to enhance overall HRQoL outcomes for MIBC patients post-radical cystectomy.