

# COVID-19 impact on bladder cancer treatment

## Impacto de COVID-19 en el tratamiento del cáncer de vejiga

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### Abstract

**Objective:** The proposed study aims to present the experience with radical cystectomy from a urology service in a public teaching, non-profit hospital with a medical residency service, during the COVID-19 pandemic period in 2020.

**Materials and methods:** We led a prospective study from February 2020 to October 2020, in which three 2<sup>nd</sup>-year urology residents, guided by one particular attending physician, performed 20 radical cystectomies in an acute public hospital.

**Results:** Most patients were male, with Muscle-invasive bladder cancer being the major indication in our sample. There was a meaningful and direct correlation between surgical time and length of stay in the Intensive Care Unit. **Conclusion:** Despite the complexity of the surgery, the execution of radical cystectomies during a pandemic period is feasible, with positive surgical results and complication rates compatible with the current literature.

**Keywords:** COVID-19. Bladder cancer. Cystectomy. Prognosis.

### Resumen

**Objetivo:** El estudio propuesto tiene como objetivo presentar la experiencia con cistectomía radical desde un servicio de urología en un hospital público docente, sin fines de lucro con el servicio de residencia médica, durante el período de pandemia de COVID-19 en 2020. **Materiales y métodos:** Realizamos un estudio prospectivo estudio de febrero de 2020 a octubre de 2020, en el que tres residentes de urología de segundo año, guiados por un médico tratante en particular, realizaron 20 cistectomías radicales en un hospital público de agudos. **Resultados:** La mayoría de los pacientes eran varones, siendo MIBC la principal indicación en nuestra muestra. Hubo una correlación significativa y directa entre el tiempo quirúrgico y la estancia en la Unidad de Cuidados Intensivos. **Conclusión:** A pesar de la complejidad de la cirugía, la realización de cistectomías radicales en período de pandemia es factible, con resultados quirúrgicos positivos y tasas de complicaciones compatibles con la literatura actual.

**Palabras clave:** COVID-19. Cáncer de vejiga. Cistectomía. Pronóstico.

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## Introduction

Bladder cancer (BC) is the 10<sup>th</sup> most prevalent type of cancer in the world, considering both genders<sup>1</sup>. Muscle-invasive BC (MIBC) occurs in 25-40% of bladder cases, representing the total mortality of the disease<sup>2</sup>.

Neoadjuvant chemotherapy is a therapeutic option, which shows a slight increase in survival rate, despite limiting side effects<sup>3</sup>. Although not without complications, radical cystectomy (RC) with lymphadenectomy is the therapeutic treatment for MIBC cases and in some non-muscle-invasive<sup>4</sup> cases, with an open or minimally invasive technique<sup>5</sup>.

The year 2020 was marked by the coronavirus infection (SARS-CoV-2/COVID-19), which causes an acute respiratory syndrome and became a pandemic within a few months<sup>6</sup>. During the year, many government authorities decided to suspend elective surgeries to increase the hospital's capacity.

There was no consensus on how to conduct the uro-oncological cases. In the case of MIBC patients, the risks of delaying treatment were balanced against the risks of possible COVID-19 infection, as these are cases of non-postponable surgeries within uro-oncology<sup>7</sup>. It is known that in MIBC, a 90-day delay for surgery reduces 3-year survival by 34%<sup>8</sup>.

Given the worldwide pandemic scenario, taking into account the changes in the surgical routine in many hospitals and the need for an early approach of this group of patients, this study aims to demonstrate the experience of RC from a urology service in a non-profit, public teaching hospital with a medical residency service during the COVID-19 pandemic period in 2020.

## Materials and methods

After obtaining institutional review board approval, this prospective study of 20 patients who consecutively underwent RC surgeries with urinary diversion was carried out in a high-acuity hospital in the state of São Paulo, between February 1 and October 31, 2020.

The etiology of the disease was colon-invasive adenocarcinoma in two patients and bladder neoplasm in 18 patients.

Demographic data (Table 1) and pre-operative clinical staging (Table 2) were evaluated, in addition to transoperative evaluation, such as duration of surgery, estimated bleeding, blood transfusion, and vasoactive drug use. In regard to the post-operative period, complications were assessed according to the

**Table 1.** Clinical and pathological characteristics of the diseased submitted to radical cystectomy

Clinical characteristics	n = 20 / Freq %
Age (years)	64,6 ± 11
30-50	3 (15)
51-60	1 (5)
61-70	10 (50)
71-80	6 (30)
Gender	
Female	6 (30)
Male	14 (70)
Comorbidities	
DM	2 (10)
SAH e AMI + SAH	5 (25)
SAH e DM	3 (15)
SAH e DM e CKD	1 (5)
None	9 (45)
Smoking	
Yes	15 (75)

AMI: acute myocardium Infarction; CKD: chronic kidney disease; DM: diabetes mellitus; SAH: Systemic Arterial Hypertension.

**Table 2.** Qualitative descriptive analysis of the staging and grade of bladder neoplasms performed during the pandemic period

Clinical staging T	n / Freq. (%)	Pathological staging T	n / Freq. (%)
Tis	0	Tis	1 (5)
Ta	5 (28)	Ta	1 (5)
T1	4 (22)	T1	5 (28)
T2	8 (44)	T2	7 (40)
T3	0	T3	1 (5)
T4	1 (6)	T4	3 (17)
Clinical staging N		Pathological staging N	
NX (não realizada)	0	NX	1 (5)
N0	14 (78)	N0	11 (62)
N1	0	N1	3 (17)
N2	2 (11)	N2	2 (11)
N3	2 (11)	N3	1 (5)
Staging M		-	-
M0	17 (95)	-	-
M1	1 (5)	-	-
Histologic grade			
TURB		Cystectomy	
Low	5 (28)	Low	0
High	13 (72)	High	(100)

Clavien-Dindo classification, which includes Intensive care unit (ICU) needs or extended post-anesthetic recovery (when ICU beds were not available), type of urinary diversion performed, final pathological staging, and length of hospital stay.

In the period referenced, the surgical procedures were performed by three 2<sup>nd</sup>-year urology medical residents, with guidance from the same attending physician.

Pearson's correlations and simple linear regression models were used, as well as ANOVA tests and *post hoc* T-test with Bonferroni's correction. Softwares, such as IBM SPSS 26 and Microsoft Excel 365, were used. All tests conducted took into consideration two-tailed alpha of 0.05 and a confidence interval of 95%.

Patients with neoplasms with Ta-T4 staging were included in the study, as well as elective surgery with clinical anesthetic clearance and written informed consent. Only one patient was excluded from the study due to a lack of information in the patient's medical records.

The clinical staging and pathological diagnosis were performed by computerized tomography, and the trans-urethral resection of the bladder or cystoscopy was collected for the purpose of the biopsy.

**Surgical procedure:** The open RC with extended pelvic lymphadenectomy was performed through an infra-umbilical medial incision.

In men, extraperitoneal time was performed through the prostatectomy with preservation of the neurovascular bundles until the release of the seminal vesicles. In neobladder candidate patients, eight Vicryl 3.0 sutures were passed through the urethra and repaired for anastomosis. Only at this moment, the peritoneal cavity was opened, and the ureters were dissected bilaterally. After that, the ligature of the bladder pedicles was performed bilaterally, and excision of the surgical sample was taken.

In women, the surgery was initiated by transperitoneal access, with the bilateral dissection of the ureters and ligature of both bladder and uterine pedicles.

After the removal of the surgical sample, extended pelvic lymphadenectomy was conducted. For urinary reconstruction, a distal ileal segment was isolated for cutaneous ureteroileal anastomosis, orthotopic neobladder, or urethrocutaneous anastomosis. Bowel transit was re-established through laterolateral enteroentero anastomosis with a linear stapler.

## Results

The presence of urothelial carcinoma with clinical stage T2, diagnosed on bladder resection biopsy, was

**Table 3.** Quantitative descriptive analysis of radical cystectomy

Table variable	Average (± DP)	Median (P25-P75)
Patient's age (Years)	64.65 (± 11)	65.0
Surgical time (min.)	260.26 (± 57)	240.0
Estimated bleeding (mL)	639 (± 386)	500.0
Hospitalization (days)	9.5 (± 4.6)	8.0
ICU PO (days)	2.1 (± 2.3)	1.5
Creatinine (preop.)	1.16 (± 0.3)	1.2
Creatinine (Hospital discharge)	0.92 (± 0.3)	0.7

the most frequent indication for performing RC (Table 2). The average age was 64.6 years (36-81 years), of which 70% were male.

The predominant urinary diversion was the Bricker, which was performed in 85% of cases, wet colostomy in 10%, and neobladder in 5%. The average duration of surgery was 260 min, with average intraoperative bleeding of 640 mL. The average length of stay was 9.5 days (Table 3). Thirteen patients (65%) were referred to the ICU in the immediate post-operative period.

Of the 18 patients operated on, there was down staging in only one patient, while there was upstaging in 9 (50%) patients (Table 4). In addition, there were no low-grade patients in pathological staging (Table 5).

There was a significant correlation between surgical time and the need for ICU in the post-operative period ( $p < 0.001$ ) and, the need and length of ICU stay was greater with a longer surgical time (230 min) (Fig. 1).

Post-operative complications were reported in the first 30 days after RC in 35% of patients, with 20% of the cases having mild complications (Clavien I/II) and in 15% Clavien III. The most frequent complications were eventration (n: 3), need for transfusion (n: 1), acute renal insufficiency (n: 1), and infection of the operative wound (n: 1). There were no deaths.

There was statistical significance regarding estimated bleeding and complications ( $p = 0.03$ ) (Table 6). The average bleeding in the 12 patients who had zero Clavien-Dindo classification was 480 ml, significantly lower than the average bleeding in the patients who had Clavien II classification (1300 mL).

There was no statistical difference between the Clavien-Dindo classifications in relation to surgical time ( $p = 0.697$ ), between the presence of comorbidities and

**Table 4.** Description of the staging evolution of patients undergoing cystectomy during the pandemic

Staging T, n (%)	Pathological						Total
	Tis	Ta	T1	T2	T3	T4	
Clinical							
Ta	0 (0)	1 (5.56)	3 (16.67)	1 (5.56)	0 (0)	0 (0)	5 (27.78)
T1	0 (0)	0 (0)	2 (11.11)	2 (11.11)	0 (0)	0 (0)	4 (22.22)
T2	1 (5.56)	0 (0)	0 (0)	4 (22.22)	1 (5.56)	2 (11.11)	8 (44.44)
T4a	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.56)	1 (5.56)
Total	1 (5.56)	1 (5.56)	5 (27.78)	7 (38.89)	1 (5.56)	3 (16.67)	18 (100)

	Upstanding
	Downstanding
	No change

**Table 5.** Description concerning the evolution of the histologic grade of the patients submitted to the cystectomy during the pandemic

Grade n, (%)	Post		Overall Total
	Low	High	
Pre			
Low	0 (0)	5 (27.78)	5 (27.78)
High	0 (0)	13 (72.22)	13 (72.22)
Overall Total	0 (0)	18 (100)	18 (100)

	Upstanding
	Downstanding

length of ICU stay ( $p = 0.404$ ), between estimated bleeding and ICU requirement ( $p = 0.122$ ), nor between surgical time and estimated bleeding ( $p = 0.229$ ).

Oral feeding was introduced on the 3<sup>rd</sup> post-operative day in all patients, with a good acceptance and daily progression until hospital discharge.

Hospital readmissions were necessary in the first few days in two cases, due to eventration, with new surgical procedures, and acute obstructive functional abdomen with conservative management.

## Discussion

Our study showed that it was possible to perform open RC within the learning curve of the junior resident physician, with an average time of 4 h. In this series, 10 (50%) patients studied did not need blood

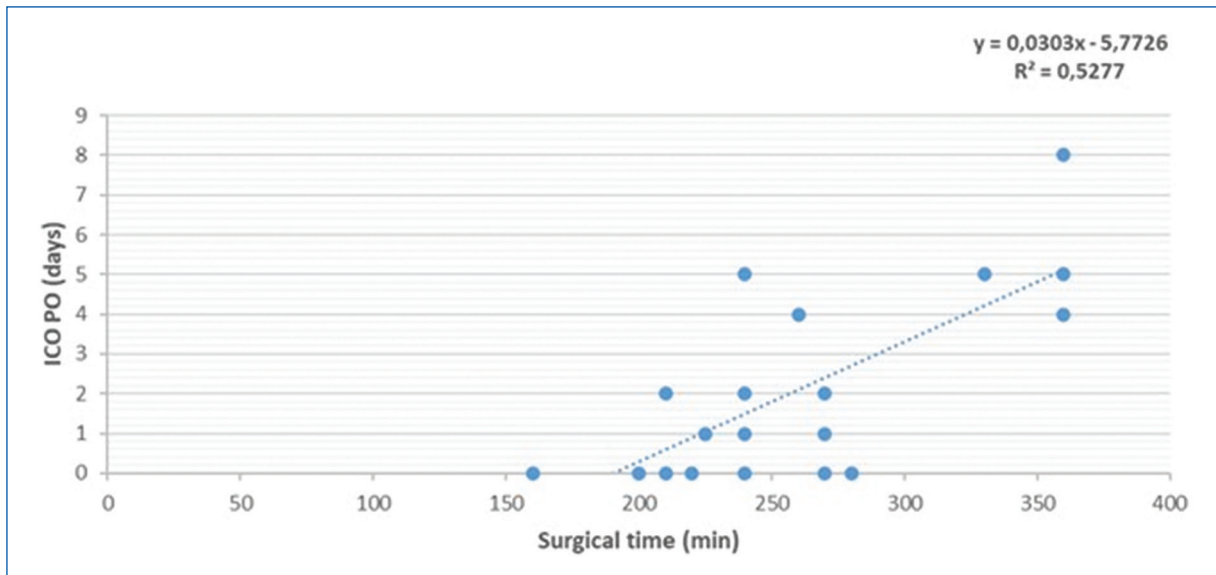
transfusions and 7 (35%) did not need post-operative intensive care, with an average hospital stay of 9.5 days.

MIBC is an aggressive disease, with high mortality rates, and when untreated, the overall survival rate reaches 15% in 2 years<sup>9</sup>. Therefore, RC with pelvic lymphadenectomy is the gold standard treatment<sup>5</sup>, resulting in better local control of the disease, increased survival, and decreased chance of metastasis, both for MIBC and non-muscle invasive cases. In these individuals, indications for early cystectomy are based on disease substage<sup>4</sup>.

In our study, in 45% of cases, early cystectomy was performed but was only confirmed to be a non-muscle invasive pathological disease in 35% of cases.

Patients who present disease progression to MIBC have a worse prognosis relative to those who already present the MIBC<sup>10</sup>. Medical condition knows that RC, before progressing to MIBC, provides a disease-free survival > 80% in 5 years<sup>11</sup>. After analyzing the risks, morbidity, impact on quality of life, and benefits of RC, along with a shared decision, early RC is selected.

Lymphadenectomy was performed in 95% of the patients. It was not performed in one patient with a synchronous lung neoplastic lesion. Lymphadenectomy can increase survival rates as it decreases tumor volume, allowing the immune system and chemotherapy drugs to target fewer cancer cells, improving efficiency. Extended pelvic lymphadenectomy has the best oncological results<sup>2</sup>, given that up to 50% of patients with lymph node involvement can be free of the disease after this procedure<sup>12</sup>. This is relevant as the incidence of lymph node metastasis is  $\leq 5\%$  for < T2, about 25% in T2, and 40-45% in T3-4<sup>2</sup>.



**Figure 1.** Results of the correlation analysis between surgical time and the number of days in the ICU.

**Table 6.** Post-operative complications

Variables	Clavien-Dindo Classification												
	0			I			II			III			p-value
	n	Average	SD	n	Average	SD	n	Average	SD	n	Average	SD	
Surgical time (min)	13	251.54	57.42	2	305	35.36	1	260	-	3	268.33	79.43	0.697
Estimated bleeding (mL)	13	480.77	285.44	2	100	707.11	1	1300	-	3	866.67	115.47	0.03

Therefore, knowing all the issues facing non-profit public hospitals with medical residency in urology, our study gathered experience with a considerable volume of RC performed over 8 months, compared to a reference center in the disease according to European guidelines<sup>13</sup>.

In addition, the relevance and importance of maintaining the assistance to uro-oncologic patients with BC amid the pandemic of COVID-19 are emphasized given the need and benefit of surgery within 90 days of diagnosis and that the delay in performing the RC is associated with a 34% reduction of survival in 3 years with the progression of the pathological stage<sup>8</sup>.

In this study, the average age was 64.6 years, compared to other studies, which were 67.8 years<sup>14</sup>. The prevalence was higher for males (70%) and smokers (75%), according to Van Osch et al<sup>15</sup>. The average

hospital stay was 9.5 days and was substantially longer for the 80-year-old patient.

Most patients were pT2 (65%) and high-grade (100%), according to Araújo et al.<sup>14</sup>, with 30% exhibiting lymph node disease. In 15% of cases, neoadjuvant chemotherapy was performed.

The analysis between surgical time and hospital stay in the ICU, with a directly proportional result, leads us to conclude that the systematization of the surgical technique, associated with the institutional protocol of pre- and post-operative care is fundamental to reduce the morbidity inherent to the surgery. Emphasizing that the RC surgery is performed by the 2<sup>nd</sup>-year urology resident in collaboration with the uro-oncology preceptorship of the service.

In this series, acute complications occurred in 35% of cases, such as surgical wound infections, temporary renal insufficiency, and eventration, with no deaths.



It should be noted that this study demonstrated a significant statistical correlation between bleeding and degrees of complication. In a different series<sup>14,16</sup>, the most common complications were prolonged paralytic ileus 14%, infection/dehiscence of operative wound 8%, evisceration 7%, pneumonia 3%, and intestinal fistula 1.5%. Furthermore, age is a predictive factor of greater complication, especially for those older than 80 years, reaching up to 67% in this age range<sup>14</sup>.

As limitations to our study, we have a small sample in a short period of time and a lack of assessments of late complications. As for positives, the analysis was prospective, with a single Proctor who has worked with the residents since 2014, with vast experience in teaching hospitals<sup>17</sup>. The standardization of the surgical technique associated with rigorous postoperative control applied routinely does not overload the hospital system.

One of the benefits of this study is public knowledge of RC on MIBC conducted in a non-profit teaching hospital during the COVID-19 pandemic, highlighting the early treatment of the disease. Another important point is the increase of knowledge about the epidemiological profile of this hospital, with exposure of data that can be compared to other national services of medical residence.

## Conclusion

Despite the surgical complexity, the execution of radical cystectomies with urinary diversion during the pandemic, in a teaching hospital, is feasible. The prioritization of this procedure in the face of other urogenital neoplasms is essential to reduce unfavorable outcomes related to the delay in the definitive treatment.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the institutional research protocols of the hospital where this study was developed.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee to carry out this study and of the clinical data of patients were taken from the electronic medical record and informed consent was not required.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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