Early postoperative complications and 90-day mortality in patients undergoing radical cystectomy

Wczesne powikłania pooperacyjne i 90-dniowa umieralność u pacjentów poddanych radykalnej cystektomii

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: The standard treatment method of muscle-invasive bladder cancer is radical cystectomy. This complex procedure consists of removing the urinary bladder with distal ureters and regional lymph nodes. Additionally, the prostate with seminal vesicles in men and uterus with ovaries in women should be excised. Therefore, this demanding oncological surgery is associated with a high occurrence of complications. The aim of this study was to assess the complications after radical cystectomy and identify the factors associated with severe complications and high mortality rate.

Materials/Methods: We retrospectively analyzed medical data of 213 patients who underwent a radical cystectomy. Preoperative risk factors were assessed based on American Society of Anesthesiologists classification (ASA) and the Charlson Comorbidity Index (CCI). Clavien-Dindo classification was also included in our analysis. We investigated various factors associated with 30-day and 90-day mortality.

Results: Complications after surgery were reported in 38% (n = 81) of patients in the studied group. Excluding perioperative high fever, the complication rate was 18%. The following complications were observed in 30-day postoperative period: wound infection (n = 6), wound dehiscence (n = 4), mechanical bowel obstruction (n = 3), hemorrhage (n = 2), cardiological (n = 8), stroke (n = 3). Observed 30-day mortality was 2.3% (n = 5), while 90-day mortality was 8.9% (n = 19). The mortality rate was associated with the stage of cancer and the type of urinary diversion.

Conclusions: Radical cystectomy is a complex and traumatic urological surgery. It is associated with a significant complication rate and mortality, and it negatively affects quality of life. Therefore, all known risk factors should be thoroughly assessed preoperatively to select optimal treatment. Furthermore, the patient should be carefully informed about the risks associated with the surgery.

Keywords: radical cystectomy, complications, mortality, bladder cancer, urinary diversion

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Abbreviations: **ASA** – American Society of Anesthesiologists classification, **BCG** – Bacillus Calmette-Guérin, **CCI** – Charlson Comorbidity Index, **ORC** – open radical cystectomy, **OS** – overall survival, **RC** – radical cystectomy, **TURBT** – transurethral resection of bladder tumor.

INTRODUCTION

Bladder cancer is the most common cancer of the urinary tract and second of the genitourinary system after prostate cancer [13]. The most important risk factors for developing this disease include smoking, exposure to industrial carcinogens and previous exposure to radiation [27].

Non-muscle invasive bladder cancer is treated by endoscopic methods – TURBT (transurethral resection of bladder tumor). Patients in the advanced stage of the disease qualify for more invasive treatment, which consists of removing the affected organ, if their general condition allows it [25].

The urinary bladder with distal ureters and regional lymph nodes are removed in both sexes. In addition, the prostate and seminal vesicles should be removed in males, whereas the uterus with the ovaries and the anterior vaginal wall in females [12, 14]. After such extensive surgery, it is necessary to restore the urinary tract with the use of urine drainage. Most often, one of the following methods is used: ileal conduit (Bricker's method), ileal neobladder or ureterocutaneostomy (used in frail patients) [13].

The frequency of complications also depends on the type of performed urinary diversion, e.g. in patients who had undergone surgery with the Bricker method, obstruction is more common, while metabolic acidosis and ureterohydronerosis is a common complication of the neobladder [10].

Open surgery is the golden standard. The first radical cystectomy (RC) with the assistance of a surgical robot was performed more than 10 years ago. Prospective studies did not show the significant advantage of that method [6]. The use of radiotherapy as a treatment method to preserve the bladder is being researched [15].

Patients with invasive bladder cancer and non-invasive high-risk cancers are qualified for such aggressive treatment as well as patients whose cancer is refractory to treatment with intravesical BCG (Bacillus Calmette-Guérin) [2, 12].

One of the most serious urological procedures is radical cystectomy (RC), because it may result in a high percentage of intraoperative complications or complications during hospitalization after surgery [2].

The aim of this study was to assess the complications after Radical Cystectomy and to identify factors associated with severe complications and high mortality rate.

MATERIALS AND METHODS

A group of 213 patients (176 men and 37 women) subjected to the RC in 2009–2014 was analyzed retrospectively. All the patients were treated in the Urology and Urological Oncology Clinic of the University Hospital in Wrocław.

Each patient's case was individually examined for preoperative risk factors – every patient was assessed in accordance with the American Society of Anesthesiologists classification (ASA) and the Charlson Comorbidity Index (CCI), as well as possible perioperative complications – Clavien-Dindo.

The following data were collected: age, gender, cancer stage, preoperative laboratory tests. The course of surgery and intraoperative blood loss were analyzed.

Furthermore, the time to start post-operative nutrition, hospital stay, and in-hospital complications were determined. Perioperative mortality was observed and the survival rates of 30 and 90 days were assessed.

Many factors influence the course of the surgery and the occurrence of complications related to the treatment. Stage of cancer and the general condition of the patient are the most significant ones. This is a very simplified division that can be extended by age, type of urinary diversion, preoperative hemoglobin and many other parameters [8]. Existing scales have been used to systematize this data.

During the qualification for surgical treatment, each patient filled out the anesthesiological questionnaire, which along with the anesthesiologist's interview, allowed us to assess the patient's condition and possible risks

Table 1. Study group characteristics, toumor stage, urinary diversion type

Age	
mean	67.5 (9.8) years
variation	35–88 years
Sex	
female	37
male	176
Pathological stage	
T0	3.4%
Ta	0.9%
Tis	8.7%
T1	5.9%
T2	18.3%
T3	26.1%
T4	36.7%
Urinary diversion	
Bricker conduit	70.9%
Neobladder	17.4%
Ureterocutaneostomy	11.7%
Laboratory tests	
Hemoglobin level [g/dl]	12.35 (±2.50)
Creatinine level [mg/dl]	1.33 (±0.45)

Table 2. Number of patients in ASA classification

ASA	n
1	7
2	112
3	87
4	7
5	0

associated with anesthesia and surgical treatment. Each patient was classified in the ASA system [Table 1]. Kapplan-Mayer curves were established to show the probability of survival depending on the performed urine diversion.

Comorbidities and medical history were determined based on the medical interview with the patient collected during admission to the hospital. To unify the collected information, the Charlson Comorbidity Index was used. Age and 16 parameters are taken into account, such as the coexistence and severity of diabetes, liver failure, cancer, cardiovascular disease, presence of AIDS and others. The indicator is used to estimate a 10-year survival [22].

RESULTS

In the studied group, the majority of patients were male, which overlaps with the global population distribution; the disease affects men four times more often than women. Females constituted 17% of the study group, whereas men constituted 83%. These proportions overlap with the study by Luke et al. [20]. The average age of operated patients also coincides with other studies [31] [Table 2].

TNM classification allows us to divide patients into groups based on the stage of cancer [Table 2]. The majority of patients had an advanced stage of the disease (62.8% were

patients with stage T3 and T4), as it can be seen in the studied population.

When they are being qualified for the procedure, the majority of patients achieved the ASA class 2 and 3 [Table 1]. A large number of patients qualified for group 3 as a result of disease burden such as unregulated type 2 diabetes, chronic obstructive pulmonary disease and myocardial infarction up to 3 months. Respiratory diseases are associated mainly with smoking, which is one of the main risk factors for bladder cancer.

The maximum possible score in Charlson Comorbidity Index is 37 points. In the study group, a maximum of 13 points and a minimum of 2 were noted with the average score for the studied group being 5.93 with a median of 6.00.

Most of the operated patients underwent the Bricker operation (ileal conduit). Almost every sixth patient had a neobladder (intestinal reservoir replacing the bladder). Simple urinary drainage (ureterocutaneostomy or nephrostomy) was the least often performed diversion [Table 2].

The listed factors such as tumor size, age, comorbidities and urinary diversion affect the time of surgery, risk of bleeding and the occurrence of complications [26] [Table 3].

During hospitalization, the most common complication was infection (generalized); nonetheless, wound infection developed in 6 patients [Table 4].

Complications were reported in 81 patients, which is 38% of the studied population. Excluding fever over 38°C, this number would be limited to 39 patients (18.3%).

The perioperative period was established to be 30 days after the surgery. Complications were divided according to the Clavien-Dindo classification, and the majority of patients were classified to group 2. Some patients were moved to the intensive care unit directly from the operating theater due to their unstable condition. Some of them required reoperation due to intestinal anastomosis dehiscence, or internal bleeding. These cases were classified to groups 3 and 4 in the Clavien classification, respectively [Table 5].

Patient's death was the most serious complication. There were 5 deaths in the study group within 30 days of the

Table 3. Comparision of patients grouped by urinary diversion type

Test group	Bricker	Neobladder	Other
Number of patients	151	37	25
Age	68.28	59.81	74.57
Number of complications	62	12	10
Number of complications (%)	41.1%	32.4%	40.0%
Number of complications without infection	28	3	7
Number of complications without infection (%)	18.5%	8.1%	28.0%
Surgery time [min]	292	354	269
Intraoperative blood loss [ml]	938.4	900	1715
Return of bowel function [days]	4.96	5.31	5
Length of hospitalization [days]	16.1	14.5	17.5
90 days mortality	7.2%	2.7%	30.4%
1-year overall survival	69.9%	91.9%	34.8%
CCI	6.07	4.32	7.65

Table 4. Complications

Complication	n	%
Generalized infection	55	67.9%
Wound infection	6	7.4%
Wound dehiscence	4	4.9%
Mechanical bowel obstruction	3	3.7%
Haemorrhage	2	2.5%
Cardiological complications	8	9.9%
Stroke	3	3.7%

Table 5. Clavien-Dindo classification

Clavien-Dindo	Number of patients	Avarage age [years]
1	62	65.4
2	114	67.7
3	15	66.6
4	17	72.5
5	5	73.8

surgery, which is a 2.4% death rate. Ninety-day mortality was also assessed, during which 19 patients died, which is a 8.9% death rate [Table 6].

Twelve out of 19 (63%) patients who died within 90 days of surgery had advanced tumor (cT3 and cT4). The study group was divided into two subgroups depending on age: up to 70 years of age or older. The average rating in the Clavien-Dindo classification was calculated. Patients up to 70

Table 6. Characteristics of patients who died within 90 days after surgery

Time to death after surgery [days]	Age	CCI	ASA
9	62	6	3
12	79	8	3
13	71	6	2
17	81	6	4
29	76	10	2
42	35	2	2
42	61	9	2
44	83	7	3
49	63	8	3
50	71	11	2
51	74	8	3
63	72	10	4
68	70	6	3
70	81	10	3
76	80	6	2
81	57	3	2
84	51	3	2
86	72	7	3
89	69	6	3

Table 7. Clavien-Dindo classification grouped by urinary diversion type

Clavien-Dindo	Number of patients	Avarage age [years]
1	62	65.4
2	114	67.7
3	15	66.6
4	17	72.5
5	5	73.8

years of age had the average of 1.86; meanwhile, the older patients had the average of 2.18.

Patients were also divided according to the type of performed urinary diversion and the frequency of complications within 30 days of surgery [Table 7].

Overall Survival time (OS) was determined on the basis of the follow up study. Kapplan-Mayer curves show significant differences in survival between groups [Fig. 1].

DISCUSSION

Radical cystectomy is a vast procedure with numerous intra- and postoperative complication [3]. Blood loss during surgery and the need for a transfusion depend on the stage of the cancer, the initial hemoglobin concentration, surgery technique (open/laparoscopic) and urinary
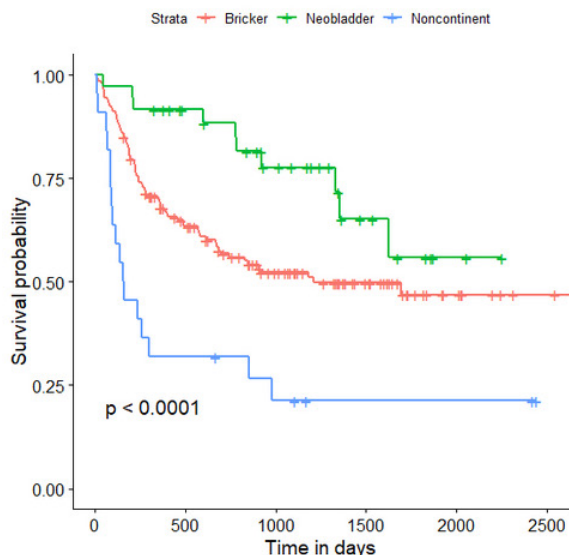
Fig. 1. Comparision of overall survival between performed type of urinary diversion using Kaplan-Meier estimator

diversion. The need for a blood transfusion in the study group was 52.1%. Causano and colleagues reported that 39.1% of the patients undergoing open radical cystectomy (ORC) require a blood transfusion. They compared the need of a transfusion with patients operated with the assistance of the robot and the result was significantly better – 21.5% [6]. Tsuturyan et al. reported the need of a transfusion in 80 out of 273 patients (29.3%). Patients with cancer in stage up to cT2 were in the majority of the study population (56.6%) [27]. Fangning et al. reported pT3 in 25.4% and pT4 in 10.9% of cases [29]. This may explain the difference compared to our study group, where patients with low-advanced disease constituted just 37.2%. Musch et al. reported that 60% of patients require a blood transfusion in the case of ORC [16]. The greatest risk of bleeding occurs when removing the bladder. Advanced tumors are accompanied by the development of pathological blood vessels and damage to these vessels increases the risk of anemia [26]. The difficulty of the procedure increases with the growth of the tumor; hence, the risk of bleeding. Recent reports prove the advantage of the robotic (average 300ml) over the open (average 800ml) method [17]. In the group we studied, the median blood loss was 1000 ml. The difference between the results from centers from highly developed countries is noteworthy [6, 26, 27]. This problem is based on the stage of cancer at the time of surgery. A higher percentage of patients with advanced disease result from low awareness among them, especially those living in rural areas [1].

Higher tumor mass creates technical difficulties associated with bladder resection, which increases the risk of intraoperative bleeding and this increases the risk of cardiovascular complications. The study group was divided depending on the type of urinary diversion. The choice of surgery technique largely depends on the stage of the disease, the patient's age and comorbidities. It has been decided to perform Bricker's surgery on most patients, i.e. 151 (70.9%).

Thirty-seven (17.4%) patients got neobladder, whereas the remaining group of patients was limited to the simplest forms of urine drainage surgery, which summed up to 25 (11.7%) patients.

The intestinal neobladder is dedicated to young patients who cooperate and are aware of the risks associated with having this urinary diversion. A patient choosing a neobladder must be aware that this is not a maintenance-free solution [22].

Analyzing the incidence of complications depending on the type of urinary diversion, the best result was obtained in a group of patients with a neobladder (32.4%). This treatment was intended for a selected group of patients, especially young patients who had good prognosis. The average length of cystectomy with a neobladder was the longest, almost 6 hours. The smallest percentage of complications most likely resulted from the fact that patients qualified for this surgery had to meet stricter criteria than others, and the stage of the disease must allow this type of surgery to be performed radically.

Patients undergoing a cystectomy in the simplest form of urinary diversion were often burdened with additional diseases. These procedures were usually palliative. In this group, up to 44% of patients experienced complications after surgery [33].

The highest percentage of grade 4 and 5 complications in the Clavien-Dindo classification was observed in these patients, affecting 40% of patients in this group.

The patient's age is also an important factor in making decisions about the surgery. With the increasing average life expectancy of the population, the limit of advanced age is rising. The study adopted a 70-year age limit and older patients had more serious complications assessed using the Clavien-Dindo scale. Advanced age is associated with a higher risk of complications [5, 32, 33].

It should be noted that the Bricker cystectomy as well as a cystectomy with a neobladder are procedures during which the digestive tract is open, which increases the risk of infection of the operating field with intestinal bacteria. In addition, the neobladder and ileal conduit are associated with the risk of urine leakage into the peritoneum. Uretero-intestinal anastomosis is a very critical stage of the procedure, which requires precision and sensitivity. Sutures that are too tight can lead to necrosis of the distal ureter and the anastomosis may sever [30].

Regardless of the type of urinary diversion, the patient receives an antibiotic as standard prophylaxis; most often it is the 1st generation cephalosporin. Patients whose surgery technique was associated with a violation of the

gastrointestinal tract received antibiotics in the postoperative period. The study group used metronidazole and second-generation cephalosporin (cefuroxime). Despite the use of antibacterial treatment, a large percentage of patients who had an infectious complication should be especially careful.

The urine culture is included in routine tests collected the day prior to surgery. However, the results are available after a few days. Therefore, standard empirical antibiotic therapy is replaced with targeted antimicrobial therapy based on the results and bacteria resistance.

Collecting the urine culture before the admission to hospital and adjusting the adequate antibiotic prophylaxis might result in lower incidence of infections.

In the case of patients operated on by the Bricker method, infections accounted for 57.4% of all complications, while in the case of neobladder as much as 75.0%. Comparing all types of urinary diversion with cystectomy, the number of complications oscillates around 40%, but patients with simple methods are at a much lower risk of infectious complications, which accounted for 18.2% of all complications in this group. As a result, this group is exposed to other complications during hospitalization, such as myocardial infarctions, strokes and others, which result from comorbidity. Available analyses indicate the frequency of complications after cystectomy from 30 to 60%. Largely, it depends on the qualification of the events as a complication. Nevertheless, it does not change the fact that cystectomy is a procedure with a high percentage of complications [9, 18].

The patients were divided into two further subgroups based on the stage of cancer (T feature); the first subgroup were patients with T0, Tis, Ta, T1 and T2, and the second subgroup were patients with T3–T4. In the case of surgery with a neobladder, as much as 68.0% of patients belonged to the first group, while in patients with simple urinary diversion as much as 85.7% belonged to the second group.

Cancer, along with an increase in the severity of the disease, negatively affects the well-being of the body, causing general cachexia, which adversely affects the postoperative results.

The average age of patients was the lowest in patients undergoing cystectomy with orthotopic neobladder (59.8 years), procedures for simple urinary drainage were performed on elderly patients (74.6 years) [Table 3].

As mentioned before, a neobladder is intended for young patients with a good prognosis, whereas simple methods are performed mainly on patients with comorbidities and with advanced cancer. This is so because violating the gastrointestinal tract entails additional trauma for a weak body, which promotes the occurrence of complications. Palliative procedures were performed mainly because

of massive bleeding, which threatened the patient's life. Bleeding was accompanied by severe pain associated with the presence of a tumor.

The most serious complication was the patient's death. Nowadays, patient mortality is a significant problem. There is a widespread belief that treatment should have a positive effect. Progress of civilization and the improvement of the quality of life are responsible for this. However, perioperative mortality in cystectomy is high [11].

Zakaria et al. reported that a 30-day mortality based on a large group of patients (2.778) was 2.81%; this result is similar to that observed in our study group (2.35%) [28, 31]. However, the 30-day period seems too short to assess early survival after surgery; the 90-day period seems to be more accurate. Analyzing the perioperative and postoperative course, the focus was on the first 30 days after surgery, because the collected documentation from this period was the most accurate. Therefore, extending the observation period could lead to incomplete data.

However, scientific reports focus on assessing a 90-day mortality. Ninety-day mortality was 8.9% in the study group, which coincides with other reports. The high 90-day mortality rate is largely caused by the severity of the disease, with the diagnosis of cT3 and cT4 predominating in these patients [5, 21, 23, 32].

The main factor affecting mortality after surgery is the severity of the disease. Comorbidities such as atherosclerosis, hypertension and diabetes also have a significant impact on the postoperative course. The period of 30 days for rehabilitation after such extensive surgery is often too short, especially when the average hospitalization period exceeds two weeks.

Therefore, the improvement of diagnostics and efforts to increase the percentage of cancer patients in the early phase of bladder muscle infiltration would most probably reduce the 90-day mortality.

In the case of various surgical procedures, with the surgeon's experience increasing, the number of complications and peri-operative mortality decreases. The radical cystectomy is a demanding procedure and thus has a long learning curve.

A high percentage of complications and a 90-day mortality rate, especially in patients with other diseases, prompt a deeper analysis of the indications for the surgery.

Often, the lack of other therapeutic options leads to a decision about surgery in palliative patients suffering from severe pain and hematuria. Frequent renal failure prevents neoadjuvant chemotherapy. Sometimes renal failure can be managed by nephrostomy, which allows normalization of renal parameters and the implementation of chemotherapy [7]. Survival after surgery largely depends on the stage of the disease, and is thus also

associated with the type of surgery. One-year survival for simple urine diversion reaches about 30%, while in patients eligible for a neobladder it is as much as 90%. As mentioned, this is due to the severity of the disease and comorbidities [Figure 1]. It is important to inform the patients and their family about the high risk of perioperative complications. It is also necessary to make the patient aware that the survival time is strongly dependent on the stage of the disease. Peri-operative mortality is not a complication that can be avoided, but is unfortunately an indispensable element in the treatment of patients with advanced bladder cancer.

It seems that the solution should not be sought by improving the quality of the procedures performed, because the complications usually do not result from technical difficulties. The main cause of high mortality and complications is cancer diagnosed too late. The greatest benefit will be gained from raising public awareness by improving basic knowledge about symptoms such as hematuria. Diseases diagnosed at the initial stage are largely curable and the risk of death is radically lower. If a decision is made about the necessity of performing a cystectomy, the patient should go to a high volume center, because the number of performed procedures reduces complications [13].

Current medicine does not provide a solution for patients with highly advanced bladder cancer, especially those who are disqualified from chemotherapy.

It seems that help can be sought in the combination of radiotherapy, chemotherapy and surgery. In some cases, trimodal therapy may be used, mainly for the elderly and patients with cancer in stages up to cT2 [19, 24].

The collected data make us realize how severe and traumatic cystectomy is. A patient qualified for this procedure should be informed about the real risk associated with surgical treatment as well as the often inevitable progression of the disease.

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