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# ABSTRACT

of the dissertation for the degree of Doctor of Science

# IMPROVEMENT OF SURGICAL AND MULTIMODAL TREATMENT TACTICS FOR MUSCLE-INVASIVE BLADDER CANCER

Specialty: 3224.01 – "Oncology"

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## Relevance of the Research

According to the World Health Organization (WHO), bladder cancer (BC) accounts for 3.1% of all oncological diseases and 40–50% of malignant neoplasms of the urinary system. In 2022, approximately 614,000 new cases of BC were registered worldwide, and over 220,000 people died from this pathology.[1] In the structure of oncological morbidity of the urinary system in the population of the Republic of Azerbaijan, BC ranks first among men and second among women. According to the cancer registry of the Republic of Azerbaijan, in 2020 the incidence of BC regardless of sex was 2.9 per 100,000 population, with a lethality rate of 21% and a mortality rate of 0.01 per 100,000 population. Over the past 10 years, there has been a significant increase in the incidence of BC in Azerbaijan. Among men, this indicator has increased by 31%, and among women by 54%.[2,3,4] According to our data, at the time of initial presentation, 64% of patients are diagnosed with superficial tumors (Ta, T1), while 27% of patients are already at stage T2–T3. Another 5% of patients present with clinical stage T4, and in 4% of cases, distant metastases are identified at the time of initial diagnosis. It is known that BC is characterized by a high tendency for recurrence and progression, which classifies it as a highly aggressive disease.

After treatment, disease recurrence develops in 15–50% of cases, among which in 15–20% there is recurrence of the tumor in the pelvic cavity, in 5–13% recurrence in the urethra, and in 10–15 % systemic progression is observed[5]. Such an unpredictable course of the

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[1] Bray, F. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer / F.Bray, J.Ferlay, I.Soerjomataram [et al.] // J Clin., - 2024. v. 74, - p. 229 – 263.

[2] Əliyev, C.Ə. Bəd xassəli şişlərin şua müalicəsi: nəzəri əsasları, tətbiqi, nəticələri / C.Ə.Əliyev, İ.H.İsayev – Bakı, - 2012. - 890 s.

[3] Аксель, Е.М., Матвеев, В.Б. Статистика злокачественных новообразований мочевых и мужских половых органов в России и странах бывшего СССР // Онкоурология, - 2019. т. 15, № 2, - с. 15-24.

[4] Алиев, Д.А., Марданлы, Ф.А., Мусаев, Т.Н. Динамика статистических показателей рака мочевого пузыря в Азербайджане // - Bakı: Azərbaycan onkologiya jurnalı, - 2016. № 2, - с. 9-12.

[5] Heney N.M. // Superficial bladder cancer: progression and recurrence / Ahmed F., Flanagan M.J. et al. // J Urology, 1983, v. 130, p.1083 –1086.

disease necessitates the search for factors that can predict its outcome, as well as enable a personalized approach to choosing treatment tactics for patients with muscle-invasive BC.

The prognosis of the disease, and accordingly the choice of treatment tactics, depends not only on the tumor parameters and the extent of its spread but also on the general health indicators of the patient, the experience of the surgeon and surgical team, and often the specialization of the institution where comprehensive treatment of patients with muscle-invasive bladder cancer (BC) is carried out. The assumption that the experience of the surgeon and surgical team, as well as the specialization of the medical facility treating patients with muscle-invasive BC, is associated with patient prognosis is well-founded. For example, in a study focused on the prognostic factors of non–muscle-invasive BC, it was found that despite the relatively extensive surgical experience in treating superficial BC across all surgeons and the fact that surgeries were performed in a single high-specialization center, the individual experience of the operating surgeon had a significant impact on the risk of recurrence following radical surgical treatment ($p = 0.0013$).[6] No such study has yet been conducted for muscle-invasive BC.

Despite advances in oncology, radiotherapy (RT), cellular and molecular biology, radical cystectomy (RC) remains the cornerstone of treatment for muscle-invasive BC.

In terms of complexity, RC is considered one of the most challenging procedures in oncology. The rate of postoperative complications ranges from 22% to 70%. In this regard, the identification of predictors of complications and the development of strategies for their prevention remain one of the priority areas in oncourology.

The most challenging issue during radical cystectomy (RC) is the selection of the urinary diversion method. Following ureterocutaneostomy (UCS) and ureterosigmoidostomy procedures, approximately 50% of patients die from pyelonephritis and chronic renal

[6] Ролевич А. И. Влияние хирурга на безрецидивную выживаемость пациентов, страдающих раком мочевого пузыря без мышечной инвазии // Ж. Онкоурология, 2016, №2 (12), с. 40 – 52.

failure. These operations do not meet modern quality of life (QoL) standards and often lead to patient disability.

Since the 1950s, particular attention has been given to diverting urine into isolated segments of the gastrointestinal tract. One of the first methods of intestinal urinary diversion is the technique proposed by E.M. Bricker, which is currently considered the gold standard.[7] However, in the quest to preserve QoL and ensure the natural passage of urine through the urethra, various techniques of orthotopic continent urinary diversion (such as ileocystoplasty according to Hautmann and Studer) were developed in the 1980s and 1990s.[8,9]

Orthotopic bladder substitution has become the standard method of bladder reconstruction. The goal of creating orthotopic urinary reservoirs is the maximum medical and social rehabilitation of patients undergoing RC.

This is achieved by forming reservoirs with adequate capacity, low intraluminal pressure, and sufficient protection of the upper urinary tract. In addition to ensuring QoL, another equally important objective of reconstructive procedures following RC is the long-term protection of the upper urinary tract, which is accomplished through the creation of anti-reflux uretero-reservoir anastomoses (URA).

The stages of forming an anti-reflux uretero-reservoir anastomosis (URA) are essentially the most critical aspect of urinary tract reconstruction following radical cystectomy (RC). Virtually all existing techniques for creating anti-reflux URAs share one common drawback–namely, a high rate of strictures and anastomotic failures. Therefore, the development of improved methods for forming orthotopic reservoirs and URAs that minimize these disadvantages is an important goal in modern oncourology.

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[7] Brady, M., Kinn, S., Stuart, P. Preoperative fasting for adults to prevent perioperative complications // Cochrane Database Syst. Rev., - 2003. № 4

[8] Hautmann, R. Urinary diversion: ileal conduit to neobladder // J. Urol., - 2003. v. 169, № 3, - p. 834-838.

[9] Studer, U. Antireflux nipples or afferent tubular segments in 70 patients with ileal low pressure bladder substitutes: long-term results of a prospective randomized trial / U.Studer, H.Danuser, G.Thalmann [et al.] // J. Urology, - 1996. № 4, - p. 1913-1917.

Given the high incidence of early postoperative complications following radical cystectomy, numerous preventive strategies have been investigated. However, the concept of optimizing perioperative patient management, implemented through the ERAS (Enhanced Recovery After Surgery) protocols, has gained the widest acceptance in clinical practice. The primary objectives of these protocols are to accelerate patient rehabilitation and reduce the rate of postoperative complications.[10,11,12]

The ERAS concept is based on the implementation of evidence-based medicine principles and a multidisciplinary approach to perioperative care. The term ERAS was introduced in 2001 to replace the previously used term "fast-track," emphasizing that the strategy was aimed not merely at early patient discharge, but primarily at enhancing functional recovery and accelerating the overall healing process.[13]

The first studies investigating the impact of ERAS protocols on the incidence of early postoperative complications following radical cystictomy have appeared relatively recently. According to the only available meta-analysis evaluating the use of ERAS protocols in radical cystectomy, which included 13 comparative randomized studies comprising 1,493 patients, the rate of postoperative complications in the ERAS group was 39.6%, compared with 51.5% in patients managed with standard perioperative care. Furthermore, the length of hospital stay in the ERAS group was, on average, 5.4 days shorter than in the non-ERAS group.[14]

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[10] Saber A. Urinary Diversion: Historical Aspect and Patient's Satisfaction // Urology and Nephrology Open Access J., - 2014. v. 1, № 3, - p. 86-93

[11] Ortega-Lucea, S., Martínez-Ubieto, J., Júdez-Legaristi, D. The results of implementing a fast-track protocol in radical cystectomy in a tertiary hospital // Acta Urol. Esp., - 2015. v. 39, № 10, - p. 620-627.

[12] McLeod, R., Fitzgerald, W., Sarr, M. Preoperative fasting for adult stop revent perioperative complications // Can. J Surg., - 2005. v. 48, № 5, - p. 409-411.

[13] Ashraf, W. Integrated enhanced recovery after surgery protocol in radicalcystectomy for bladder tumour - A retroprospective study // BJUI Compass, - 2024. v. 5, Issue 11, - p. 1069-1080.

[14] Cerantola, Y. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery society recommendations // Clin Nutr., - 2013. v. 32, № 6, - p. 879-887.

In a study conducted by Australian researchers, the median postoperative hospital stay following radical cystectomy was 7 days in the ERAS group and 12 days in the standard management group ($p = 0.0003$). In addition, the mean time to complete recovery of bowel function after surgery was 5 and 7.5 days in the respective groups ($p = 0.016$).[15]

Overall, according to the available literature data, ERAS protocols contribute to a reduction in the duration of hospitalization and decrease the incidence of early postoperative complications of Clavien–Dindo grades I and II.[16]

In contemporary literature, there is a growing body of work supporting the multimodal organ-preserving approach in the treatment of patients with muscle-invasive bladder cancer (BC).

The selection criteria for multimodal therapy (MMT) in patients with muscle-invasive bladder cancer include disease stage, histologically verified low- or intermediate-grade malignancy, absence of ureterohydronephrosis, multifocal disease, and carcinoma in situ. Patient motivation and compliance are also considered essential selection criteria.[17]

The MMT strategy for patients with muscle-invasive bladder cancer comprises three principal components: surgery, radiotherapy (RT), and concurrent chemotherapy (CT). Surgical management may include either open bladder resection or transurethral resection (TURBT). During radiotherapy, the bladder and regional lymph nodes are irradiated with a total dose of 40–45 Gy, followed by a boost dose up to 60–65 Gy. At the same time, particular attention should be paid to the "organs at risk," which are most susceptible to radiation-induced injury, including the rectum, the femoral head and neck, and the small

[15] Yanada, B. Implementation of the enhanced recovery after surgery protocol for radical cystectomy patients: A single centre experience // Investig. Clin. Urol., - 2024. v. 65, № 1, - p. 32-39.

[16] Tyson, M., Chang, S. Enhanced Recovery Pathways Versus Standard Care After Cystectomy: A Meta-analysis of the Effect on Perioperative Outcomes // J Eur. Urology, - 2016. v. 70, № 6, - p. 995-1003. doi: 10.1016/j.eururo.2016.05.031.

[17] Rodel, C. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results // J Clin. Oncol., - 2002. v. 20, - p. 3061-3071.

intestine. The accepted tolerance doses are as follows: for the rectum – V50 ≤ 60% and V60 ≤ 50%; for the femoral head – V50 ≤ 50%; and for the small intestine – V45 ≤ 25%.

Unlike bimodal therapy, the addition of chemotherapy in MMT exerts a dual effect: firstly, enhancement of radiosensitization, and secondly, cytotoxic activity against micrometastatic disease.[18]

Organ-preserving multimodal therapy offers several advantages: avoidance of extensive surgical intervention, reduced financial burden, preservation of sexual function, decreased risk of chronic infection of the upper urinary tract, and ultimately, improved quality of life (QoL). However, it is important to remember that the primary goal in oncology is to achieve the highest possible survival rates, with QoL being a secondary, albeit important, consideration.[19,20]

As is well known, the success of oncological treatment is determined not only by achieving a durable and long-term therapeutic response, but also by preserving patients' quality of life (QoL).[21] At present, patient survival alone can no longer be considered the sole criterion for evaluating treatment efficacy. In modern oncology, the concept of cure implies not only clinical recovery, but also the patient's return to their previous social and functional status.[22]

In the meta-analysis conducted by Yang L. et al., 29 randomized studies investigating the quality of life of patients after radical cystectomy were analyzed. Based on the FACT and SF-36 questionnaires, the authors assessed the QoL of 3,754 patients with bladder cancer who underwent radical cystectomy. According to the results of the

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[18] Seiwert, T., Salama, J., Vokes, E. The concurrent chemoradiation paradigm – general principles // Nat. Clin. Pract. Oncol., - 2007. № 4, - p. 86-100.

[19] Lee K.S. et al. Hautmann and Studer orthotopic neobladders: a contemporary experience // J. Urol. – 2003. – Vol. 169, № 6. – P. 2188 – 2191.

[20] Карицкий, А.П. Реабилитация онколгического больного как основа повышения качества жизни // Вопросы онкологии, - 2015. № 2, - с. 180-184.

[21] Галкина, Г.Н. Качество жизни после цистэктомии с различными способами отведения мочи // Журнал Медицинские науки. Клиническая медицина, - 2007. № 4, - с. 77-84.

[22] Семиглазова, Т.Ю., Ткаченко, Г.А., Чулкова, В.А. Психологические аспекты лечения онкологических больных // Злокачественные опухоли, - 2016. № 4s1, - с. 54-58.

meta-analysis, no statistically significant differences in overall QoL parameters were identified between patients who underwent urinary diversion according to the Bricker technique and those who received an orthotopic neobladder reconstruction ($p = 0.31$). However, it is important to note that patients following Bricker diversion demonstrated higher levels of physical functioning ($p = 0.002$) compared with patients after orthotopic reconstruction. In contrast, emotional well-being scores were higher among patients who underwent orthotopic urinary diversion ($p = 0.003$). The authors also noted that quality-of-life indicators improve gradually and reach their maximum approximately one year after surgery. Data regarding long-term QoL outcomes beyond this period remain insufficient.[23]

In another meta-analysis, a comparative assessment of quality of life was also performed between patients who underwent Bricker urinary diversion and those who received an orthotopic ileal neobladder. No substantial differences between the groups were observed according to the modular questionnaire scores. However, statistically significant differences related to urinary diversion outcomes were identified in favor of patients after the Bricker procedure ($p = 0.0001$).[24]

Similarly, a meta-analysis including 18 randomized studies did not demonstrate statistically significant differences between the two groups overall. Nevertheless, better quality-of-life outcomes were reported among patients who underwent orthotopic urinary diversion. The most pronounced advantages were observed in social adaptation and psycho-emotional well-being, whereas no significant differences in physical activity were identified between the groups.[25]

In 2021, Kotov S. published the results of a study demonstrating that preliminary data favored orthotopic continent urinary diversion in

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[23] Yang L. A systematic review and meta-analysis of quality of life outcomes after radical cystectomy for bladder cancer // Surg. Oncol., - 2016. v. 25, № 3, - p. 281-297.

[24] Goldberg, H. Orthotopic neobladder vs. ileal conduit urinary diversion: A long-term quality-of-life comparison / // Urol. Oncol., - 2016. v. 34, - p. 121

[25] Cerruto, M. Systematic review and meta-analysis of non RCT's on health related quality of life after radical cystectomy using validated questionnaires: Better results with orthotopic neobladder versus ileal conduit // Eur. J Surg. Oncol., - 2016. v. 42, № 3, - p. 343-360

nearly all domains of the QLQ-BLM30 modular questionnaire.[26] Across all studies, the authors emphasized that more detailed and accurate assessment of quality-of-life outcomes requires long-term investigations involving larger cohorts of bladder cancer patients who underwent radical cystectomy with intestinal urinary diversion.

Thus, the aforementioned findings allow the following conclusions to be drawn:

1. Radical cystectomy (RC) remains the cornerstone of treatment for muscle-invasive bladder cancer (MIBC). Following bladder removal, urinary diversion becomes a critical and highly relevant issue in selecting the optimal reconstructive approach. Although ureterocutaneostomy (UCS) is considered the safest method of urinary diversion, more than 50% of patients develop ascending urinary tract infection leading to pyelonephritis and subsequent chronic renal failure. In addition, UCS is regarded as a disabling procedure that does not meet current standards of functional rehabilitation and quality of life.

2. The high incidence of early postoperative complications following intestinal urinary diversion often limits the widespread adoption of these procedures. With the introduction of ERAS protocols into clinical practice, aimed at preventing postoperative complications, the overall complication rate has decreased. However, this reduction has mainly been attributed to a decline in Clavien–Dindo grade I and II complications, whereas the incidence of severe complications and postoperative mortality has remained unchanged.

3. Currently, two principal approaches to urinary diversion are used: incontinent heterotopic diversion (Bricker procedure) and continent orthotopic diversion in its various modifications. The majority of published studies have focused on individual urinary diversion techniques, while comparative analyses evaluating the impact of different diversion methods on long-term oncological and functional outcomes remain incomplete.

[26] Котов, С.В. Анализ качества жизни пациентов после радикальной цистэктомии с формированием ортотопического необладдера или илеокондуита // Вестник урологии, - 2021. т. 9, № 1, - с. 47-55.

4. At present, the influence of the extent of pelvic lymphadenectomy and the number of metastatic lymph nodes on survival outcomes in patients with muscle-invasive bladder cancer has not yet been fully established.

5. The extensive nature of radical cystectomy frequently limits its application in patients with significant comorbidity burden, which has contributed to the growing interest in trimodal therapy (TMT) for muscle-invasive bladder cancer. The outcomes of TMT appear comparable to those of radical cystectomy; however, clear criteria for selecting patients for one therapeutic approach versus another have yet to be definitively established.

Thus, the optimization of surgical treatment strategies, improvement of perioperative patient management, and development and implementation of new protocols aimed at preventing complications remain highly relevant directions in the comprehensive management of muscle-invasive bladder cancer.

All the above formed the rationale for conducting the present study.

**Aim of the Study**. To improve the effectiveness of treatment in patients with muscle-invasive bladder cancer (BC) by developing surgical intervention methods, enhancing perioperative management strategies, and individualizing treatment planning based on prognostic factors.

## Objectives of the Research

1. To examine the frequency and nature of complications associated with surgical and multimodal treatment methods in patients with muscle-invasive BC.

2. To develop a new method for forming orthotopic reservoirs and uretero-reservoir anastomoses and to evaluate their effectiveness.

3. To identify and analyze prognostic factors for survival in patients with muscle-invasive BC.

4. To develop a method for predicting the risk of disease recurrence (recurrence-free survival, RFS) in patients with muscle-invasive BC after radical cystectomy (RC).

5. To conduct a comparative assessment of survival outcomes of surgical and multimodal treatment methods in patients with muscle-invasive BC.

6. To provide a comparative evaluation of quality of life (QOL) in patients with muscle-invasive BC after RC.

7. To develop a treatment strategy for muscle-invasive BC.

## Key Propositions Submitted for Defense

1. The developed method of ureteral implantation into blind pouches of the reservoir during the formation of an orthotopic continent urinary reservoir after RC significantly reduces the incidence of URA failure and infectious-inflammatory complications in the early postoperative period. It also decreases the frequency of urine reflux into the upper urinary tract and the long-term development of URA strictures. The use of the developed urinary diversion method leads to high levels of quality of life (QoL) and improves the five-year overall survival (OS) rates in patients with bladder cancer (BC) compared to ureterocutaneostomy (UCS) and the Bricker procedure.

2. The immediate effect of implementing an optimized enhanced recovery protocol after RC is significantly higher compared to the standard management approach during the early postoperative period.

3. The developed multivariate prognostic model for calculating the absolute risk of disease recurrence (local recurrence, progression, death from the underlying disease) and recurrence-free survival (RFS) in patients with muscle-invasive BC after RC–which includes predictors such as the extent of local tumor spread, lymph node involvement, Charlson Comorbidity Index (CCI), histological tumor type, and the experience of the surgical team–allows for a reliable calculation of recurrence risk and RFS using a mathematical formula and graphical nomogram.

4. The study of statistical correlations between treatment outcomes and prognostic factors in patients with muscle-invasive BC has enabled the development and justification of clinical indications for surgical and multimodal treatment approaches.

## Scientific Novelty of the Study

The scientific novelty of the study lies in a new approach to the treatment of patients with muscle-invasive BC, incorporating improved surgical techniques, the development and implementation of postoperative management protocols, and treatment planning based on

individualized prognostic assessment.

The scientific substantiation and development of a new method for orthotopic reservoir creation expands the indications for performing orthotopic reconstruction after RC. The newly developed method of tunneled ureteral implantation into the constructed "pouches" of the reservoir significantly reduces the incidence of uretero-reservoir anastomosis (URA) failure.

The developed mathematical model for assessing the risk of disease recurrence makes it possible to determine the individual long-term prognosis of treatment outcomes based on factors related to the patient, the disease, and the treatment approach.

Based on the conducted research, clinical indications for selecting surgical and multimodal treatment strategies have been scientifically justified. A detailed assessment of quality of life (QoL) after RC was carried out using the functional and symptom scales of the QLQ-C30 questionnaire and its bladder cancer-specific module BLM-30, analyzing their dependence on demographic, clinical, and therapeutic factors.

**Practical Significance of the Study**

The newly developed method of orthotopic ileoplasty (IP) has been shown to significantly improve both immediate and long-term outcomes of radical surgical treatment in patients with muscle-invasive bladder cancer (MIBC). The implementation of the modified surgical technique and an optimized perioperative management protocol focused on enhanced recovery allows for a reduction in complications during both early and late postoperative periods, decreases operative time, and shortens the length of hospital stay following RC.

The prognostic factors identified in patients with MIBC and the mathematical model developed on their basis for predicting long-term outcomes enabled the creation and implementation of clear recommendations for choosing treatment strategies in MIBC. Applying these findings in clinical practice by oncologists and urologists will improve patient selection for specific treatment modalities and aid in planning adjuvant therapy, thereby increasing the survival of patients with bladder cancer.

The results of this study can be used in the development of edu-

cational and methodological materials and integrated into the curriculum of oncology and urology departments.

## Thesis Approbation

The main provisions and findings of the scientific research were presented at 18 different congresses, symposia, conventions, and conferences held both in Azerbaijan and abroad in Russia, Belarus, Ukraine, Georgia, and Spain between 2014 and 2023. The preliminary discussion of the dissertation was held at the interdepartmental conference of the departments of the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan (April 4, 2025, Protocol No. 1), and at the Scientific Seminar of the BED 1.02 One-Time Dissertation Council of the National Oncology Center (May 8, 2026, Protocol No. 1).

A total of 48 scientific publications were prepared based on the research materials. Of these, 15 articles and 6 abstracts were published in Azerbaijan, and 7 articles and 20 abstracts in international journals.

## Implementation in Clinical Practice

The newly developed orthotopic IP (ileoplasty) method involving the creation of URA (uretero-reservoir anastomoses) has been patented (Patent Application Az-Patent №. 2018/035 dated 26.09.2018; Eurasian Patent №037515 – "Method of Orthotopic Ileocystoplasty in Patients with Bladder Cancer" dated 07.04.2021) and implemented in the clinical practice of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan, the Republican Scientific and Practical Center for Oncology and Medical Radiology of Belarus, and the National Center of Urology of Georgia.

The dissertation was carried out at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

## Structure and Volume of the Dissertation

The dissertation is presented in 305 pages (380109 characters) and includes the following sections: introduction (12086 characters), literature review (73026 characters), 7 chapters covering materials, methods, and discussion (199724 characters), conclusion (31727

characters), key findings and practical recommendations (4943 characters), reference list (58603 characters), and appendices.

The study is illustrated with 57 figures, 64 tables, and 33 graphs. The reference list includes 302 bibliographic sources, of which 14 are by domestic authors and 288 are foreign.

## Materials and Methods of the Study

This study includes data from 359 patients with muscle-invasive bladder cancer (MIBC) who received treatment at the clinic of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan from 2008 to 2017. All patients were divided into two groups: the organ-removal group – the radical surgical treatment group, and the organ-preserving group – the multimodal therapy (MMT) group. The radical surgical treatment group consisted of 257 consecutively performed radical cystectomies (RC) with various methods of urinary diversion. The volume of cystectomy, according to generally accepted principles of radicalism, included removal of the bladder (UB) along with the adjacent peritoneum and perivesical tissue, seminal vesicles and prostate gland in men, uterus with appendages and anterior vaginal wall in women. In 246 (95%) cases, the operation was accompanied by pelvic lymphadenectomy (LAE). The boundaries of standard pelvic LAE were: upper – the upper third of the common iliac artery, lateral – the genitofemoral nerve, lower – the obturator fossa; also, presacral and lymph nodes along the internal iliac vessels were removed.

Bricker's operation (E. Bricker) was performed in 58 (22.6%) patients. Hautmann’s ileocystoplasty – in 121 (47.1%) cases. For the remaining 78 (30.3%) patients, ureterocutaneostomy (UCS) was performed as a method of urinary diversion. This method was mainly used in weakened patients with a high surgical risk.

Since 2014, as part of this study, an ERAS protocol aimed at accelerated recovery of patients after RC has been optimized and implemented into clinical practice at the Department of Onco-Urology of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The organ-preserving MMT group consisted of 102 (100%) patients with muscle-invasive bladder cancer (MIBC) stages II–IV without distant metastases, including 88 (86.3%) men and 14 (13.7%) women.

All patients underwent comprehensive treatment between 2008 and 2018. At the first stage of multimodal therapy, surgical intervention was performed. After 3 weeks, a follow-up cystoscopy with biopsy from the tumor bed was conducted. In the absence of residual tumor tissue, chemoradiotherapy was administered. Radiation therapy was carried out using 3D planning on a Clinac 2300/CD linear electron accelerator (Varian Medical Systems, USA) with photon beam energies of 6–15 MeV.

After completion of therapy, cystoscopy was recommended every 3 months for the first 2 years, and contrast-enhanced thoracoabdominal CT scans every 6 months. In 37 cases where no effect was observed during follow-up examinations, salvage cystectomy was performed.

To assess health-related quality of life (QoL), a specific questionnaire for oncology patients QLQ-C30 v.3.0 and the specialized module for muscle-invasive bladder cancer QLQ-BLM30 were used, developed by the European Organization for Research and Treatment of Cancer (EORTC, https://www.eortc.org). After processing patient responses according to EORTC guidelines, 22 scales were generated: a multi-item global health status scale, 6 functional scales, and 15 symptom scales. Standardization of responses and conversion to point-based scales were carried out using linear transformation. As a result, all scores were presented on a 0–100 scale: higher scores on functional scales indicated better functioning, while higher scores on symptom scales reflected more pronounced symptoms and problems.

The presentation of data and statistical analysis was carried out in accordance with the requirements for biomedical research.

Comparison of two groups on quantitative variables that did not follow a normal distribution was performed using the non-parametric Mann–Whitney test. Comparison among three groups was done using the non-parametric Kruskal–Wallis test. Comparisons of two or more groups on qualitative variables were conducted using Pearson's $\chi^2$ test,

and for binary variables (2×2 contingency tables), the $\chi^2$ test with Yates correction or Fisher's exact test was applied according to the applicability conditions (if any expected frequency in a cell was less than 5).

To evaluate long-term treatment outcomes, the following metrics were calculated: overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS), using the Kaplan–Meier method. In calculating RFS, an event was considered as the occurrence of local recurrence, distant metastases, or death from the primary disease without previously diagnosed recurrence. Differences in survival were assessed using the generalized $\chi^2$ test and the log-rank test.

To analyze the prognostic factors for the development of complications, binary logistic regression was used to calculate odds ratios (OR), 95% confidence intervals (CI) for ORs, and the statistical significance of the differences in odds.

To identify risk factors for disease recurrence, both univariate and multivariate Cox proportional hazards regression analyses were used. Hazard ratios (HR), 95% confidence intervals for HRs, and significance levels of the risk differences were calculated. Based on the coefficients of the developed multivariate mathematical model, a nomogram for predicting RFS was constructed. In a broad sense, a nomogram is a graphical representation of a mathematical relationship. In our study, the nomogram was developed following the general format proposed by M.W. Kattan, which is widely used in oncology. The accuracy of the prognostic model was evaluated using the concordance index (c-index), which equals the area under the receiver operating characteristic (ROC) curve (AUC), calculated via ROC analysis.

In all cases, differences were considered statistically significant at a p-value of less than 0.05. All p-values were two-sided. Calculations were performed using the software packages Statistica 10.0, SPSS v23.0, and the Python programming environment.

## Research Results

The outcomes of the conducted treatments were assessed based on the frequency of complications, survival indicators, and quality of life (QoL). Identifying predictors of complications, developing methods for their prevention, predicting disease recurrence, and improving

QoL indicators are among the top priorities of modern oncology.

In order to increase the effectiveness of treatment for patients with muscle-invasive bladder cancer (MIBC), we developed and implemented in clinical practice a new method for forming an orthotopic continent ileal reservoir and optimized the perioperative management strategy for patients who underwent radical cystectomy (RC). A treatment strategy for MIBC was developed based on the analysis of the outcomes of surgical and multimodal treatment methods, QoL after RC, and a method for predicting recurrence risk (RFS) post-RC.

In the group of 257 (100%) patients who underwent RC, intraoperative mortality was 0.4% (n = 1), and the frequency of intraoperative complications was 13.2% (n = 34). The most common intraoperative complications included bleeding from the dorsal venous complex and major vessels, trauma to the rectum and obturator nerve, as well as intestinal wall necrosis. The average blood loss was 597 ml (ranging from 100 to 2500 ml), and the mean volume of intraoperative blood transfusion was 950 ml. In the early postoperative period, the average volume of blood transfusion was 310 ml. The main risk factors for bleeding from the dorsal venous complex were body mass index (BMI) and surgeon experience ($p = 0.001$ and $p = 0.004$, respectively). A statistically significant relationship was also established between the frequency of injuries to major vessels and surgeon experience ($p = 0.028$), as well as the presence of metastatically affected lymph nodes – N+ ($p = 0.033$).

In 4 cases (1.6%), during pelvic lymphadenectomy (LAE), complete transection of the obturator nerve was recorded; its continuity was restored by suturing the ends. Although no statistically significant association was found with any of the analyzed factors ($p > 0.05$), it should be noted that all obturator nerve injuries occurred during the first 100 surgeries performed.

Rectal injury was also recorded in 4 cases (1.6%). When analyzing the predictors of this complication, only one factor was statistically significant – pT4 stage ($p = 0.028$).

The main predictors of intraoperative complications in this study were surgeon experience (fewer than 50 operations), high BMI ($p = 0.001$), and local tumor spread at pT3–pT4 stages ($p = 0.02$). The analysis results

allow us to present the following practical recommendations: to reduce the number of intraoperative complications during RC, patients with elevated BMI and/or locally advanced disease should be operated on by the most experienced surgeons. This approach will help minimize intraoperative complications, ensure faster recovery, and shorten the length of hospital stay after RC.

In the cohort of 257 BC (bladder cancer) patients who underwent radical cystectomy (RC) with various urinary diversion methods, 191 complications were recorded within a 30-day period in 112 (43.6%) patients. Of these, 66 (25.7%) experienced only one complication, 38 (14.8%) had 2–3 complications, and 8 (3.1%) had four or more complications. Severe complications (grades 3–5 according to the Clavien-Dindo classification) were observed in 48 (18.7%) patients, of whom 12 (4.7%) died as a result.

Grade I and II complications were the most frequently observed postoperative adverse events.

Within the structure of grade I complications, prolonged lymphorrhea was the most common finding, with the initial daily lymphatic drainage volume reaching up to 800 mL. In 6 (2.3%) cases, persistent lymphorrhea resulted in the formation of lymphoceles, 4 of which subsequently led to deep vein thrombosis (DVT) of the lower extremities. It should be noted that in 1 (0.4%) case, DVT secondary to lymphocele formation resulted in pulmonary embolism with a subsequent fatal outcome.

Among grade II complications, urinary tract infections (UTIs) predominated, including cases progressing to septic shock. Considering that the majority of patients, prior to admission to the urology department of the National Center of Oncology, had undergone bladder catheterization and bladder irrigation for gross hematuria, outpatient cystoscopy, as well as transurethral resection of the bladder in other institutions, the likelihood of pre-existing urinary infection was high. In order to detect urinary infection preoperatively, most patients underwent urine culture with antibiotic susceptibility testing. However, due to certain circumstances, bacteriological urine analysis was not performed in 77 (30%) patients.

Analysis of causal relationships demonstrated that the absence

of bacteriological testing mainly corresponded to the early period of implementation of radical cystectomy at the institution and correlated with the total number of procedures performed. A similar correlation was observed regarding the incidence of infectious urinary tract complications. Thus, a direct relationship was identified between the reduction in urinary tract infection rates and the increasing surgical experience of the operating team.

Negative urine cultures were identified in 98 (38.1%) patients, whereas bacteriuria caused by various microorganisms was detected in 82 (31.9%) patients. The second most common category of grade II complications consisted of gastrointestinal atony (n = 20), including gastric atony in 5 (1.9%) patients and paralytic ileus in 15 (5.8%) patients. Importantly, none of these complications required reoperation.

According to the method of urinary diversion, patients who developed gastrointestinal atony were distributed as follows: 6 (2.3%) cases were observed in patients after Hautmann ileocystoplasty, 5 (1.9%) cases occurred in patients who underwent Bricker urinary diversion, and the incidence of gastrointestinal atony among patients subjected to ureterocutaneostomy was 3.5% (n = 9).

Gastrointestinal atony was diagnosed based on both clinical and radiological findings. Upon manifestation of symptoms suggestive of atony, nasogastric intubation was performed along with stimulation of intestinal motility using anticholinesterase agents. In cases of insufficient therapeutic response, patients received indirect-acting muscarinic and nicotinic cholinomimetic agents (Ubretid). Objective assessment of treatment efficacy was performed radiologically following oral administration of a barium contrast solution.

It is important to note that among all 20 patients in whom gastrointestinal atony was observed, only 6 (2.3%) cases were attributable to surgical complications, including neobladder leakage in 1 case, neobladder–urethral anastomotic leakage in 2 cases, and ureteroenteric anastomotic leakage in 3 cases. Notably, neobladder suture insufficiency necessitated relaparotomy.

The influence of the urinary diversion method on the incidence of gastrointestinal atony was also evaluated. The analysis demonstrated a comparable distribution of gastrointestinal atony between

patients who underwent intestinal urinary diversion and those subjected to ureterocutaneostomy. Specifically, gastrointestinal atony was documented in 11 (4.3%) patients with ileal urinary diversion and in 9 (3.5%) patients after ureterocutaneostomy.

In addition, the impact of the anesthesia technique on the incidence and characteristics of gastrointestinal atony was assessed. Of the 20 (7.8%) patients who developed gastrointestinal atony, 15 (5.8%) underwent surgery under general anesthesia, whereas in the remaining 5 (1.9%) cases, radical cystectomy was performed under combined anesthesia. The distribution of patients according to the duration of gastrointestinal atony, depending on the type of anesthesia and surgical approach, is presented in Table 1.

**Table 1**

**Incidence and Duration of Gastrointestinal Atony According to Surgical Approach and Type of Anesthesia**

| Surgical Approach and Type of Anesthesia | GI atony No/yes (days) | | | | Total |
|---|---|---|---|---|---|
| | No GI Atony | GI Atony <5 Days | GI Atony 5–8 Days | GI Atony >8 Days | |
| Combined anesthesia + extraperitoneal approach | 59 (22,9%) | 1 (0,4%) | 1 (0,4%) | - | 2 (0,8%) |
| General anesthesia + extraperitoneal approach | 17 (6,7%) | - | 2 (0,8%) | - | 2 (0,8%) |
| Combined anesthesia + transabdominal approach | 136 (52,9%) | 2 (0,8%) | 1 (0,4%) | 2 (0,8%) | 5 (1,9%) |
| General anesthesia + transabdominal approach | 25 (9,7%) | 3 (1,2%) | 3 (1,2%) | 5 (1,9%) | 11 (4,3%) |
| Total | 237 (92,2%) | 6 (2,3%) | 7 (2,7%) | 7 (2,7%) | 20 (7,8%) |

The data presented in Table 1 demonstrate that the most effective strategy associated with the lowest incidence of gastrointestinal atony was the combination of an extraperitoneal bladder removal

approach performed under combined anesthesia. In addition, patients managed with the extraperitoneal approach exhibited the shortest duration of gastrointestinal atony. It is important to note that the method of urinary diversion did not have a significant impact on either the incidence or the duration of gastrointestinal paresis. The distribution of patients with gastrointestinal atony among the urinary diversion groups was nearly identical. Univariate analysis demonstrated that the duration of gastrointestinal atony was significantly influenced by the type of anesthesia, whereas the incidence of atony was primarily associated with the surgical approach.

Within the structure of grade III complications, a total of 38 adverse events were recorded, including 12 grade IIIa and 26 grade IIIb complications. All 12 grade IIIa complications were managed under local anesthesia in the interventional radiology department, with the exception of cases requiring wound suturing and surgical debridement of pressure ulcers.

Among grade IIIb complications, several cases deserve particular attention. In 2 (0.8%) patients with enteroenteric anastomotic leakage and in 1 (0.4%) patient with leakage of the sigmoid colon anastomosis following its resection due to locally advanced tumor spread, relaparotomy was completed with the creation of an ileostomy and colostomy, respectively. All three stomas were subsequently reversed within a period ranging from 3 to 6 months.

Among complications associated with intestinal reservoirs, the following were observed: all cases of ureteroenteric anastomotic leakage (n = 6) were managed surgically by ureteral reimplantation into the posterior or lateral wall of the reservoir. It should be emphasized that this complication was observed exclusively in patients who underwent orthotopic ileocystoplasty. In 1 case, leakage of the anterior wall sutures of the orthotopic reservoir was documented and successfully corrected by resuturing. In another case, necrosis of the ileal conduit following the Bricker procedure was identified on postoperative day 7. The necrotic bowel segment was resected, and bilateral ureterocutaneostomy was performed.

Among the 10 reoperations performed for eventration, one resulted in a fatal outcome caused by acute coronary insufficiency.

Reoperation for intra-abdominal bleeding, which was attributed to diffuse hemorrhage from the pelvic floor, was completed with pelvic tamponade.

Of particular interest, in our opinion, was a case of strangulation of a small bowel segment within the inguinal ring on postoperative day 6 following radical cystectomy with ureterocutaneostomy. The patient underwent relaparotomy, resection of the necrotic bowel segment with restoration of intestinal continuity, and alloplastic repair of the inguinal canal.

All remaining grade IIIb complications were managed with the appropriate standard surgical interventions.

Among severe complications, 30 grade IV complications were recorded, including 21 grade IVa and 9 grade IVb complications. Within the structure of grade IVa complications, there were 8 cases of infectious and inflammatory processes, 6 cardiovascular complications, 4 gastrointestinal complications, 2 respiratory complications, and 1 complication involving the central nervous system. All 9 grade IVb complications resulted in the development of multiple organ failure.

Early postoperative mortality (grade V complications) was 4.66% (n = 12). The cause of death in 3 (1.2%) patients during the early postoperative period was acute coronary insufficiency. It is important to note that all patients underwent preoperative transthoracic echocardiography and cardiology consultation. All three patients had a concomitant diagnosis of chronic ischemic heart disease, and their cardiac risk was assessed as moderate. Following appropriate preoperative preparation, radical cystectomy with ileal urinary diversion was performed.

In 1 (0.4%) case, acute coronary insufficiency developed as a consequence of intraoperative blood loss, whereas in the remaining 2 cases it resulted from exacerbation of pre-existing chronic cardiovascular disease triggered by surgical and anesthetic stress. In all three cases, acute myocardial infarction of varying localization was diagnosed and confirmed clinically, as well as by electrocardiography, echocardiography, and laboratory findings.

The cause of death in 1 patient was pulmonary edema that developed in the setting of septic shock accompanied by acute renal

failure. In another patient, sepsis resulted in fulminant multiple organ failure, which led to a fatal outcome.

Particular attention was devoted to evaluating the incidence of complications depending on the method of urinary diversion. It was established that the increased surgical complexity associated with different urinary diversion techniques did not result in a statistically significant increase in the overall complication rate. The number of patients who developed complications after ureterocutaneostomy and intestinal urinary diversion was nearly identical, as presented in Table 2.

**Table 2**

**Association Between the Incidence of Postoperative Complications, Mortality, and the Method of Urinary Diversion**

| Parameter | Ureterocutaneostomy (n = 78) | Ileocystoplasty (n = 121) | Bricker Procedure (n = 58) | Total (n = 257) | p-value |
|---|---|---|---|---|---|
| Total number of patients with complications | 34 (43.6%) | 50 (41.3%) | 27 (46.6%) | 111 (43.2%) | 0.80 |
| Reoperations due to complications (Grade III) | 12 (15.4%) | 14 (11.6%) | 8 (13.8%) | 34 (13.2%) | 0.73 |
| Mortality (30 days) | 6 (7.7%) | 5 (4.1%) | 1 (1.7%) | 12 (4.7%) | 0.25 |

To identify predictors of early postoperative complications, univariate and multivariate analyses were conducted. It was found that the risk of any complication was statistically significantly associated with increased age (OR 1.51; 95% CI 1.05–2.18; p = 0.028), high or low body mass index (p = 0.003), elevated Charlson comorbidity index (CCI) (p = 0.025), a positive preoperative urine culture (OR 3.2; 95% CI 1.73–5.92; p = 0.0002), higher clinical local tumor stage (OR 2.95; 95% CI 1.34–6.51; p = 0.007), earlier operation period (OR 0.85; 95% CI 0.77–0.94; p = 0.001), fewer RCs performed by the surgeon (OR 6.02; 95% CI 1.59–22.8; p = 0.008), and increased blood loss (OR

1.07; 95% CI 1.0–1.13; p = 0.038). Borderline significance was noted for factors such as the identity of the surgeon and operation duration.

As for the risk of severe complications, the same factors were statistically significant except for the cT category, operation duration, and blood loss.

According to multivariate analysis, independent predictors of any postoperative complications included local tumor spread cT4 (OR 4.52; 95% CI 1.74–11.7; p = 0.002), age (a 10-year increase in age corresponded to an OR of 1.87; 95% CI 1.12–3.13; p = 0.017), a positive urine culture (OR 2.16; 95% CI 1.08–4.34; p = 0.032), and a small number of surgeries performed by the surgeon (each additional 10 RCs reduced the OR to 0.89; 95% CI 0.80–0.99; p = 0.038). Severe postoperative complications were associated with a positive urine culture (OR 4.05; 95% CI 1.68–9.78; p = 0.002) and age (a 10-year increase corresponded to an OR of 2.44; 95% CI 1.21–4.89; p = 0.013).

Thus, the independent factors statistically significantly associated with the risk of complications after RC with pelvic LND were local tumor spread (cT4), a positive preoperative urine culture, and a low number of surgeries performed by the surgeon. The risk of severe complications was associated with a positive urine culture and patient age.

In accordance with the objectives of the study and aiming to reduce the number of complications in the early and late postoperative periods, in 2014 we developed and patented a method of orthotopic IC by creating a new technique of uretero-reservoir anastomosis (Figure 1) (Patent application Az-Patent No. 2018/035 dated 26.09.2018; Eurasian Patent №. 037515 – "Method of orthotopic ileocystoplasty in patients with bladder cancer" dated 07.04.2021).

To form the reservoir, a segment of the ileum 60–65 cm in length is resected at a distance of 20–25 cm from the ileocecal junction. Intestinal continuity is restored by side-to-side ileoileal anastomosis. The isolated segment of the small intestine is rinsed from its contents using a mild betadine solution. The resected segment is incised longitudinally along the antimesenteric border, leaving intact terminal ends approximately 4 cm in length. The unincised terminal segments are sutured with a two-layer stitch, thereby forming blind "pouches" of the reservoir.

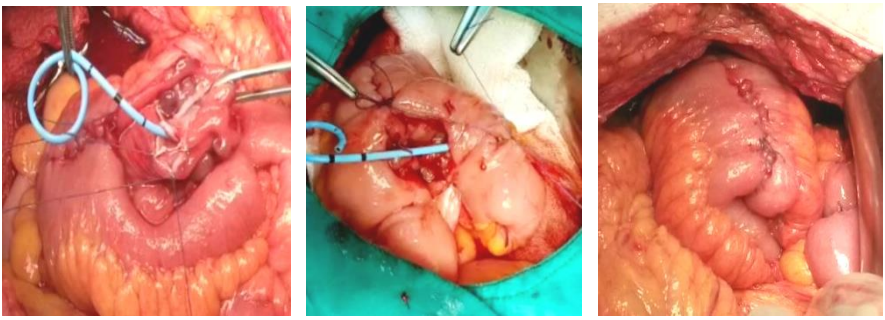

**Figure 1. Stages of uretero-reservoir anastomosis formation**

The detubularized intestinal segment is folded in a W-shape, the adjacent edges of the incisions are sutured with continuous stitches, and then the anterior wall of the reservoir is closed up to the middle. The left ureter is passed through the sigmoid mesentery. The distal ends of the ureters are implanted directly through the posterolateral wall of the blind pouch into the formed reservoir. The anterior wall of the ureter is obliquely incised (spatulated) and secured with single interrupted sutures to the inner surface of the pouch. The ureter is stented with a 6F JJ stent. After forming the anastomosis, the lateral surfaces of the pouch are sutured with 2–3 interrupted stitches in such a way as to wrap the ureter externally. Once the anastomoses are completed, the distal ends of the JJ stents are inserted into the cavity of the formed reservoir, and then the anterior wall of the reservoir is completely closed. After that, the reservoir-to-urethral anastomosis is performed.

The treatment outcomes of 121 (100%) patients with bladder cancer who underwent radical cystectomy with orthotopic ileocystoplasty at the Department of Oncourology of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan between 2008 and 2017 were analyzed.

In order to evaluate the effectiveness of the proposed technique, all patients were divided into two groups. Group I (study group) included 62 (51.2%) patients who, between 2014 and 2017, underwent modified Hautmann ileocystoplasty according to our proposed technique. Group II (control group) consisted of 59 (48.8%) patients. The

control group consisted of patients who underwent orthotopic Hautmann ileocystoplasty between 2008 and 2013. All surgical procedures were performed in accordance with contemporary oncological principles of radicality.

The main criteria used to evaluate the effectiveness of our proposed technique for orthotopic ileal neobladder reconstruction and ureteroenteric anastomosis formation were as follows:

1. Evaluation of the incidence of ureteroenteric anastomotic leakage
2. Evaluation of the incidence of ureteroenteric anastomotic strictures
3. Evaluation of the incidence of urinary reflux
4. Evaluation of the incidence of infectious and inflammatory urinary tract complications

In addition to the above-mentioned criteria, a comparative analysis of the immediate treatment outcomes was also performed.

The minimum follow-up period for all patients was 6 months. The early postoperative period was defined as the first 30 days following radical cystectomy. The incidence of ureteroenteric anastomotic strictures, urinary reflux, and infectious-inflammatory urinary tract complications was assessed during the period from 1 to 6 months postoperatively.

The duration of hospital stay was somewhat shorter in the study group compared with the control group. The mean length of hospitalization in the study group was 18 (SE 0.73; range 3–36) days, whereas in the control group the average hospital stay was 22.2 (SE 1.39; range 1–60) days. Comparative analysis demonstrated a statistically significant difference between the groups ($p = 0.007$).

Analysis of operative duration revealed higher values in the control group compared with the study group. The mean duration of radical cystectomy with modified ileocystoplasty was 269.2 minutes (SE 5.47; range 200–380 minutes). In the control group, the mean operative time was 323.7 minutes (SE 7.23; range 200–430 minutes). Statistical analysis demonstrated a significant difference between the groups ($p < 0.001$). It should be noted that the factor of modified ileocystoplasty also also demonstrated statistically significant results;

however, its impact was less pronounced compared with the influence of surgeon experience ($p < 0.05$).

The mean intraoperative blood loss in the study and control groups was 542.7 mL (SE 42.4; range 150–1800 mL) and 673.7 mL (SE 65.3; range 100–2000 mL), respectively. These findings demonstrated lower blood loss in favor of patients from the study group. However, it is important to emphasize that no direct association was established between the method of urinary diversion and the volume of blood loss ($p = 0.92$).

In the study group, 30-day mortality was 4.8% (n = 3). In the control group, early postoperative mortality was 3.4% (n = 2). In both groups, the causes of death were cardiovascular complications.

Complications were assessed according to the Clavien–Dindo classification. In the group of patients who underwent modified ileocystoplasty, 46 complications were recorded within 30 days after surgery in 24 (38.7%) patients. In the control group, early postoperative complications (n = 40) were observed in 29 (49.2%) patients.

The incidence of ureteroenteric anastomotic leakage in the modified ileocystoplasty group was 1.6% (n = 1), whereas in the control group this parameter reached 8.5% (n = 5). Comparative analysis demonstrated a statistically significant difference in the incidence of ureteroenteric anastomotic leakage between the groups ($p < 0.001$). No repeat surgical interventions for ureteroenteric anastomotic leakage were required in the study group, whereas in the control group 4 patients required reintervention, including 1 relaparotomy and 3 cases of antegrade ureteral stenting.

Within 6 months following modified ileocystoplasty, ureteroenteric anastomotic strictures were identified in 2 (3.2%) patients, compared with 1 (1.7%) patient in the control group.

During retrograde cystography in both groups, the volume of the constructed reservoir and the incidence of vesicoureteral reflux during tight retrograde filling were assessed. Regardless of the reservoir construction technique, retrograde cystography was performed 2 weeks postoperatively prior to urinary catheter removal. The volume of the retrogradely instilled contrast medium was recorded during each examination. The fluid instillation was discontinued upon the patient

experiencing a sensation of reservoir fullness. The mean reservoir volume during retrograde filling in the study and control groups was 135 ml (SE18.3) and 129 ml (SE16.5), respectively.

Vesicoureteral reflux into the upper urinary tract, evaluated radiologically via cystography, was not detected in any cases within the modified IP group. Conversely, urinary reflux was registered in 7 (11.9%) patients in the control group.

As stated above, the incidence of early postoperative infectious-inflammatory complications was 16.1% in the study group and 20.3% in the control group.

The analysis of results demonstrated that the proposed method is effective and technically less complex to perform. The immediate outcomes of radical cystectomy (RC) with the proposed orthotopic ileoplasty (IP) variant were satisfactory. A comparative analysis of the results showed that the modified IP significantly reduced both the number of hospital bed days and the rate of complications. The duration of surgery was also shortened due to the reduced time required for the reconstructive stage. Analysis of data concerning the incidence of anastomotic leakage and uretero-reservoir strictures demonstrated positive results in favor of the modified IP ($p = 0.003$). Among patients who underwent IP using our proposed method, no cases of urinary reflux into the upper urinary tract were registered, whereas in the control group, the reflux rate was 12%. Analysis of urinary tract infection rates also showed favorable results in the study group.

Thus, the proposed method of ileoplasty (IP) is technically less complex and safer to perform. The obtained results show that the modified IP significantly improves immediate outcomes, which justifies its implementation in clinical practice.

The second approach aimed at preventing early postoperative complications was the improvement of patient management strategy during the perioperative period.

Since 2014, optimized ERAS protocols have been implemented in the clinical practice of the Department of Oncourology of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (NCO MoH AR). The scheme developed based on ERAS

protocols includes 8 items of preoperative preparation, 2 intraoperative components, and 7 items for early postoperative management (Table 3).

**Table 3**

**Patient perioperative management and optimization protocol**

| Phase | Recommendations / Interventions |
|---|---|
| **Diagnostic workup** | 1. Standard of care guidelines<br>2. Optional/Additional: FEGDS*, Echocardiography**, urine culture and susceptibility testing |
| **Preoperative period** | 1. Patient education and counseling<br>2. No prolonged fasting<br>3. No routine mechanical bowel preparation (MBP)<br>4. Microenemas 12 hours prior to surgery<br>5. Preoperative fluid and carbohydrate loading<br>6. Combined antibiotic prophylaxis<br>7. Compression stockings 24 hours prior to surgery; subcutaneous administration of anticoagulants 8 hours prior to surgery<br>8. Intravenous proton pump inhibitors (PPIs) 8 hours prior to surgery |
| **Intraoperative period** | 1. Extraperitoneal radical cystectomy (whenever feasible)<br>2. Internal urinary diversion using double-J (JJ) stents |
| **Early postoperative period** | 1. Removal of the nasogastric tube on postoperative day (POD)<br>2. Gum chewing (sham feeding)<br>3. Total parenteral nutrition (TPN) for the first 2 postoperative days<br>4. Early enteral nutrition (partial) starting from POD 1<br>5. Early patient mobilization<br>6. Continuous epidural analgesia<br>7. Urethral catheter removal on POD 11–12*** |

Notes:

* FEGDS – fibroesophagogastroduodenoscopy;

**Echocardiography – transthoracic echocardiography;

*** – specifically for patients undergoing Hautmann ileal neobladder (ileocystoplasty).

Based on the analysis of our own outcomes, we recommend that all patients undergo routine upper endoscopy (gastroscopy), echocardiography, and urine culture and susceptibility testing, regardless of the planned urinary diversion technique. The observed Grade IIIb and IVa complications included two cases of gastrointestinal hemorrhage. Endoscopic evaluation revealed the presence of pre-existing chronic gastric ulcers in these patients. A retrospective analysis demonstrated that both cases occurred during the period when preoperative gastroscopy was not yet routinely performed for all patients. The subsequent implementation of routine screening gastroscopy completely eliminated the occurrence of postoperative gastric bleeding from chronic ulcers.

To evaluate the clinical efficacy of the implemented perioperative management protocol, the study cohort was divided into two distinct groups: Group I comprised 108 (42%) patients managed prior to protocol implementation, and Group II included 149 (58%) patients treated following its introduction (from 2014 onward). The length of hospital stay (LOS), the incidence and specific nature of complications in relation to ERAS protocol adherence, and 30-day mortality rates were comprehensively analyzed and compared between the two groups.

In the group of patients treated after implementation of the optimized ERAS protocol, the average number of hospital bed-days was significantly reduced ($p = 0.004$). Additionally, there was a statistically significant reduction in the frequency of complications of grades I–II ($p = 0.038$) and grades III–IV ($p = 0.041$). A comparative analysis of 30-day mortality rates did not show statistically significant results.

To assess the influence of ERAS protocols on complication rates, predictors such as surgeon experience, BMI, and Charlson Comorbidity Index (CCI) were also studied. The results showed that the use of the optimized ERAS protocol reduces the incidence of early postoperative complications and shortens the number of hospital bed-days to 17 days. It should be noted that the most commonly observed complications (grades I–II) after RC described in the literature are usually consistent across many studies, and the effectiveness of ERAS in reducing their incidence has been proven. However, no study to date

has demonstrated a reduction in the frequency of grade V complications with ERAS protocol use. The causes of these complications are entirely technical in nature.

The analysis of the immediate results of organ-preserving multimodal therapy (MMT) included 102 patients. The frequency and nature of intraoperative and early postoperative complications, toxic manifestations of chemotherapy (CT), as well as complications associated with radiotherapy (RT), were studied. Given that some patients underwent surgery in other clinics, information on intraoperative and early postoperative complications for those patients was unavailable. Among the 77 patients who underwent organ-preserving surgeries at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (NCO MoH AR), intraoperative complications were recorded in 6 cases (7.8%). Of these, in 2 cases (2.6%) during transurethral resection (TUR) of the bladder tumor, perforation of the lateral wall due to obturator nerve reflex was observed. This complication occurred in patients with low body weight. In 1 case, during open resection with pelvic lymphadenectomy (PLND) in a patient with a high BMI (36 kg/m²), complete transection of the obturator nerve was recorded. The nerve was repaired using 3 interrupted sutures. Another case involved intraoperative blood loss of 1300 ml during open resection of a bladder tumor measuring 8 x 7 cm. According to our assessment, this complication was also due to a high BMI (41 kg/m²) and the tumor's location.

During an open resection with ureterocystoneostomy, while mobilizing the left ureter below the bifurcation of the left iliac artery, damage to the internal iliac artery occurred in one case, caused by local tumor spread. In another case, during resection of the bladder floor, the abdominal cavity was opened, and the wall of the small intestine was slightly damaged. The integrity of the intestine was restored using standard interrupted sutures. According to our assessment, this complication resulted from insufficient surgical experience.

Within 30 days after surgery, among the 77 patients operated on at the National Center of Oncology (NCO), 15 complications developed in 12 patients (15.6%). No deaths were recorded in the early postoperative period. The most severe complication was a myocardial

infarction in a 74-year-old patient with severe comorbid cardiovascular pathology. Hematuria was observed in 6 patients (7.8%) after TUR, and in 2 cases (2.6%) it required repeat endoscopic intervention. Among these 6 patients, active irrigation and bladder lavage led to pyelonephritis due to ascending urinary tract infection in 3 cases (3.9%). Lymphorrhea was observed for a prolonged period in 2 patients (2.6%) who underwent open resection with PLND. No repeated interventions were performed due to lymphorrhea .

Thus, the main causes of intraoperative complications were elevated or low BMI, high Charlson Comorbidity Index (CCI), increased depth of tumor invasion, and surgical experience. In our opinion, high CCI and local tumor spread were the main factors contributing to the development of early postoperative complications.

Among the toxic manifestations of chemotherapy (CT), grade III and IV complications were evaluated and observed in 21 patients (20.6%). No deaths related to CT toxicity were recorded.

Among grade III toxic manifestations, hematological (n = 8) and gastrointestinal (n = 10) complications were identified. All 10 cases were managed with conservative therapy. Among grade IV toxicities, 4 complications (3.9%) were recorded. In one case, a patient with severe thrombocytopenia received a transfusion of three doses of platelet mass, followed by conservative inpatient therapy. A persistent dynamic small bowel obstruction became the reason for performing a diagnostic laparotomy. Manifestations of acute liver failure with an increase in transaminases more than 6 times were observed in 1 patient. One patient was diagnosed with a posterior myocardial infarction during chemotherapy.

Among radiation-related systemic reactions, 5 patients (4.9%) experienced complications, which in 4 patients (3.9%) manifested as chronic kidney failure of varying severity, and in 1 patient (0.9%) as moderate neutropenia. No deaths related to chemotherapy were recorded.

In terms of local radiation therapy (RT) reactions, 97 complications of varying severity were observed in 70 patients (68.6%). Among these, 1 complication occurred in 44 patients (43.1%), 2 complications in 22 patients (21.6%), and 3 complications in 3 patients (2.9%).

According to the RTOG classification, grade I radiation reactions were observed in 30 cases: dermatitis (n = 4), cystitis (n = 22), and proctitis (n = 4). Grade II complications were predominantly inflammatory processes in the lower urinary tract – 18 cases (17.6%). There were 9 cases (8.8%) each of dermatitis and proctitis. One patient (0.98%) developed enteritis. Grade III complications were recorded in 23 cases (22.5%). Among them, 5 patients (4.9%) developed dermatitis in the form of moist desquamation and significant skin edema. Cystitis with pronounced symptoms (dysuria, lower abdominal pain, hematuria) developed in 10 patients (9.8%). Scrotal complications occurred in 4 patients (3.9%): epididymitis in 1 and orchitis in 3 cases, all with intense pain. In terms of gastrointestinal tract complications, 1 patient (0.98%) developed acute enteritis with symptoms of partial paralytic intestinal obstruction; 3 patients (2.9%) experienced proctitis with heavy mucous discharge from the rectum and severe pain symptoms.

Severe grade IV complications that led to the termination of radiation therapy (RT) were observed in 7 patients (6.9%). In one case, after 15 RT sessions (total dose 30 Gy), the patient developed skin necrosis. In another patient, after 18 sessions, bleeding and severe pain unrelieved by potent analgesics were noted. In the remaining 5 patients (4.9%), acute urinary retention due to bladder tamponade with blood clots occurred.

Analysis of the immediate results of organ-preserving treatment showed that the risk of developing any complication during multimodal therapy (MMT) was associated with factors such as sex, low body mass index (BMI – underweight), and an increased number of RT sessions. Severe complications were linked to older age and high Charlson comorbidity index (CCI) scores.

In the analysis of long-term treatment outcomes in both groups, the endpoints studied included adjusted survival, overall survival (OS), and recurrence-free survival (RFS).

The long-term outcomes analysis included 238 patients with stage II–IV bladder cancer (BC) without distant metastases, who underwent radical cystectomy (RC) with various urinary diversion methods. The impact of demographic parameters, general health indicators,

laboratory data, urinary diversion methods, tumor process characteristics, and surgical parameters on survival outcomes was evaluated.

The median follow-up time was 93.3 months (ranging from 37.5 to 174.8 months). During the follow-up period, 84 patients (35.3%) died from the primary disease, and 55 patients (23.1%) died from other causes, including 15 patients (6.3%) due to Covid-19. The 5-year RFS before the first clinical event – defined as the occurrence of local recurrence, distant metastases, or death from the primary disease without prior diagnosis of recurrence – was 63.1% (SE 3.2%); the RFS median was not reached. The 5-year adjusted survival was 65.3% (SE 3.2%), with no median reached. The 5-year OS rate was 54.1% (SE 3.2%), with a median OS of 65.7 months.

Statistically significant predictors were identified for each survival indicator.

The main predictors of cancer-specific survival (CSS) in patients with bladder cancer (BC) after radical cystectomy (RC) were the Charlson Comorbidity Index (CCI), the degree of tumor differentiation and local extension, lymph node (LN) involvement, disease stage, and the experience of the surgical team. No statistically or clinically significant associations with CSS were found for the following analyzed variables: sex, age, BMI, ASA risk classification, hemoglobin level, creatinine level, tumor localization, presence of hydronephrosis, histological tumor type, and intraoperative blood loss.

For patients with favorable (≤7 points) and unfavorable (>7 points) CCI scores, the 5-year CSS was 69.4% (SE 3.5%) and 50.8% (SE 7.4%) respectively, with the median not reached in the first group and 54.1 months in the second ($p = 0.003$). Regarding tumor grade ($p = 0.014$), the 5-year CSS was 83.1% (SE 5.8%) for low-grade tumors and 61.5% (SE 3.7%) for high-grade tumors. The degree of local tumor extension had the highest statistical significance ($p < 0.001$) . The 5-year CSS in patients with pT2 tumors was significantly higher than in those with pT3–4 tumors, amounting to 76.9% (SE 3.4%) vs. 47.0% (SE 9.1%) with a median of 51.7 months for pT3 ($p = 0.002$), and 35.8% (SE 7.7%) with a median of 41.0 months for pT4 ($p < 0.001$). CSS between pT3 and pT4 stages did not differ significantly ($p = 0.29$). LN involvement was also a highly significant predictor

($p < 0.001$ when comparing all survival curves simultaneously). In the absence of LN metastases, 5-year CSS was 79.2% (SE 3.1%). For pN1 it was 51.3% (SE 13.3%) with a median of 56.7 months; for pN2 – 4.3% (SE 4.1%) with a median of 24.3 months; and for pN3 – 0.0% (SE 8.3%) with a median of 21.0 months. The differences were statistically significant between all groups ($p < 0.01$), except between pN2 and pN3 ($p = 0.41$). It is noteworthy that all patients with pN3 died from the primary disease.

Given such differences in survival based on local tumor extension and LN involvement, the prognostic value of the overall disease stage was also statistically significant ($p < 0.001$). The 5-year CSS was 86.5% (SE 3.1%) for stage II ($p < 0.001$ compared to stages III and IV), 37.9% (SE 5.1%) for stage III with a median of 41.7 months, and 0.0% for stage IV ($p = 0.12$ compared to stage III).

A statistically significant correlation with cancer-specific survival (CSS) was also found with the experience level of the surgical team. For patients operated on by teams with fewer than 50 surgeries performed, the CSS was significantly lower–41.2% (SE 8.3%) with a median survival of 39.0 months–compared to 73.3% (SE 6.6%) for teams with 50–100 surgeries performed ($p = 0.014$). Further increases in the number of surgeries performed did not have a statistically significant impact on CSS ($p = 0.58$).

The relationship between CSS and urinary diversion methods was analyzed separately. The CSS for patients who underwent the Hautmann procedure (n=116, 48.7%) and the Bricker procedure (n=56, 23.5%) was identical throughout the follow-up period ($p = 0.88$); the 5-year CSS was 70.6% (SE 4.4%) and 71.0% (SE 6.1%) respectively, and the median was not reached in either group. Patients who underwent ureterocutaneostomy (UCS) (n=66, 27.8%) had significantly lower survival rates, with a 5-year CSS of 50.5% (SE 6.0%) and a median of 40.2 months ($p = 0.002$). However, UCS was used in cases that were either salvage procedures or performed due to life-threatening indications. Therefore, patients in the ileoplasty (IP) and UCS groups were not comparable, primarily due to differences in disease stage.

A separate analysis by stage II and III revealed the following: in patients with stage II muscle-invasive bladder cancer, the method of

urinary diversion was the only predictor of CSS ($p = 0.010$), whereas in stage III, the method of urinary diversion did not affect CSS ($p = 0.63$). Specifically, the 5-year CSS in stage II patients who underwent IP was 91.1% (SE 2.5%), with no median reached, compared to 66.1% (SE 1.0%) for those who underwent UCS, also with no median reached. In stage III, the 5-year CSS was 36.4% (SE 6.5%) and 40.6% (SE 8.5%) respectively, with median survival of 42.3 and 34.1 months.

In the analysis of overall survival (OS), it was found that, in addition to all the predictors that had a statistically significant association with CSS, age was also significantly associated with OS. All patients were divided into four age groups: under 50 years, 50–59 years, 60–69 years, and 70 years and older. A comparison of OS across the four groups using the generalized chi-square test revealed statistically significant differences ($p = 0.012$).

In the pairwise comparison of the groups using the Log-Rank test, it was found that the overall survival (OS) rate was statistically significantly lower in the group of patients over 70 years old compared to all other groups ($p < 0.05$). The three younger age groups did not show statistically significant differences in survival among themselves.

In the analysis of comorbidity factors (Charlson Comorbidity Index, CCI), it was established that OS among patients with a CCI score below 7 was 59.5% (SE 3.6%), with a median of 79.5 months, whereas in patients with a CCI score of 7 or more, OS was 35.3% (SE 6.6%), with a median of 38.4 months ($p < 0.001$).

It is known that tumor differentiation grade affects the course and outcome of the disease regardless of tumor location. In our study, high-grade tumors were observed in 80.8% (95% CI: 75.1–85.5%) of cases, while low-grade tumors were four times less frequent—45 out of 238 total cases, accounting for 19.2% (95% CI: 14.5–24.9%). The 5-year OS in patients with low-grade tumors was statistically significantly higher ($p = 0.013$) and amounted to 66.7% (SE 7.0%) with the median not reached, compared to 51.3% (SE 3.6%) and a median of 62.6 months among patients with high-grade tumors.

The factor of local tumor spread had a highly statistically significant impact on OS ($p < 0.001$ when comparing all three survival

curves simultaneously). Thus, the 5-year OS in patients with pT2, pT3, and pT4 tumors was 65.9% (SE 3.8%) with a median of 91.6 months, 32.4% (SE 7.7%) with a median of 40.8 months, and 28.6% (SE 7.0%) with a median of 33.7 months, respectively. Differences between the groups of patients with T2 vs T3 and T2 vs T4 were statistically significant ($p < 0.001$), while the difference between T3 and T4 was not significant ($p = 0.94$).

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With a similarly high level of statistical significance ($p < 0.001$), overall survival (OS) was also influenced by the extent of lymph node (LN) involvement and, quite logically, the disease stage. In the absence of LN metastases (pN0), the 5-year OS was 65.3% (SE 3.5%) with a median of 89.5 months. For pN1, the 5-year OS was 46.7% (SE 12.9%) with a median of 48.3 months. For pN2 and pN3, the 5-year OS was 3.4% (SE 3.9%) and 0.0% (SE 8.3%) respectively, with median survivals of 23.5 and 21.0 months.

Analysis of survival depending on disease stage showed that 5-year OS for stage II was 74.5% (SE 3.8%) with a median of 109.3 months, while for stage III it was 28.7% (SE 4.5%) with a median of 41.7 months ($p < 0.001$). Survival in stage IV patients, which was 0%, differed significantly from that in stage II ($p = 0.016$), but due to the small number of patients in stage IV, no statistically significant difference was found compared to stage III ($p = 0.19$).

The results of analyzing the impact of the surgical team's experience on overall survival were also significant ($p = 0.002$). When fewer than 50 surgeries had been performed, OS was significantly lower—29.5% (SE 6.9%). Performing more than 50 surgeries was associated with improved OS, although further increases in the number of operations did not have a statistically significant impact ($p = 0.77$).

When calculating the association between OS and factors such as sex, BMI, ASA classification, laboratory values, tumor location, presence of hydronephrosis, histological tumor type, and intraoperative blood loss, no statistically significant correlations were found.

One of the key criteria for assessing long-term outcomes, in addition to OS (overall survival) and CSS (cancer-specific survival), is RFS (recurrence-free survival). When calculating RFS, an event was defined as the occurrence of a local recurrence, distant metastases, or death from the primary disease without a previously diagnosed recurrence. Accordingly, RFS is always lower than cancer-specific survival.

As previously noted, the long-term outcome analysis included 238 (100%) patients. Among this cohort, 10 (4.2%) had a local recurrence, 42 (17.6%) showed disease progression, and 3 (1.3%) had both local recurrence and progression. A total of 43 (16.1%) patients died from the primary disease without a diagnosed recurrence. The 5-year

RFS for the entire cohort was 63.1% (SE 3.2%), with the median RFS not reached.

According to our data, the factors associated with RFS in patients with muscle-invasive bladder cancer (MIBC) were: the Charlson comorbidity index (CCI) ($p = 0.006$), tumor grade ($p = 0.017$), tumor local extension ($p < 0.001$), pN category according to the TNM classification ($p < 0.001$), disease stage ($p < 0.001$), and the surgical team's experience (less than or more than 50 surgeries, $p = 0.029$).

The analysis of long-term treatment outcomes in patients with MIBC after radical cystectomy (RC) also allows us to conclude the following: surgical treatment in our study achieved high survival rates. The best results, with 5-year CSS exceeding 80%, were observed in patients with low-grade tumors – 83.1% (SE 5.8%) – and stage II disease – 86.5% (SE 3.1%). Over 75% 5-year CSS was also seen in patients with T2 tumor stage – 76.9% (SE 3.4%) – and no lymph node metastases – 79.2% (SE 3.1%) (Figure 2).

A similar survival analysis was conducted among patients who underwent organ-preserving multimodal therapy (MMT). As previously mentioned, this group consisted of 102 patients with stage II–IV muscle-invasive bladder cancer (MIBC). The median follow-up time was 88.4 months (ranging from 61.6 to 128.4 months).

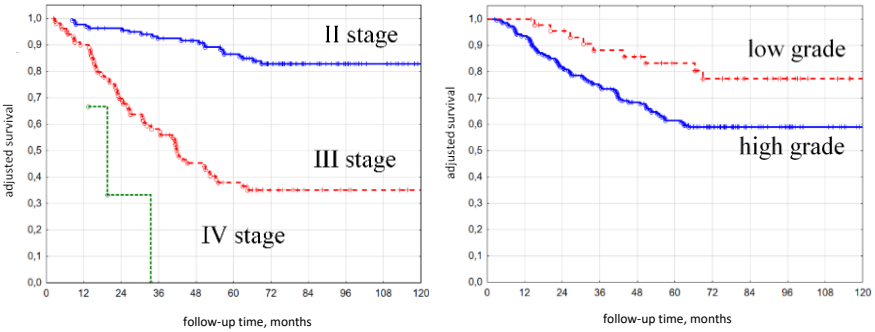


**Figure 2. Cancer-specific survival rates depending on stage and tumor grade**

During the follow-up period, 73 (71.6%) patients died from the primary disease, and 5 (4.9%) patients died from other causes. The

5-year cancer-specific survival (CSS) rate was 33.7% (SE 4.8%), with a median CSS of 43.1 months. The 5-year overall survival (OS) rate was 31.4% (SE 4.6%), with a median OS of 41.3 months.

It is important to note that the survival of patients who received MMT was extremely low. Since fewer than 5% of patients died from causes unrelated to the primary disease, and the 5-year OS and CSS rates differed by only 2.3%, we decided it was not appropriate to analyze both survival types separately by prognostic factors. Instead, we analyzed CSS, which more accurately reflects the outcomes of MMT in MIBC patients.

The influence of the following variables on CSS was studied: sex, age, general health indicators (BMI, Charlson Comorbidity Index, ASA score), laboratory data, local tumor extension, tumor size and location, presence of hydronephrosis, lymph node involvement, and disease stage. The following variables were found to be significantly associated with CSS:

Sex: CSS in women was significantly lower than in men ($p = 0.021$); Age: CSS in patients under 50 was significantly lower than in the 51–60 ($p = 0.030$) and 61–70 ($p = 0.012$) age groups; Tumor size: CSS in patients with tumors less than 3 cm was significantly higher than in those with larger tumors ($p < 0.001$); Local tumor extension: CSS was lower in patients with stage cT3 compared to cT2 ($p = 0.007$) and cT4 ($p = 0.040$); Lymph node involvement: CSS was higher in patients without lymph node metastases ($p = 0.005$).

Based on the obtained data in both groups (radical cystectomy and multimodal therapy), a comparative analysis of long-term treatment outcomes was conducted. The hazard ratio (HR) for death from the primary disease in the MMT group compared to the radical surgical treatment group was 2.37 (95% CI: 1.73–3.25; $p < 0.001$). However, when comparing the MMT and radical surgery groups, it was found that the groups were not comparable across all analyzed variables, including sex, age, Charlson Comorbidity Index (CCI), presence of hydronephrosis, tumor location, and disease stage. To ensure an accurate survival comparison, matched groups were created from the initial cohorts using the Propensity Score Matching (PSM) method. It

was established that in these matched groups, the 5-year cancer-specific survival (CSS) rate in the radical surgery group was twice as high as in the MMT group – 60.4% (SE 6.5%), with median CSS not reached, versus 30.9% (SE 6.8%), with a median of 44.2 months ($p = 0.005$), respectively. Thus, the comparative analysis of long-term treatment outcomes demonstrates the superiority of radical surgical treatment, both in the original patient groups and in the matched cohorts comparable across all studied parameters.

As shown above, the long-term outcomes of MMT cannot be considered satisfactory overall. However, the MMT group is highly heterogeneous: in some cases, MMT was a forced therapeutic measure, while in others, patients categorically refused radical cystectomy (RC). Nevertheless, in our study, it was found that in tumors up to and including 3 cm, cancer-specific survival (CSS) after MMT reached 72% (SE 9.0%), which is comparable to the outcomes of RC.

In further analysis, we excluded from the group of patients with tumors ≤3 cm those with an initially poor prognosis – patients with uretrohydronephrosis, locally advanced tumors (T3–T4), and those with metastatic lymph node involvement. As a result, we formed a favorable prognosis group (n=25), in which the 1-year CSS was 100.0% (SE 4.2%), the 3-year CSS was 85.7% (SE 7.6%), and the 5-year CSS was 76.2% (SE 9.3%), with the median CSS not reached. We then selected patients from the RC group with the same characteristics (n=49) and compared survival outcomes. The 3-year CSS was 84% (SE 5.2%), and the 5-year CSS was 77.8% (SE 6.2%). The difference in 5-year CSS between the multimodal therapy group and the RC group was only 1.6% ($p = 0.799$). The CSS data for both groups are illustrated in Figure 3.

Thus, taking into account the obtained data and the higher quality of life (QoL) resulting from organ preservation, MMT is indicated for patients classified in the favorable prognosis group.

In accordance with the objectives and goals of this study, based on the results obtained, we identified and analyzed the risk factors for disease recurrence.

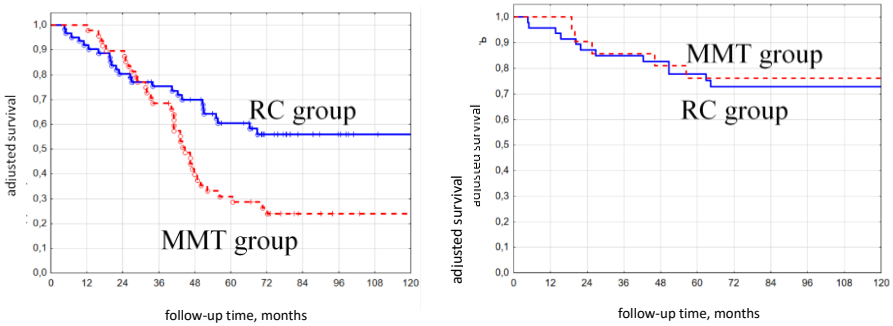


**Figure 3. Cancer-specific survival of MIBC patients in matched groups (Left) and favorable prognosis groups (Right) following surgical and multimodal treatment**

In patients with invasive bladder cancer (MIBC), the following risk factors for disease recurrence were identified: A Charlson Comorbidity Index (CCI) score of 7 or more, which increases the risk by 1.95 times (95% CI 1.24–3.07, $p = 0.004$); A non-urothelial histological tumor type, increasing the risk by 2.88 times (95% CI 1.17–7.12, $p = 0.022$); High-grade tumors, where the risk is 2.12 times higher compared to low-grade tumors (95% CI 1.09–4.09, $p = 0.026$); Local tumor extension T3 and T4 ($p < 0.001$), which increase the risk compared to T2 by 2.39 times (95% CI 1.36–4.21, $p = 0.002$) and 3.81 times (95% CI 2.36–6.14, $p < 0.001$), respectively; Metastatic lymph node involvement ($p < 0.001$): N1 increases the risk compared to N0 by 3.12 times (95% CI 1.47–6.63, $p = 0.003$), N2 – by 9.17 times (95% CI 5.52–15.22, $p < 0.001$), N3 – by 12.3 times (95% CI 5.89–25.51, $p < 0.001$); Disease stages III and IV ($p < 0.001$), where the risk increases compared to stage II by 6.09 times (95% CI 3.73–9.95, $p < 0.001$) and 17.6 times (95% CI 5.12–60.21, $p < 0.001$), respectively; Surgical team experience of fewer than 50 performed operations ($p = 0.003$), which increases the risk by 2.09 times (95% CI 1.30–3.35, $p = 0.002$).

In the multivariate analysis, independent predictors of the risk of disease recurrence were confirmed to be: the degree of local tumor spread, the extent of lymph node involvement, disease stage, Charlson Comorbidity Index (CCI), histological tumor type, and the experience of the surgical team. Based on the multivariate analysis, a prognostic

model was developed to calculate the absolute risk of disease recurrence (local recurrence, progression, or death from the primary disease) in patients with muscle-invasive bladder cancer (MIBC). This model allows for calculating the probability of disease recurrence at any time point after surgery, using a formula that includes the following predictors: local tumor spread, lymph node involvement, disease stage, CCI, tumor histological type, and surgical team experience.

The predictive accuracy (discrimination) of the developed mathematical model for 3-year recurrence risk was 0.834 (95% CI: 0.771–0.897; $p < 0.001$). Based on the coefficients from the multivariate model, a nomogram was constructed to visually estimate 1-year and 3-year recurrence-free survival (RFS) for patients after radical cystectomy (RC) (Figure 4).

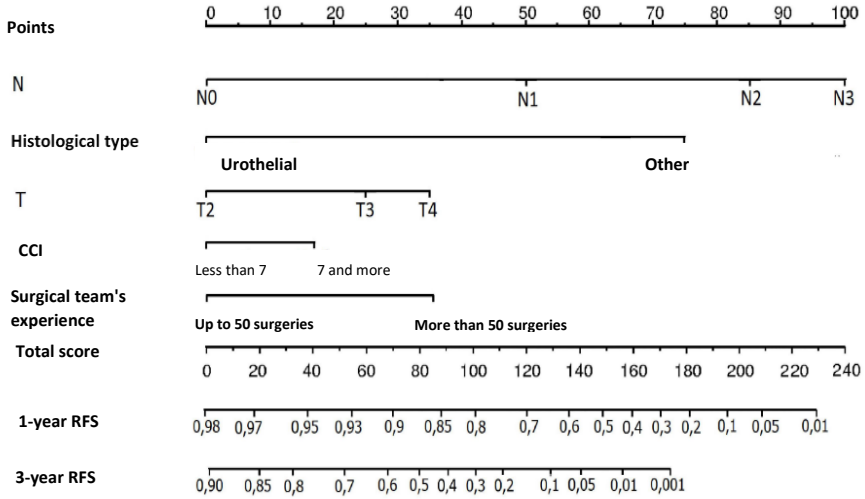


**Figure 4. Nomogram Predicting RFS in Patients with Muscle-Invasive Bladder Cancer (MIBC) after Radical Cystectomy (RC)**

To calculate the specific probabilities for an individual patient using the nomogram, the following steps must be performed:

1. Locate the patient's specific clinical parameters on each corresponding axis.

2. Draw a vertical line upward from each parameter to the top "Points" axis to determine the score assigned to each variable.

3. Calculate the sum of the obtained points.

4. Locate the resulting total score on the "Total Points" axis.

5. Draw a vertical line downward from the total score to the "1-year RFS" and "3-year RFS" axes.

The resulting values represent the estimated probabilities; multiplying these values by 100% yields the corresponding survival rates as percentages.

Below are examples of nomogram-based calculations for the same patients whose absolute risk was previously determined.

**Clinical Example.** Patient G. Tumor stage: pT3 (25 points), N1 (50 points). Histological type: urothelial carcinoma (0 points). Lymph node yield (LNY) > 6 (17 points). Surgical team experience: fewer than 50 procedures (36 points). The total score is 128 points. The 1-year RFS = 0.65 (65%), and the 3-year RFS = 0.1 (10%). Consequently, the risk of disease recurrence within 1 year is 0.35, and within 3 years is 0.90, which is fully consistent with the estimated risks. These data are graphically illustrated in Figure 5.

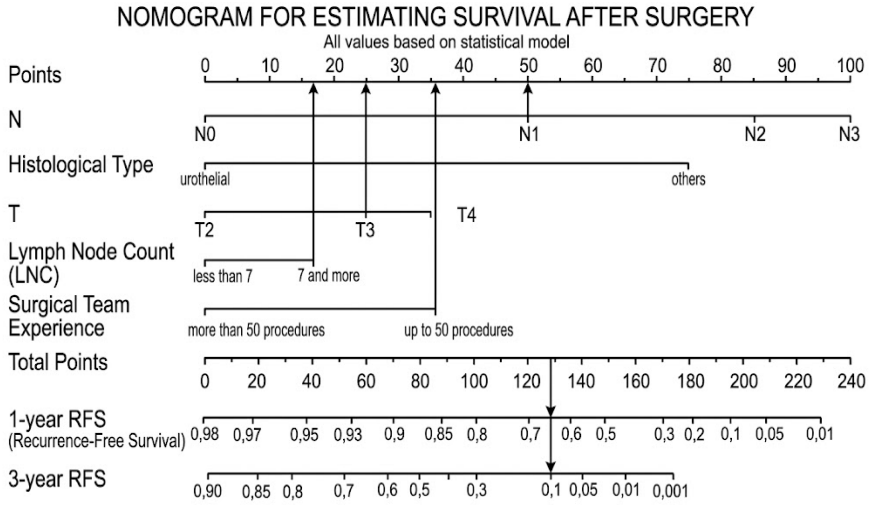


**Figure 5. Nomogram predicting recurrence-free survival (RFS) for Patient G. (Clinical Example).**

Based on the obtained data, a comparative analysis of long-term outcomes was performed for both the RC and MMT groups. Reflecting the DSS data presented above, the hazard ratio (HR) for cancer-specific mortality in the MMT group compared to the radical surgical approach was 2.37 (95% CI: 1.73–3.25; $p < 0.001$).

Initially, due to the heterogeneity of the MMT cohort and occasional deviations from strict selection criteria—particularly when MMT was utilized as a salvage or forced treatment modality—the radical surgery and MMT groups were non-comparable across several baseline parameters. Following baseline statistical analysis, the MMT and radical surgery groups indeed demonstrated significant imbalances across all analyzed variables.

To address this, a multivariate analysis was subsequently conducted within well-balanced cohorts generated via propensity score matching (PSM). It was established that while DSS did not differ significantly between the matched groups at 30 months of follow-up, the 5-year DSS rate in the radical surgery group was twice as high as that in the multimodal therapy group: 60.4% (SE: 6.5%; median DSS not reached) versus 30.9% (SE: 6.8%; median DSS: 44.2 months; $p = 0.005$), respectively.

Thus, the comparative analysis of long-term treatment outcomes demonstrates the superiority of radical surgical treatment. This survival advantage was consistently observed both in the unadjusted initial cohorts and within the well-balanced, matched patient groups, independent of the distribution of key prognostic variables such as sex, age, tumor differentiation grade, and clinical lymph node status.

Considering the fact that in oncology, quality of life (QoL) is the second most important criterion for evaluating treatment effectiveness, we conducted an analysis of this criterion in a group of 138 patients who underwent RC. It was found that the following characteristics of the patient, disease, and treatment significantly affect QoL indicators: sex, age, BMI, Charlson Comorbidity Index (CCI), disease stage, and method of urinary diversion after RC. Statistically and clinically significant differences in QoL perception between men and women were observed in overall health status and all functional scales

(except for the "Cognitive Functioning" scale), as well as in the symptom scales “Fatigue” and “Body Image” (mean score differences ranging from 15.7 for the “Emotional Functioning” scale to 45.2 for the “Social Functioning” scale, $p < 0.05$). Women demonstrated lower QoL scores across all scales, indicating that they tend to perceive all aspects of their life and health more critically and emotionally. As age increases in patients with MIBC after RC, QoL perception significantly declines across nearly all scales of the EORTC QLQ-C30 questionnaire and QLQ-BLM30 module ($p < 0.001$). An exception is the “Emotional Functioning” scale, where lower scores were recorded in patients under 50 years of age (average 50.4 points), which may suggest that younger patients experience the disease and treatment more emotionally. Regarding BMI, it should be noted that obese patients show significantly lower scores in role, emotional, social, and sexual functioning, and more pronounced symptoms such as shortness of breath, constipation, catheter use difficulties, and body image issues ($p < 0.05$). It was found that higher CCI (Charlson Comorbidity Index) scores are associated with lower indicators of overall health, all assessed types of functioning, and higher levels of symptoms ($p < 0.001$). With advancing disease stage, statistically and clinically significant deterioration was observed in overall health and in physical, role, emotional, and social functioning, as well as an increase in symptom severity such as fatigue, insomnia, financial difficulties, urinary symptoms and problems, future outlook, and body image ($p < 0.001$). In our study, the method of urinary diversion had the most pronounced impact on all scales of the EORTC QLQ-C30 questionnaire ($p < 0.001$), except for cognitive functioning and the symptom of diarrhea. Notably, for the Hautmann method, scores on functional scales averaged no less than 79 points and exceeded those for the Bricker and Cutaneous Ureterostomy (CU) methods by 18 to 52 points ($p < 0.05$), representing substantial and clinically significant differences.

A comparative analysis of the obtained results with the EORTC reference values for oncology patients of all tumor sites and stages showed that in our study, patients with muscle-invasive bladder cancer (MIBC) after RC had mean and median scores across all scales that were almost identical to the reference values. For example, on the

"Physical Functioning" scale, the values were 79.3 and 86.7 points versus the reference 78.5 and 86.7, respectively; "Role Functioning" – 78.0 and 83.3 versus 73.4 and 83.3; "Emotional Functioning" – 72.9 and 75.0 versus 73.9 and 75.0. A similar trend was observed for the symptom scales: fatigue – 27.2 and 33.3 vs. 32.4 and 33.3; pain – 19.7 and 16.7 vs. 25.4 and 16.7; insomnia – 35.8 and 33.3 vs. 26.7 and 33.3 points. Considering the severity of the disease, the stage, and especially the disabling nature of the treatment, these results should be regarded as positive.

## CONCLUSIONS

1. The rate of early complications following radical cystectomy (RC) with various urinary diversion methods in patients with muscle-invasive bladder cancer (MIBC) was 43.2% (95% CI: 36.9–49.9%). Statistically significant predictors of early postoperative complications included: age ($p = 0.028$), body mass index ($p = 0.003$), Charlson Comorbidity Index ($p = 0.024$), positive preoperative urine culture ($p = 0.0002$), local tumor extension ($p = 0.023$), surgeon's experience ($p = 0.0001$), and intraoperative blood loss ($p = 0.038$) [37, 38, 39, 40].

2. The developed and patented method (Eurasian Patent No. 037515) for constructing an orthotopic ileal neobladder through ureteral implantation into the "blind pouches" of the reservoir significantly reduced the duration of surgery, the incidence of uretero-reservoir anastomotic leakage ($p < 0.001$), and urinary tract infectious-inflammatory complications ($p < 0.001$) in the early postoperative period. It also significantly decreased the incidence of uretero-reservoir anastomotic strictures in the long-term period ($p < 0.001$) [23,36].

3. Predictors associated with improved cancer-specific survival (CSS) after RC included: Charlson Comorbidity Index score < 7 points ($p = 0.003$), low-grade tumor differentiation ($p = 0.014$), tumor stage pT2 ($p < 0.001$), absence of lymph node involvement ($p < 0.001$), disease stage II ($p < 0.001$), and surgical team experience exceeding 50 operations ($p = 0.004$). For patients with muscle-invasive bladder cancer treated with multimodal therapy (MMT), the following were identified as predictors of CSS: sex ($p = 0.021$), age ($p = 0.030$), tumor size

($p < 0.001$), local tumor extension ($p = 0.007$), and lymph node involvement ($p = 0.005$). A significant factor affecting CSS was performing the surgery at a specialized institution ($p = 0.012$) [46].

4. The developed multivariate model and the formula derived from it for calculating the individual risk of disease recurrence for any follow-up period, as well as the graphical nomogram built on its basis for predicting 1-year and 3-year recurrence-free survival (RFS), are intended for clinical use. The model demonstrates high discriminatory power and prognostic accuracy: for 1-year RFS – 0.814 (95% CI: 0.715–0.915, $p < 0.001$), and for 3-year RFS – 0.834 (95% CI: 0.771–0.904, $p < 0.001$) [48].

5. In groups matched by key prognostic indicators, the 5-year cancer-specific survival (CSS) in the radical cystectomy (RC) group was significantly higher than in the multimodal therapy (MMT) group: 60.4% (SE 6.5%) vs. 30.9% (SE 6.8%) ($p < 0.005$) [48].

6. It was found that the quality of life (QoL) in patients with muscle-invasive bladder cancer after RC, assessed using the functional and symptom scales of the EORTC QLQ-C30 and QLQ-BLM30 questionnaires, has statistically significant associations with the following predictors: sex ($p < 0.05$), age ($p < 0.001$), body mass index ($p < 0.05$), Charlson Comorbidity Index ($p < 0.001$), disease stage ($p < 0.001$), and urinary diversion method ($p < 0.001$) [46].

7. Based on the findings of the present study, for patients with stage II bladder cancer, orthotopic urinary diversion should be the preferred method, as it is an independent statistically significant predictor of cancer-specific survival ($p = 0.010$). The 5-year CSS after ileocystoplasty was 91.1% (SE 2.5%) compared to 66.1% (SE 1.0%) for cutaneous ureterostomy. For patients with stage III bladder cancer, CSS was not associated with the urinary diversion method ($p = 0.63$). In patients with T2N0M0 disease, solitary tumors up to 3 cm, and no hydronephrosis, multimodal therapy may be considered, showing a 5-year CSS of 76.2% (SE 9.3%) compared to 77.8% (SE 6.2%) after radical cystectomy ($p = 0.801$) [46,48].

## PRACTICAL RECOMMENDATIONS

1. Multimodal therapy (MMT) can be proposed as the primary treatment method for patients with muscle-invasive bladder cancer (MIBC) who have a favorable prognosis (stage T2N0M0, solitary tumors no larger than 3 cm, absence of hydronephrosis, and urothelial histological type) and no absolute contraindications. For patients who do not fall into the favorable prognosis category, radical cystectomy (RC) is indicated.

2. In stage II bladder cancer patients undergoing RC, cutaneous ureterostomy (CU) should not be used as a method of urinary diversion, as it worsens both quality of life and survival outcomes in this patient group.

3. When performing RC, preference should be given to the orthotopic ileocystoplasty method (Eurasian Patent № 037515), which improves both short-term and long-term treatment outcomes.

4. To reduce the number of intraoperative complications, patients with a high BMI and/or locally advanced disease should be operated on by the most experienced surgical teams.

5. The management of patients in the early postoperative period after RC should follow the optimized ERAS protocol, whose immediate effectiveness is significantly higher compared to standard postoperative care strategies.

6. The use of the developed mathematical model for predicting recurrence-free survival (RFS) after RC allows for individualized forecasting of long-term treatment outcomes for each patient and will support the selection of optimal treatment strategies and identification of patients requiring more intensive follow-up.

### List of Publications Related to the Dissertation Topic

1. Мусаев Т.Н. Органосохраняющие операции при раке мочевого пузыря / А.М.Ализаде, А.Х.Керимов, Р.С.Зейналов, О.В.Аджалов // Материалы V съезда онкологов и радиологов стран СНГ, - Ташкент: - 2008. - с.363
2. Мусаев Т.Н. Актуальные вопросы в лечении больных инвазивным раком мочевого пузыря / О.В.Аджалов, Ф.А.Гулиев,

А.М.Ализаде, Т.Н. Мусаев // Азербайджанский журнал онкологии и гематологии, - Баку: - 2010. №1, - с.187-190
3. Мусаев Т.Н. Современные возможности хирургического лечения инвазивного рака мочевого пузыря / Т.Н.Мусаев, Ф.А.Гулиев // Азербайджанский журнал онкологии и гематологии, - Баку: - 2011. №2, - с.31-35
4. Мусаев Т.Н. Значимость лимфаденэктомии в лечении инвазивного рака мочевого пузыря / Т.Н.Мусаев, Ф.А.Гулиев // Азербайджанский журнал онкологии и гематологии, - Баку: - 2012. №2, - с.23-27
5. Мусаев Т.Н. Значимость фотодинамической диагностики у пациентов с поверхностными опухолями мочевого пузыря // Материалы съезда онкоурологов стран СНГ, - Киев: - 2012. - с.41
6. Мусаев Т.Н. Результаты радикального хирургического лечения инвазивного рака мочевого пузыря (РМП) / Ф.А.Гулиев, А.М.Али-заде // Ümumilli lider H.Əliyevın 90 illik yubileyinə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2013. - s.55
7. Мусаев Т.Н. Результаты радикальных цистэктомий (РЦЭ), выполненных по жизненным показаниям / Ф.А.Гулиев // Евразийский онкологический журнал, Тезисы VIII съезда онкологов и радиологов Евраазии, - Казань: - 2014. - с.727
8. Мусаев Т.Н. Результаты радикальных цистэктомий выполненных по жизненным показаниям /Т.Н. Мусаев, Ф.А.Гулиев // Белорусский Онкологический журнал, - Минск: - 2015. т.9, №3, - с.5-11
9. Мусаев Т.Н. Гетеротопическое отведение мочи после радикальной цистэктомии / Т.Н. Мусаев, Ф.А.Гулиев // Azərbaycan onkologiya jurnalı, - Bakı: - 2015. №2, - с.45-50
10. Мусаев Т.Н. Осложнения после радикальной цистэктомии с различными методами деривации мочи / Ф.А.Гулиев // Ümumilli lider H.Əliyevın ad gününə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2015. - s.35
11. Мусаев Т.Н. Динамика статистических показателей рака мочевого пузыря в Азербайджане / Д.А.Алиев, Ф.А.Марданлы, Т.Н. Мусаев // Azərbaycan onkologiya jurnalı, - Bakı: - 2016. №2, - с.9-11

12. Мусаев Т.Н. Влияние микрофлоры мочевых путей на частоту инфекционных осложнений после радикальной цистэктомии (РЦЭ) / З.Ш.Везирова // Евраазийский онкологический журнал. Тезисы IX съезда онкологов и радиологов Евраазии, - Минск: - 2016. - с.389
13. Мусаев Т.Н. Эффективность трансуретральной резекции в лечении мышечно-инвазивного рака мочевого пузыря / Ф.А.Гулиев // Ümumilli lider H.Əliyevın anadan olmasının 93-cü ildönümünə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2016. - s.65
14. Мусаев Т.Н. Результаты лечения больных с осложненным течением рака мочевого пузыря / Ф.А.Гулиев, Э.Ш.Халилов // Материалы 11 конгресса Российского общества онкоурологов, - Москва: - 2016. - с.78
15. Мусаев Т.Н. Ортотопическое отведение мочи после радикальной цистэктомии // Georgian Medical News, - Тбилиси: - 2017. т.263, №2, - с.29-35
16. Мусаев Т.Н. Оптимизация периоперационного ведения больных с тонкокишечной деривацией мочи после радикальной цистэктомии / Т.Н.Мусаев, З.Ш.Везирова // Казанский медицинский журнал, - Казань: - 2017. т.98, № 6, - с.900-906
17. Мусаев Т.Н. Спасительная цистэктомия у пациентов с мышечно-инвазивным раком мочевого пузыря / Т.Н.Мусаев, Ф.А.Гулиев, Р.Керимбейли // Azərbaycan tibb jurnalı, - Баку: - 2017. №4, - с.43-50
18. Мусаев Т.Н. Профилактика атонии желудочно-кишечного тракта у пациентов после радикальной цистэктомии с тонкокишечной деривацией мочи / Ф.А.Гулиев, А.Г.Гасымов, Ф.Г.Гулиев, Э.Ш.Халилов // Ümumilli lider H.Əliyevın ad gününə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2017. - s.26
19. Мусаев Т.Н. Инфекционно-воспалительные осложнения у пациентов, перенесших радикальную цистэктомию с различными вариантами отведения мочи / З.Ш.Везирова // Материалы 12 конгресса Российского общества онкоурологов, - Москва: - 2017. - с.48

20. Мусаев Т.Н. Профилактика атонии желудочно-кишечного тракта в раннем послеоперационном периоде у пациентов, перенсших радикальную цистэктомию с различными вариантами отведения мочи / Ф.А.Гулиев // Материалы 12 конгресса Российского общества онкоурологов, - Москва: - 2017. - с.49
21. Мусаев Т.Н. Пути профилактики и оптимизация тактики лечения атонии желудочно-кишечного тракта в раннем послеоперационном периоде у пациентов, перенесших радикальную цистэктомию / Т.Н. Мусаев, Ф.А.Гулиев, А.Г.Гасымов, Ф.Г.Гулиев // Azərbaycan təbabətinin müasir nailiyyətləri, - Баку: - 2018. №4, - с.185-190
22. Мусаев Т.Н. Интраоперационные осложнения радикальной цистэктомии с различными вариантами деривации мочи / Т.Н. Мусаев, Ф.А.Гулиев // Урология, - Москва: - 2018. №4, - с.101-104
23. Мусаев Т.Н. Модифицированная ортотопическая илеоцистопластика у больных раком мочевого пузыря после радикальной цистэктомии / Т.Н.Мусаев, Ф.А.Гулиев // Cərrahiyyə Jurnalı, - Баку: - 2018. №4, - с.48-56
24. Мусаев Т.Н. Интраоперационные осложнения радикальной цистэктомии / Ф.А.Гулиев, Э.Ш.Халилов // Евразийский онкологический журнал. К X съезду онкологов и радиологов стран СНГ и Евразии, - Сочи: - 2018. - т.6, №1, - с.259
25. Мусаев Т.Н. Оптимизация периоперационного ведения больных с тонкокишечной деривацией мочи после радикальной цистэктомии / З.Ш.Везирова, А.Г.Гасымов, Ф.А.Гулиев // Евразийский онкологический журнал. К X съезду онкологов и радиологов стран СНГ и Евразии, - Сочи: - 2018. - т.6, №1, - с.258
26. Мусаев Т.Н. Сравнительный анализ эффективности трансуретральной резекции (ТУР) и магнитнорезонансной томографии (МРТ) в стадировании рака мочевого пузыря / Ф.А.Гулиев, Э.Ш.Халилов, А.Т.Казымов // Ümumilli lider H.Əliyevın ad gününə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2018. - s.29
27. Мусаев Т.Н. Частота и характер интраоперационных осложнений радикальной цистэктомии с различными вариантами

деривации мочи / Ф.А.Гулиев, Э.Ш.Халилов // Материалы 13 конгресса Российского общества онкоурологов, - Москва: - 2018. - с.57
28. Мусаев Т.Н. Периоперационное ведение и проблемы безопасности пациентов, перенесших радикальную цистэктомию / Т.Н.Мусаев, З.Ш.Везирова // Белорусский онкологический журнал, - Минск: - 2018, т.3, №1, - с.34-40
29. Мусаев Т.Н. Анализ 30-ти дневных осложнений радикальной цистэктомии с деривацией мочи по Брикеру // Azərbaycan onkologiya Jurnalı, - Баку: - 2019. №1, - с.32-37
30. Мусаев Т.Н. Частота и характер осложнений после радикальной цистэктомии у пациентов пожилого и старческого возраста / Э.Ф.Мирзаев, Ф.А.Гулиев // Материалы 14 конгресса Российского общества онкоурологов, - Москва: - 2019. - с.70
31. Мусаев Т.Н. Предикторы 30-дневной летальности после радикальной цистэктомии / Э.Ф.Мирзаев // Материалы 14 конгресса Российского общества онкоурологов, - Москва: - 2019. - с.71
32. Musayev T.N. Intraoperative complications of radical cystectomy with different types of urinary diversion // Abstracts from The First Georgian Urological Association (GUA) – Caucasus/Central Asia (CCA) Urological Meeting Dedicated to the memory of Prof. Laurent Managadze EUROPEAN UROLOGY SUPLEMENTS (ELSEVIER), - Tbilisi: - 2019. v.18, Issue 12, - p.3645
33. Musayev T.N. Implementation of optimized ERAS protocols after radical cystectomy / F.A.Gulyiev, E.Sh.Khalilov, Z.Sh.Vezirova // Abstracts from The First Georgian Urological Association (GUA) – Caucasus/Central Asia (CCA) Urological Meeting Dedicated to the memory of Prof. Laurent Managadze EUROPEAN UROLOGY SUPLEMENTS (ELSEVIER), - Tbilisi: - 2019. v.18, Issue 12, - p.3645
34. Musayev T.N. Salvage cystectomy in patients with muscle-invasive bladder cancer // Abstracts from The First Georgian Urological Association (GUA) – Caucasus/Central Asia (CCA) Urological Meeting Dedicated to the memory of Prof. Laurent Managadze EUROPEAN UROLOGY SUPLEMENTS (ELSEVIER), - Tbilisi: -

2019. v.18, Issue 12, - p.3645
35. Musayev T.N. Осложнения радикальной цистэктомии с различными вариантами деривации мочи // Azərbaycan təbabətinin müasir nailiyyətləri, - Баку: - 2020. №2, - с.14-21
36. Мусаев Т.Н. Способ модифицированной ортотопической илеоцистопластики у больных раком мочевого пузыря // Бюллетень Евразийского патентного ведомства, - Москва: - 2020. №201900195, 19 с
37. Мусаев Т.Н. Ранние осложнения радикальной цистэктомии с различными видами отведения мочи: анализ факторов прогноза // Онкоурология, - Москва: - 2020. т.16, №1, - с.78-89
38. Мусаев Т.Н. Инфекция в моче, как один из предикторов ранних послеоперационных осложнений радикальной цистэктомии / Ф.А.Гулиев, З.Ш. Везирова // Материалы 15 конгресса Российского общества онкоурологов, - Москва: - 2020. - с.69
39. Мусаев Т.Н. Прогнозирование частоты осложнений после радикальной цистэктомии на основании показателей общего здоровья больных раком мочевого пузыря // Материалы 15 конгресса Российского общества онкоурологов, - Москва: - 2020, - с.68
40. Мусаев Т.Н. Предикторы ранних послеоперационных осложнений радикальной цистэктомии с различными вариантами деривации мочи / Ф.А.Гулиев // Евразийский онкологический журнал. Материалы XI съезда онкологов и радиологов стран СНГ и Евразии, - Казань (Online): - 2020. - т.8, №2, - с.534
41. Мусаев Т.Н. Влияние протоколов ERAS на реабилитацию пациентов после радикальной цистэктомии (РЦ) с различными вариантами деривации мочи // Евразийский онкологический журнал. Материалы XI съезда онкологов и радиологов стран СНГ и Евразии, - Казань (Online): - 2020. - т.8, №2, - с.534
42. Мусаев Т.Н. Отсроченные осложнения радикальной цистэктомии с различными вариантами деривации мочи // Urologiya və reproduktiv təbabət jurnalı, - Баку: - 2021. т.4, №1, - с.39-49
43. Мусаев Т.Н. Стриктуры уретеро-интестинального и резервуаро-уретрального анастомозов после радикальной цистэктомии с тонкокишечной деривацией мочи / Т.Н.Мусаев,

Ф.А.Гулиев // Azərbaycan onkologiya Jurnalı, - Баку: - 2021. №2, - с.16-20
44. Мусаев Т.Н. Результаты мультимодальной терапии больных мышечно-инвазивным раком мочевого пузыря (РМП) / Ф.А.Гулиев, Э.Ш.Халилов, Э.Ф.Мирзаев // Евразийский онкологический журнал. Материалы XIII съезда онкологов и радиологов стран СНГ и Евразии, - Казахстан: - 2022. - т.10, №2, - с.489
45. Мусаев Т.Н. Отсроченные осложнения радикальной цистэктомии // Ümumilli lider H.Əliyevın ad gününə həsr olunmuş elmi-praktiki konfransın materialları, - Bakı: - 2022. - s.24
46. Мусаев Т.Н. Результаты радикального хирургического лечения больных раком мочевого пузыря // Əziz Əliyev adına elmi-praktiki jurnal “Tibb və Elm” №2, 2024, c. 101-111.
47. Мусаев Т.Н. Мультимодальное лечение мышечно-инвазивного рака мочевого пузыря // Sağlamlıq Jurnalı, № 1 (32), 2025, c. 11 – 19.
48. Мусаев Т.Н. Сравнительный анализ результатов лечения больных мышечно-инвазивным раком мочевого пузыря // Əziz Əliyev adına elmi-praktiki jurnal “Tibb və Elm” №1, 2026, c. 50-59.

## LIST OF ABBREVIATIONS

**RFS** – Recurrence-Free Survival
URA – urthero resorvoir anastomosis
**IP** – Ileoplasty
**CCI** – Charlson Comorbidity Index
**BMI** – Body Mass Index
**QoL** – Quality of Life
**RT** – Radiotherapy
**LN** – Lymph Node
**MMT** – Multimodal Therapy
**UB** – Urinary Bladder
**OS** – Overall Survival
**BC** – Bladder Cancer
**RC** – Radical Cystectomy
**CSS** – Cancer-Specific Survival
**CU** – Cutaneous Ureterostomy
**CT** – Chemotherapy

The defense will be held on 29 june 2026 at 14⁰⁰ at the meeting of the One-time dissertation council BED 1.02 of Spreme Attestation Commission under the President of the Republic of Azerbaijan operating at the National Oncology Center of the Ministry of Health of the Republic of Azerbaijan.

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