

Article

Contemporary Trends and Predictors of pT0 in Radical Cystectomy Specimens Among Non-Muscle and Muscle-Invasive Bladder Cancer Patients: A Propensity Score-Matched Analysis from a Single Tertiary Centre in the United Kingdom

Francesco Del Giudice ^{1,2,3,*}, Valerio Santarelli ^{1,†}, Katarina Spurna ³, Syed Ghazi Ali Kirmani ³, Noor Huda Bhatti ³, Yasmin Abu-Ghanem ³, Elsie Mensah ³, Benjamin Challacombe ³, Samuel J. Davies ³, Mohammad Hegazy ³, Youssef Ibrahim ³, Mohammed Gad ³, Amir Khan ⁴, Roberta Corvino ¹, Felice Crocetto ⁵, Jan Łaszkiewicz ⁶, Bernardo Rocco ⁷, Benjamin I. Chung ², Ramesh Thuraraja ³, Muhammad Shamin Khan ^{3,‡} and Rajesh Nair ^{3,‡}

¹ Department of Maternal-Infant and Urological Sciences, “Sapienza” University of Rome, Umberto I Hospital, 00185 Rome, Italy

² Department of Urology, Stanford University School of Medicine, Stanford, CA 94304, USA

³ Guy’s and St. Thomas’ NHS Foundation Trust, Guy’s Hospital, London SE1 7EH, UK

⁴ Division of Urology, University of Maryland School of Medicine, Baltimore, MD 21201, USA

⁵ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples “Federico II”, 80131 Naples, Italy

⁶ University Centre of Excellence in Urology, Wrocław Medical University, 50367 Wrocław, Poland

⁷ Department of Urology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, 00136 Rome, Italy

* Correspondence: francesco.delgiudice@uniroma1.it; Tel.: +39-0649974201

† These authors contributed equally to this work.

‡ These authors are co-last authors.



Academic Editor: Fumitaka Koga

Received: 9 August 2025

Revised: 16 September 2025

Accepted: 19 September 2025

Published: 24 September 2025

Citation: Del Giudice, F.; Santarelli, V.; Spurna, K.; Ali Kirmani, S.G.; Bhatti, N.H.; Abu-Ghanem, Y.; Mensah, E.; Challacombe, B.; Davies, S.J.; Hegazy, M.; et al. Contemporary Trends and Predictors of pT0 in Radical Cystectomy Specimens Among Non-Muscle and Muscle-Invasive Bladder Cancer Patients: A Propensity Score-Matched Analysis from a Single Tertiary Centre in the United Kingdom. *Cancers* **2025**, *17*, 3110. <https://doi.org/10.3390/cancers17193110>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary

In bladder cancer patients treated with radical cystectomy with or without neoadjuvant chemotherapy, the achievement of no residual tumour is related to better survival outcomes. The aim of the study was to identify the main clinical and pathological features in this population as it could lead to refine treatment choices including bladder-sparing strategies. We examined patients with both Non Muscle-Invasive and Muscle Invasive Bladder Cancer treated between 2009 and 2024. Findings showed how obtaining a cancer-free status after treatment was more likely in male patients (for NMIBC), undergoing neoadjuvant chemotherapy (for MIBC), and without additional risk factors, such as BCG unresponsiveness and concomitant CIS (for both NMIBC and MIBC). These findings support personalization of care through tailoring of therapeutic choices to patient and tumour characteristics.

Abstract

Introduction: Absence of residual cancer in radical cystectomy (RC) specimens is a well-known positive prognostic factor for non-muscle and muscle-invasive bladder cancer (NMIBC and MIBC) in patients with or without neoadjuvant chemotherapy (NAC). Understanding the clinical and pathological features associated with a final pT0 status can provide valuable prognostic insights, serve as a surrogate marker for survival outcomes, and help identify candidates suitable for bladder-sparing strategies. **Methods:** Temporal trends and clinical/demographic characteristics across clinically high-/very-high-risk NMIBC or MIBC RC patients from 2009 to 2024 were explored. Subsequently, RC pT0 patients were propensity score-matched (PSM, 1:1 ratio) with the >pT0 population based on age-adjusted

CCI and preoperative clinical stage (cTis-T1 vs. cT2). Multivariable regression modelling was applied to explore predictors of pT0 status stratified according to clinical NMIBC or MIBC status. **Results:** A total of 655 RCs performed with curative intent were included (43% for MIBC, 57% for NMIBC). Of these, 117 were pT0 at final pathological assessment (68 NMIBC and 49 MIBC). Subsequently, 228 PSM patients (114 pT0 vs. 114 >pT0) were extracted from the original cohort and stratified according to preoperative clinical stage (MIBC vs. NMIBC). In multivariable analysis, male gender was associated with an increased likelihood of pT0 status in the NMIBC cohort (adjusted odds ratio [aOR] 2.89, 95% CI 1.13–7.90). Conversely, BCG failure and concomitant CIS independently reduced the chances of achieving pT0 status (aOR: 0.40, 95% CI 0.19–0.99; aOR: 0.16, 95% CI 0.03–0.97). For MIBC patients, as expected, NAC more than doubled the chances of achieving pT0 status (aOR: 2.20, 95% CI 1.01–6.82). On the other hand, the concomitant presence of CIS reduced the likelihood of pT0 achievement (aOR 0.22, 95% CI, 0.06–0.80). In both cohorts, the presence of variant histology (VH) demonstrated a negative association with pT0 achievement; however, the estimated effect did not reach statistical significance ($p = 0.09$ and $p = 0.08$). **Conclusions:** Our findings suggest potentially raising the threshold for RC consideration in high-risk or very-high-risk NMIBC patients with a favourable risk profile. MIBC patients without additional risk factors (CIS and VH) are more likely to achieve a tumour-free status, particularly when adequately receiving NAC.

Keywords: bladder cancer; radical cystectomy; downstaging; NMIBC

1. Introduction

Radical cystectomy (RC) is the current gold-standard surgical treatment with or without neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (MIBC). Non-muscle-invasive bladder cancer (NMIBC) accounts for 75% of new BC diagnoses and can effectively be treated conservatively in most cases, with Transurethral Resection of Bladder Tumour (TURBT) followed by adjuvant intravesical chemotherapy or Bacillus Calmette–Guérin (BCG) [1,2]. However, when conservatively managed, up to 45% of high-risk or very-high-risk NMIBC patients may progress to muscle-invasive disease within 5 years [3]. Risk classifications have been used as a useful tool to risk stratify NMIBC, serving as a guide for appropriate treatment recommendations, surveillance schedules, and recruitment into clinical trials [4]. The European Association of Urology (EAU) expanded the spectrum to the ‘very-high-risk’ class in addition to the existing low, intermediate, and high-risk stratifications [5]. These updated prognostic risk groups are based on patients’ and tumour characteristics as well WHO 1973 and WHO 2004/2016 grade classifications, predicting the risk of progression to MIBC at 1, 5, and 10-years. The calculated probability of progression at 10 years is as low as 3% for low-risk disease but as high as 59% for very-high-risk patients. Accordingly, current EAU guidelines include recommendations for offering upfront RC to high-risk patients and strongly recommend it for the very-high-risk group [6]. However, this novel risk stratification is not without limitations. Firstly, it does not take into account the positive prognostic effect of adjuvant BCG treatment, which has been demonstrated to reduce the risk of progression [7]. Secondly in BCG-unresponsive NMIBC, other treatment options, mainly Immune Checkpoint Inhibitors (ICIs), have emerged as valid and safe alternatives to upfront RC [8]. Finally, current risk stratification does not consider additional prognostic features, such as Carcinoma In Situ (CIS) in the prostatic urethra, variant histology (VH), a history of recurrence, and recurrence rate by year [9].

While the absence of residual cancer in RC specimens (pT0) is commonly perceived by urologists as a positive prognostic pathological finding, it raises concerns of overtreatment for NMIBC as RC has serious detrimental impacts on patients' Quality of Life (QoL) [10,11].

In the case of MIBC, pT0 in RC specimens with or without prior NAC confers an overall and cancer-specific survival benefit [10,12]. However, those with final pT0 staging may be potential candidates for bladder-sparing surgery (BSS). The aim of our study is to analyse preoperative clinical and pathological characteristics from our institutional pT0 cohort of RC patients. The key objective is to identify those variables which increase the likelihood of achieving a pT0 status at final pathology in two distinct cohorts—NMIBC and MIBC. Lastly, we provide a contemporary overview of pT0 trends following RC, with the goal of enhancing patient counselling and refining the prognostic implications associated with this pathological outcome.

2. Materials and Methods

2.1. Study Cohort

All patients undergoing radical cystectomy at our institution between 2009 and 2024 for either high-/very-high-risk NMIBC or T2N0M0 MIBC with curative intent were retrospectively reviewed from our prospectively maintained institutional RC database. Clinical, anthropometric, and demographic characteristics (i.e., gender, Age-adjusted Charlson Comorbidity Index [ACCI], body mass index [BMI], age, renal function) were recorded. Patients' management at the time of RC was according to the Trust, National, and EAU Guidelines. The inclusion criteria were as follows: the absence of distant metastases at preoperative clinical staging; histologically confirmed diagnosis of urothelial or mixed histology, primary or recurrent BC; at least one prior TURBT before RC; RC performed as primary treatment option with curative intent; the ability to sign an informed consent for the procedure and the adoption of de-identified data for research purposes. Exclusion criteria were the presence of radiologically suspected or histologically confirmed distant metastases and previous External Beam Pelvic Radiation Therapy (EBRT) or cystectomy (not RC) performed for indications other than BC (e.g., chronic pelvic pain syndrome, radiation cystitis, palliative or salvage intent).

Preoperative local and distant staging was performed with TURBT and a combination of Computerized Tomography (CT), pelvic multiparametric Magnetic Resonance Imaging (mpMRI), or fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT), as appropriate for indications and contraindications for each diagnostic modality in accordance with Urothelial Multidisciplinary Team (MDT) recommendations. According to MDT recommendations and following the latest EAU guidelines, NAC was offered only to cisplatin-eligible MIBC patients and performed with a combination of cisplatin and at least one additional chemotherapeutic agent. The high risk of disease progression was discussed with high-/very-high-risk NMIBC patients, as well as the possible complications and impact on Quality of Life (QoL) associated with RC, in line with the principles of shared and informed decision-making. In accordance with EAU guidelines, predictors of higher risk of disease progression not included in current risk stratification (such as BCG unresponsiveness and histological variants) were also discussed. In accordance with EAU guidelines, BCG failure broadly refers to any HG disease occurring during or after BCG therapy [13].

2.2. Surgical Procedure

All RCs were performed by a team of three experienced consultants (MSK, RT, RN) at the same institution and in the setting of a UK-certified Robotic Clinical Fellowship programme. All patients underwent RC with an open or robotic-assisted approach, carried

out with the standardized technique previously described [14]. The diversion of choice (intracorporeal or extracorporeal Ileal Conduit [IC], Orthotopic Neobladder, or Ureterocutaneostomy [UCS]) was selected after adequate patient counselling and MDT assessment. The decision to perform a Pelvic Lymphadenectomy (PLND), with either a standard or extended template, was left to the surgeon's discretion, in accordance with preoperative staging and MDT discussions.

All RC specimens were analysed by experienced uropathologists with >20 years of experience in urological malignancies. The histological subtype, pathological T (pT) and N (pN) stage, number of lymph nodes, grade, surgical margins, concomitant CIS, and lymph-vascular invasion were recorded in the final histopathological report, in accordance with the American Joint Committee on Cancer (AJCC) guidelines. pT0 status was defined as the absence of residual cancer in the RC specimen.

2.3. Statistical Analysis

Statistical analyses were performed with STATA version 18.1 (Stata Corporation, College Station, TX, USA) and SPSS version 27.0 (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA: IBM Corp.), following the standardized methodology previously described [15]. Descriptive statistics summarized baseline characteristics of the study population. Pertinent continuous variables were reported as the median and interquartile range (IQR) and categorical variables as numbers and percentages. To balance baseline characteristics, a 1:1 propensity score match (PSM) analysis using the nearest-neighbour method with a calliper size of 0.1 was performed between pT0 and non-pT0 patients based on Age-adjusted CCI and preoperative clinical stage (NMIBC vs. MIBC). Subsequently, pertinent study information of the matched cohorts was reported, stratified according to clinical stage (cTis-T1 vs. cT2) and pathological T stage (pT0 or >pT0). Quantitative data and pairwise intergroup comparison of variables was conducted with the Mann-Whitney test or the ANOVA one-way test. Lastly, clinically relevant variables were selected for multivariable logistic regression modelling to identify independent predictors of the absence of residual cancer in RC specimens (pT0) separately for MIBC and NMIBC patient cohorts.

3. Results

3.1. Description of the Study Cohort

A total of 655 patients, 498 (76%) males and 157 (24%) females, who underwent RC with curative intent at our institution were included the analysis. The general characteristics of the studied population are described in Table 1. The median age, BMI, and ACCI were 69.6 (IQR 62.7–75.3), 27.5 (IQR 22.7–32.3), and 5 (3–6), respectively. Of these, 373 (57%) had high- or very-high-risk NMIBC, while 282 (43%) had MIBC. Of the entire cohort, 117 (17.9%) had pT0 in the RC specimen. The rate of patients achieving a pT0 status was the highest in 2009 (41% of NMIBC and 25% for MIBC) and the lowest in 2018 (4% of NMIBC and 0% of MIBC), showing variable prevalence patterns during the years (Figure 1). Subsequently, 114 of the 117 pT0 patients were matched with patients with 114 >pT0 patients based on the ACCI and according to the original preoperative clinical stage (NMIBC vs. MIBC). A comparison of preoperative, perioperative, and pathological characteristics between pT0 and >pT0 patients is reported in Table 2, stratified by preoperative cT stage group. In the NMIBC group, pT0 patients were more frequently males ($n = 54$ [83.1%] males and $n = 11$ [16.9%] females) when compared to the >pT0 cohort ($n = 43$ [66.2%] males and $n = 22$ [33.8%] females ($p = 0.027$)) and had lower rates of BCG treatment failure (53.8% vs. 46.2%, $p = 0.018$).

Table 1. The baseline characteristics of the study population before propensity score matching. **BMI:** body mass index; **ACCI:** Age-adjusted Charlson Comorbidity Index; **EGFR:** Estimated Glomerular Filtration Rate; **MDM:** Multidisciplinary Meeting; **CT:** Computerized Tomography; **MRI:** Magnetic Resonance Imaging; **LG:** low grade; **HG:** high grade; **BCG:** Bacillus Calmette–Guérin; **NAC:** neoadjuvant chemotherapy.

Variable	Total N = 655
Sex	
-Male	498 (76%)
-Female	157 (24%)
Age	69.6 (62.7–75.3)
BMI	27.5 (24.2–30.7)
ACCI	5 (3–6)
Ethnicity	
-White	508 (77.53%)
-Black	28 (4.3%)
-Asian	21 (3.21%)
-Other	98 (14.96%)
EGFR	73 (60–86)
Creatinine (mg/L)	86 (75–102)
Discussed in Pelvic MDM	
-No	255 (39%)
-Yes	400 (61%)
CT	
-No	28 (4.3%)
-Yes	627 (95.7%)
MRI	
-No	563 (86%)
-Yes	92 (14%)
Grade	
-LG	34 (5.2%)
-HG	621 (94.8%)
MIBC vs. NMIBC	
-NMIBC	373 (57%)
-MIBC	282 (43%)
Clinical T Stage	
-T0	3 (0.5%)
-Ta	74 (11.3%)
-Tis	30 (4.6%)
-T1	266 (40.5%)
-T2	272 (41.5%)
-T3	9 (1.4%)
-T4	1 (0.2%)
Clinical N Stage	
-Nx	62 (9.5%)
-N0	586 (89.5%)
-N1	7 (1%)
BCG Failure	
-No	355 (54.2%)
-Yes	300 (45.8%)

Table 1. Cont.

Variable	Total N = 655
NAC	
-No	493 (75.3%)
-Yes	162 (24.7%)
Pathological T Stage	
-T0	117 (17.9%)
->T0	538 (82.1%)



Figure 1. Rates of pT0 achievement by year across $n = 655$ radical cystectomies with curative intent performed between 2009 and 2024. **NMIBC**: non-muscle-invasive bladder cancer; **MIBC**: muscle-invasive bladder cancer.

Table 2. General characteristics based on preoperative stage category (NMIBC vs. MIBC) and final pathological T Stage (T0 vs. >pT0). **BMI**: body mass index; **ACCI**: Age-adjusted Charlson Comorbidity Index; **EGFR**: Estimated Glomerular Filtration Rate; **MDM**: Multidisciplinary Meeting; **BCG**: Bacillus Calmette–Guérin; **UCS**: Ureterocutaneostomy; **IC**: Ileal Conduit; **CT**: Computerized Tomography; **MRI**: Magnetic Resonance Imaging; **PET CT**: positron emission tomography CT; **LG**: low grade; **HG**: high grade; **CIS**: Carcinoma In Situ; **NAC**: neoadjuvant chemotherapy; **OT**: operative time; **EBL**: estimated blood loss; **LOS**: length of stay.

Variable	Total $n = 228$	NMIBC $n = 130$		p Value	MIBC $n = 98$		p Value
		>pT0 $n = 65$	pT0 $n = 65$		>pT0 $n = 49$	pT0 $n = 49$	
Sex							
-Male	169 (74.1%)	43 (66.2%)	54 (83.1%)	0.027	33 (67.3%)	39 (79.6%)	0.170
-Female	59 (25.9%)	22 (33.8%)	11 (16.9%)		16 (32.7%)	10 (20.4%)	
Ethnicity							
-White	182 (79.8%)	51 (78.5%)	52 (80%)	0.4	37 (73.5%)	42 (85.7%)	0.5
-Black	10 (4.4%)	2 (3.1%)	4 (6.2%)		3 (6.1%)	1 (2%)	
-Asian	7 (3.1%)	1 (1.5%)	4 (6.2%)		1 (2%)	1 (2%)	
-Other	29 (12.7%)	11 (16.9%)	5 (7.7%)		8 (16.3%)	5 (10.2%)	
Age	69.3 (62.7–75.1)	69.1 (62.3–76.8)	70.6 (63.2–76.1)	0.7	66 (56.7–74.3)	70 (63.5–75.2)	0.05
BMI	27.5 (24–30.7)	27.7 (23.7–32.3)	27.4 (24.7–29.9)	0.44	27.2 (23.4–29.9)	27.3 (24–32.5)	0.17
ACCI	5 (3–6)	5 (2.5–6)	5 (4–6)	0.75	5 (2–6)	5 (3–6.26)	0.6

Table 2. Cont.

Variable	Total <i>n</i> = 228	NMIBC <i>n</i> = 130			MIBC <i>n</i> = 98		
		>pT0 <i>n</i> = 65	pT0 <i>n</i> = 65	<i>p</i> Value	>pT0 <i>n</i> = 49	pT0 <i>n</i> = 49	<i>p</i> Value
EGFR	75 (62.5–87)	73 (63–86.5)	77 (63–98.5)	0.13	75 (66–86.75)	71 (55–87)	0.07
Creatinine (mg/L)	84 (73–96)	87 (77–96)	83 (67–91)	0.04	83.5 (75–96.25)	90 (69–106)	0.18
Discussed in Pelvic MDM							
-No	64 (28.1%)	14 (21.5%)	21 (32.3%)	0.16	16 (32.7%)	13 (26.5%)	0.5
-Yes	164 (71.9%)	51 (78.5%)	44 (67.7%)		33 (67.3%)	36 (73.5%)	
BCG failure							
-No	117 (51.3%)	17 (26.2%)	30 (46.2%)	0.018	32 (65.3%)	38 (71.4%)	0.18
-Yes	111 (48.7%)	48 (73.8%)	35 (53.8%)		17 (34.7%)	11 (22.4%)	
NAC							
-No	169 (74.1%)	64 (98.5%)	62 (95.4%)	0.3	27 (55.1%)	16 (32.7%)	0.04
-Yes	59 (25.9%)	1 (1.5%)	3 (4.6%)		22 (44.9%)	33 (67.3%)	
Technique							
-Open	61 (26.8%)	21 (32.3%)	14 (21.5%)	0.16	13 (26.5%)	13 (26.5%)	0.6
-Robotic	166 (72.8%)	44 (67.7%)	51 (78.5%)		36 (73.5%)	35 (71.4%)	
Laparoscopic	1 (0.4%)	0	0		0	1 (2%)	
Diversion Type							
-UCS	1 (0.4%)	1 (1.5%)	0	0.56			0.045
-IC	210 (92.1%)	61 (93.8%)	4 (6.2%)		47 (95.9%)	41 (83.7%)	
-Neobladder	17 (7.5%)	3 (4.6%)	61 (93.8%)		2 (4.1%)	8 (16.3%)	
Lymph Node Excision Technique							
-Not Performed	17 (7.5%)	5 (7.7%)	9 (13.8%)	0.5	3 (6.1%)	0	0.2
-Standard	166 (72.8%)	48 (73.8%)	44 (67.7%)		36 (73.5%)	38 (77.6%)	
-Extended	45 (19.7%)	12 (18.5%)	12 (18.5%)		10 (20.4%)	11 (22.4%)	
Clinical T Stage							
-Ta	35 (15.4%)	16 (24.6%)	19 (29.2%)	0.004	0	0	0.004
-Tis	8 (3.5%)	7 (10.8%)	1 (1.5%)		0	0	
-T1	87 (38.1%)	42 (64.6%)	45 (67.7%)		0	0	
-T2	88 (38.6%)	0			39 (79.6%)	49 (100%)	
-T3	9 (3.9%)	0			9 (18.4%)	0	
-T4	1 (0.4%)	0			1 (2%)	0	
Clinical N Stage							
-Nx	24 (10.4%)	10 (15.4%)	6 (9.2%)	0.29	4 (8.2%)	4 (8.2%)	0.6
-N0	202 (88.6%)	55 (84.6%)	58 (89.2%)		45 (91.8%)	44 (89.8%)	
-N1	3 (0.9%)	0	1 (1.5%)		0	1 (2%)	
Grade							
-LG	12 (5.3%)	3 (4.6%)	7 (10.8%)	0.19	0	2 (4.1%)	0.15
-HG	216 (94.7%)	62 (95.4%)	58 (89.2%)		49 (100%)	47 (98%)	
Histological Variant							
-No	202 (88.6%)	58 (89.2%)	63 (96.9%)	0.08	37 (75.5%)	44 (89.8%)	0.06
-Yes	26 (11.4%)	7 (10.8%)	2 (3.1%)		12 (24.5%)	5 (10.2%)	
Additional CIS							
-No	153 (67.1%)	30 (46.2%)	41 (63.1%)	0.05	37 (75.5%)	45 (91.8%)	0.029
-Yes	75 (32.9%)	35 (53.8%)	24 (36.9%)		12 (24.5%)	4 (8.2%)	

Table 2. Cont.

Variable	Total <i>n</i> = 228	NMIBC <i>n</i> = 130		<i>p</i> Value	MIBC <i>n</i> = 98		<i>p</i> Value
		>pT0 <i>n</i> = 65	pT0 <i>n</i> = 65		>pT0 <i>n</i> = 49	pT0 <i>n</i> = 49	
pT Stage							
-T0	114 (50%)	0	65 (100%)		0	49 (100%)	
-Ta	15 (6.6%)	14 (21.5%)	0	<0.001	1 (2%)	0	<0.001
-Tis	20 (8.8%)	17 (26.2%)	0		3 (6.1%)	0	
-T1	21 (9.2%)	18 (27.7%)	0		3 (6.1%)	0	
-T2	22 (9.6%)	9 (13.8%)	0		13 (26.5%)	0	
-T3	28 (12.3%)	4 (6.2%)	0		24 (49%)	0	
-T4	8 (3.5%)	3 (4.6%)	0		5 (10.2%)	0	
pN Stage							
-Nx	17 (7.5%)	5 (7.7%)	6 (9.2%)	0.5	4 (8.2%)	2 (4.1%)	0.03
-N0	191 (83.7%)	57 (87.7%)	58 (89.2%)		30 (61.2%)	46 (93.8%)	
-N1	10 (4.0%)	2 (3.1%)	1 (1.5%)		6 (12.2%)	1 (2%)	
-N2	9 (3.9%)	1 (1.5%)	0		8 (16.3%)	0	
-N3	1 (0.4%)	0	0		1 (2%)	0	
Lymph Node Yield	17 (12–22)	17 (13–23)	15 (10–22)	0.3	17 (12–21)	17.5 (12.7–21.2)	0.7
Positive Surgical Margins							
-No	220 (96.5%)	64 (98.5%)	65 (100%)	0.3	42 (85.7%)	49 (100%)	0.006
-Yes	8 (3.5%)	1 (1.5%)	0		7 (14.3%)	0	

In the MIBC group, pT0 patients were significantly older (median age: 70 [IQR 63.5–75.2] vs. 66 [IQR 56.7–74.3], $p = 0.05$) and a higher number had received NAC ($n = 33$ [67.3%] vs. $n = 22$ [44.9%], $p = 0.04$). In both groups, pT0 patients were less likely to have CIS at preoperative TURBT (36.9% vs. 53.8% for NMIBC, $p = 0.05$, and 8.2% vs. 24.5% for MIBC, $p = 0.029$). Moreover, pT0 patients of both groups had lower rates of VH at TURBT specimen, but the difference did not reach significance ($p = 0.08$ and $p = 0.06$), mainly due to the relatively low prevalence of histological variants (only 11.4% of the whole TUR samples). Only one pT0 patient per group had cN+ at final histology.

3.2. Predictors of pT0 Status by Clinical Stage Group

Conditional multivariate logistic regression exploring the likelihood of pT0 across the PSM population is shown in Tables 3 and 4 for NMIBC and MIBC, respectively. In the first group, across the explored variables, male gender was only associated with an increased likelihood of pT0 (aOR: 2.89, 95% CI 1.13–7.30). Conversely, previous BCG treatment failure and additional CIS significantly and independently decreased the likelihood of pT0 in NMIBC patients (aOR: 0.40, 95% CI 0.19–0.92, and OR: 0.16, 95% CI 0.03–0.97). For MIBC patients, only concomitant CIS preoperatively was found to be a negative predictor of final pT0 status (aOR: 0.22, 95% CI 0.06–0.83). On the other hand, NAC more than doubled the likelihood of absence of residual tumour in the final pathological analysis (aOR: 2.20, 95% CI 1.01–6.82, $p = 0.049$). In both groups, the presence of VH at TURBT predicted a detrimental impact on pT0 status, but the impact did not reach statistical significance, very likely due to the fact that only few cases presented with reported preoperative VH across the specific population (aOR: 0.49, 95% CI 0.20–1.08 and aOR: 0.36, 95% CI 0.10–1.21 for NMIBC and MIBC, respectively).

Table 3. Multivariate regression exploring predictors of T0 in NMIBC patients. **aOR**: adjusted odds ratio; **CI**: Confidence Interval; **MDM**: Multidisciplinary Meeting; **BCG**: Bacillus Calmette–Guérin; **CIS**: Carcinoma in Situ.

Variable	aOR	95% CI	p Value
Male gender	2.89	1.13–7.30	0.026
Discussed in Pelvic MDM	0.71	0.32–1.4	0.3
BCG Failure	0.40	0.19–0.99	0.05
Additional CIS	0.16	0.025–0.97	0.04
Histological variant	0.49	0.21–1.08	0.08

Table 4. Multivariate regression exploring predictors of T0 in MIBC patients. **aOR**: adjusted odds ratio; **CI**: Confidence Interval; **MDM**: Multidisciplinary Meeting; **CIS**: Carcinoma in Situ.

Variable	aOR	95% CI	p Value
Male gender	1.97	0.74–5.25	0.26
Discussed in Pelvic MDM	1.14	0.41–3.16	0.8
Neoadjuvant Chemotherapy	2.20	1.01–6.82	0.049
Additional CIS	0.22	0.06–0.80	0.02
Histological variant	0.36	0.1–1.21	0.09

4. Discussion

In recent years, BSS has been discussed as a possible alternative to RC in selected cases, provisionally demonstrating similar survival outcomes, but the evidence base is relatively less robust [16]. Hence, RC remains the gold standard to achieve a cure in localized disease. It is also considered a safer option for those patients with poor adherence to follow-up. However, RC is a urological intervention with high morbidity, possibly resulting in a significant decline in patients' perceived QoL [11,17,18]. Despite recent increased attention towards multimodal rehabilitation programmes, RC negatively impacts urinary, bowel, and sexual function and affects perceived body image, which can lead to psychological sequelae [19,20].

Current guidelines recommend platinum-based NAC for platinum-eligible cT2–T4N0M0 patients [21]; recent evidence confirms the positive prognostic significance of pT0 status after RC and suggests that the survival benefit of NAC is strictly dependent on the increased probability of downstaging to pT0 disease [10,12,22]. Delayed time to RC and suboptimal chemotherapy are the main factors associated with a poor response to NAC, which ultimately affects survival outcomes [23]. A higher tumour grade and cT have also been associated with failure to achieve complete pathological response and an increased risk of later upstaging [14,24]. Regarding VH, studies focusing on the ideal treatment approach are scarce. Some studies show that tumours with variant histologic patterns have a greater pathological response to NAC, while others report lower rates of ypT0 when compared to Pure Urothelial Carcinoma (PUC) [25,26]. The main limitation of currently available studies lies in the tendency to treat histological variants as a single entity. This approach, justified by the low overall prevalence of histological variants, overlooks the distinct microscopic and nuclear features that characterize each variant, which may significantly influence their individual responsiveness to chemotherapy.

The risk of progression for NMIBC is defined by clinical and pathological patient and tumour characteristics. Upfront RC is recommended for high-risk NMIBC and strongly recommended for the very-high-risk group; NAC is not recommended for these sub-groups of patients given the localized nature of the disease [27]. Accordingly, the absence of

residual tumour on the bladder specimen is an indicator of an adequate and complete resection. For this group, RC is proposed only in cases of high-risk progression as it has a negative impact on cancer-specific survival.

In this study, we described preoperative and perioperative characteristics of pT0 patients at RC. Additionally, we compared our pT0 cohort with matched >pT0 counterparts to accurately define predictors of pT0 status at RC. In the high-risk and very-high-risk NMIBC group, we found that female sex, the presence of additional CIS, and previous BCG treatment were associated with lower rates of pT0 in RC specimens. Pure or mixed VH showed a clear tendency towards a lower probability of pT0, despite it not reaching significance, very likely due to the relatively small prevalence of this at TUR pathology. Of the aforementioned variables, only concomitant CIS is considered in the currently adopted risk stratification.

To more efficiently identify patients who would clearly benefit from an upfront RC, more comprehensive risk stratification is required. The higher rates of progression to extravesical disease and worse survival outcomes of female patients have already been demonstrated [28–30]. Our results, paired with the lower psychological impact of the long-term functional complications of RC, could suggest a lower threshold for proposing definite treatment in female patients compared to male patients [31].

Regarding MIBC, in addition to the well accepted role of NAC in increasing the likelihood of a final pT0 status, we found that the absence of CIS or histological variants could predict a higher probability of no evidence of residual cancer in RC specimens. Moreover, in our cohort, only cT2 patients successfully achieved a pT0 status, specifically in 27 (55%) and in 16 (32.7%) >pT0 and pT0 patients, respectively, among those with MIBC who did not receive NAC. Considering that NAC has been the standard of care for cT2–T4N0M0 since 2008, these rates might seem relatively high. However, the vast majority of our MIBC cohort had organ-confined disease (i.e., cT2N0M0). In this particular group, the role of NAC in reducing cancer-specific mortality (CSM) was recently formally validated, compared to its well established role in non-organ-confined disease [32,33]. Accordingly, following MDT assessment and patient counselling, NAC was omitted in a relevant portion of the study population, in the light of the still uncertain survival benefit and possibly high rate of unfit patients. The high prevalence of cT2N0M0 patients also partially explains the relatively high representation of pT0 patients who did not undergo NAC, since, when possible, an aggressive TUR procedure was performed, particularly in patients with resectable tumours and without a clear preoperative stage. The rate of complete pathological response (pCR) to NAC in our matched cohort ($n = 33$ patients, 60%) was higher than that reported in the literature (30–40%) [34,35]. This discrepancy may be explained by PSM, with 50% of our cohort represented by pT0 patients, and by precise patient selection following MDT discussion and the latest guidelines in our high-volume reference centre. Nonetheless, our aim was not to define predictors of NAC response, but to provide a wider description of the pT0 population. Given the high accuracy of novel diagnostic and follow-up modalities, such as multiparametric Magnetic Resonance Imaging (mpMRI) with VI-RADS score determination and Photodynamic diagnosis (PDD), and given the promising role of Immune Checkpoint Inhibitors (ICIs) for non-metastatic BC and their possible association with EBRT, a deep understanding of pT0 predictors could help in tailoring and integrating future multimodality treatment strategies. These results gain additional interest as BSS is becoming increasingly popular. Understanding predictors of a favourable pathological outcome, particularly for NMIBC patients who did not receive NAC, might raise the threshold for RC consideration in this particular class of patients. This is particularly true as the therapeutic arsenal for NMIBC is expanding to systemic treatment, particularly in BCG-refractory disease [9]. Regarding MIBC, while it is true that

regimens adopted during NAC and Trimodality Therapy (TMT) differ, a more thorough understanding of the clinical and pathological characteristics associated with downstaging and pCR after NAC could help better define predictors of favourable outcomes of BSS. As research is focusing on expanding ICI indications from TMT to the NAC setting, factors currently predicting a better response to ICIs might become selection criteria for NAC [36]. Finally, in the context of personalised medicine, a precise classification of predictors of good response to one regimen or another (ICIs vs. platinum-based) might help in offering tailored treatment in the context of NAC and TMT.

The steady temporal trend in pT0 status since 2009 reported in our study, despite constant fluctuations over the years, is confirmation of the lack of clear advancements in BC management in the last 20 years. An increasing rate of pT0 status could have indicated an improvement in earlier tumour detection, TUR precision, and NAC efficacy. On the contrary, a trend towards a reduction in pT0 rates could have suggested an increasing number of BSSs being adopted as a result of precise patient selection criteria for MIBC, and the availability of novel adjuvant therapeutic options for BCG-refractory NMIBC. However, recent and potential future positive results of large multicentre studies, particularly regarding the adoption of ICIs for NMIBC and their introduction into NAC regimens, could help shape future trends of pT0 status [37].

Several limitations of our study must be acknowledged. First, the retrospective nature and the relatively small sample size could have influenced the results. Relevant information, such as tumour size, BCG treatment duration, and NAC regimens, were not available. Although PSM helped in obtaining similar and comparable study groups, this study is still susceptible to potential biases arising from unobserved confounders. Moreover, it could have introduced selection and collider biases with unpredictable effects on the explored variables. Lastly, we did not explore or report survival outcomes and trajectories since this was not in the original scope of the present analysis.

5. Conclusions

In the present study, we explored temporal trends and predictors of pT0 status in a cohort of high- and very-high-risk NMIBC and MIBC patients. In addition to the already accepted negative predictive role of additional CIS, we found female sex and BCG failure to be independently associated with a lower likelihood of pT0 status in the NMIBC cohort. These findings may improve the accuracy of current risk stratification models by refining NMIBC patient selection and enhancing the prediction of pathological outcomes. Regarding MIBC, cT2N0M0 without additional risk factors (concomitant CIS or VH) could benefit from re-evaluation with novel diagnostic techniques (mpMRI and Re-TURBT with PDD), before or after chemotherapy, to select those patients with a higher success probability using a bladder-sparing approach. Finally, while BC with histological variants has already been associated with a poorer prognosis, in the future, specific histological subtypes should be evaluated as a separate entity to allow for personalisation of individual care.

Author Contributions: Conceptualization, M.S.K.; methodology, E.M. and Y.I.; software, M.G. and J.L.; validation, B.I.C. and R.T.; formal analysis, N.H.B., E.M. and B.C.; investigation, S.G.A.K., S.J.D., M.H., Y.I. and M.G.; resources, S.G.A.K., N.H.B., Y.A.-G., M.H. and R.C.; data curation, F.D.G., V.S., Y.A.-G., B.C., A.K. and F.C.; writing—original draft, K.S., F.C. and J.L., B.R.; writing—review and editing, F.D.G., V.S., K.S., B.R., B.I.C., R.T., M.S.K. and R.N.; visualization, S.J.D.; supervision, F.D.G., B.R. and R.N.; project administration, F.D.G., B.I.C., M.S.K. and R.N.; funding acquisition, A.K. and R.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study as it is a retrospective observational cohort study with no interventional or experimental arms.

Informed Consent Statement: All patients have been included from our de-identified institutional database which is updated yearly.

Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

References

1. Babjuk, M.; Burger, M.; Compérat, E.M.; Gontero, P.; Mostafid, A.H.; Palou, J.; van Rhijn, B.W.G.; Roupret, M.; Shariat, S.F.; Sylvester, R.; et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ)—2019 Update. *Eur. Urol.* **2019**, *76*, 639–657. [\[CrossRef\]](#)
2. Gontero, P.; Birtle, A.; Capoun, O.; Compérat, E.; Dominguez-Escrig, J.L.; Liedberg, F.; Mariappan, P.; Masson-Lecomte, A.; Mostafid, H.A.; Pradere, B.; et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ)—A Summary of the 2024 Guidelines Update. *Eur. Urol.* **2024**, *86*, 531–549. [\[CrossRef\]](#)
3. Sylvester, R.J.; van der Meijden, A.P.; Oosterlinck, W.; Witjes, J.A.; Bouffieux, C.; Denis, L.; Newling, D.W.; Kurth, K. Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials. *Eur. Urol.* **2006**, *49*, 466–477. [\[CrossRef\]](#)
4. Lobo, N.; Hensley, P.J.; Bree, K.K.; Nogueras-Gonzalez, G.M.; Navai, N.; Dinney, C.P.; Sylvester, R.J.; Kamat, A.M. Updated European Association of Urology (EAU) Prognostic Factor Risk Groups Overestimate the Risk of Progression in Patients with Non-muscle-invasive Bladder Cancer Treated with Bacillus Calmette-Guérin. *Eur. Urol. Oncol.* **2022**, *5*, 84–91. [\[CrossRef\]](#)
5. Sylvester, R.J.; Rodríguez, O.; Hernández, V.; Turturica, D.; Bauerová, L.; Bruins, H.M.; Bründl, J.; van der Kwast, T.H.; Brisuda, A.; Rubio-Briones, J.; et al. European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel. *Eur. Urol.* **2021**, *79*, 480–488. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Scilipoti, P.; Longoni, M.; de Angelis, M.; Zaurito, P.; Ślusarczyk, A.; Soria, F.; Pradere, B.; Krajewski, W.; D’Andrea, D.; Mari, A.; et al. Outcomes of BCG vs upfront radical cystectomy for high-risk non-muscle-invasive bladder cancer. *BJU Int.* **2025**, *136*, 47–54. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Diamant, E.; Roumiguié, M.; Ingels, A.; Parra, J.; Vordos, D.; Bajot, A.-S.; Chartier-Kastler, E.; Soulié, M.; de la Taille, A.; Rouprêt, M.; et al. Effectiveness of Early Radical Cystectomy for High-Risk Non-Muscle Invasive Bladder Cancer. *Cancers* **2022**, *14*, 3797. [\[CrossRef\]](#)
8. Necchi, A.; Roumiguié, M.; Kamat, A.M.; Shore, N.D.; Boormans, J.L.; Esen, A.A.; Lebre, T.; Kandori, S.; Bajorin, D.F.; Krieger, L.E.M.; et al. Pembrolizumab monotherapy for high-risk non-muscle-invasive bladder cancer without carcinoma in situ and unresponsive to BCG (KEYNOTE-057): A single-arm, multicentre, phase 2 trial. *Lancet Oncol.* **2024**, *25*, 720–730. [\[CrossRef\]](#)
9. McFadden, J.; Tachibana, I.; Adra, N.; Collins, K.; Cary, C.; Koch, M.; Kaimakiotis, H.; Masterson, T.; Rice, K. Impact of variant histology on upstaging and survival in patients with nonmuscle invasive bladder cancer undergoing radical cystectomy. *Urol. Oncol. Semin. Orig. Investig.* **2024**, *42*, 69.e11–69.e16. [\[CrossRef\]](#) [\[PubMed\]](#)
10. May, M.; Bastian, P.J.; Burger, M.; Bolenz, C.; Trojan, L.; Herrmann, E.; Wülfing, C.; Müller, S.C.; Ellinger, J.; Buchner, A.; et al. Multicenter evaluation of the prognostic value of pT0 stage after radical cystectomy due to urothelial carcinoma of the bladder. *BJU Int.* **2011**, *108*, E278–E283. [\[CrossRef\]](#)
11. Choi, H.; Park, J.Y.; Bae, J.H.; Tae, B.S. Health-related quality of life after radical cystectomy. *Transl. Androl. Urol.* **2020**, *9*, 2997–3006. [\[CrossRef\]](#)
12. Tilki, D.; Svatek, R.S.; Novara, G.; Seitz, M.; Godoy, G.; Karakiewicz, P.I.; Kassouf, W.; Fradet, Y.; Fritsche, H.-M.; Sonpavde, G.; et al. Stage pT0 at Radical Cystectomy Confers Improved Survival: An International Study of 4,430 Patients. *J. Urol.* **2010**, *184*, 888–894. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Tholomier, C.; Souhami, L.; Kassouf, W. Bladder-sparing protocols in the treatment of muscle-invasive bladder cancer. *Transl. Androl. Urol.* **2020**, *9*, 2920–2937. [\[CrossRef\]](#)
14. Del Giudice, F.; Abu-Ghanem, Y.; Nair, R.; Mensah, E.; Kam, J.; Ibrahim, Y.; Gad, M.; Chatterton, K.; Amery, S.; Alao, R.; et al. Contemporary Trends and Predictors Associated with Adverse Pathological Upstaging Among Non-Metastatic Localized Clinical T2 Muscle-Invasive Bladder Cancers Undergoing Radical Cystectomy: Outcomes from a Single Tertiary Centre in the United Kingdom. *Cancers* **2025**, *17*, 1477. [\[CrossRef\]](#) [\[PubMed\]](#)

15. Santarelli, V.; Carino, D.; Corvino, R.; Saliccia, S.; De Berardinis, E.; Krajewski, W.; Nowak, Ł.; Łaszkiewicz, J.; Szydełko, T.; Nair, R.; et al. Surgical Technique and Perioperative Outcomes of the “Sapienza” Urology Residency Program’s Trocar Placement Configuration During Robotic-Assisted Radical Prostatectomy (RARP): A Retrospective, Single-Centre Observational Study Comparing Experienced Attendings vs. Post-Graduate Year I–III Residents as Bedside Assistants. *Cancers* **2024**, *17*, 20. [\[CrossRef\]](#)
16. Ditunno, F.; Vecchia, A.; Montanaro, F.; Pettenuzzo, G.; Franco, A.; Manfredi, C.; Triggiani, L.; De Nunzio, C.; De Sio, M.; Cerruto, M.; et al. Trimodal therapy vs radical cystectomy in patients with muscle-invasive bladder cancer: A systematic review and meta-analysis of comparative studies. *BJU Int.* **2024**, *134*, 684–695. [\[CrossRef\]](#)
17. Barbos, V.; Feciche, B.; Latcu, S.; Croitor, A.; Dema, V.; Bardan, R.; Faur, F.I.; Mateescu, T.; Novacescu, D.; Bogdan, G.; et al. The Assessment of SF-36 Survey for Quality-of-Life Measurement after Radical Cystectomy for Muscle-Invasive Bladder Cancer: A Systematic Review. *Diseases* **2024**, *12*, 56. [\[CrossRef\]](#)
18. Akdemir, E.; Stuiiver, M.M.; van de Kamp, M.W.; van der Hulst, J.B.-; Mertens, L.S.; Hendricksen, K.; van Harten, W.H.; May, A.M.; Sweegers, M.G. Long-term quality of life in patients with bladder cancer following radical cystectomy. *BJU Int.* **2024**, *135*, 675–683. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Månsson, Å.; Davidsson, T.; Hunt, S.; Månsson, W. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: Is there a difference? *BJU Int.* **2002**, *90*, 386–390. [\[CrossRef\]](#)
20. Hedgepeth, R.C.; Gilbert, S.M.; He, C.; Lee, C.T.; Wood, D.P., Jr. Body Image and Bladder Cancer Specific Quality of Life in Patients with Ileal Conduit and Neobladder Urinary Diversions. *Urology* **2010**, *76*, 671–675. [\[CrossRef\]](#)
21. Witjes, J.A.; Bruins, H.M.; Carrión, A.; Cathomas, R.; Compérat, E.; Efstathiou, J.A.; Fietkau, R.; Gakis, G.; Lorch, A.; Martini, A.; et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2023 Guidelines. *Eur. Urol.* **2023**, *85*, 17–31. [\[CrossRef\]](#)
22. Mediavilla, E.; Portillo, J.A.; Truán, D.; Campos-Juanatey, F.; Gala, L.; Fuentes, J.; Carrión, C.; Gutiérrez, J.L. Predictive factors of evolution of patients after pT0 radical cystectomy due to bladder cancer. *Arch. Esp. Urol.* **2014**, *67*, 764–769.
23. Boeri, L.; Soligo, M.; Frank, I.; Boorjian, S.A.; Thompson, R.H.; Tollefson, M.; Tarrel, R.; Quevedo, F.J.; Cheville, J.C.; Karnes, R.J. Clinical predictors and survival outcome of patients receiving suboptimal neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer: A single-center experience. *World J. Urol.* **2019**, *37*, 2409–2418. [\[CrossRef\]](#)
24. Li, H.; Hu, J.; Zu, X.; Chen, M.; Chen, J.; Zou, Y.; Deng, R.; Qin, G.; Li, W.; Tang, J.; et al. A novel signature to predict the neoadjuvant chemotherapy response of bladder carcinoma: Results from a territory multicenter real-world study. *Front. Genet.* **2022**, *13*, 1047481. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Catarino, R.; Alves, L.; Pereira, D.; Costa, G.; Pereira, J.; Cardoso, A.; Braga, I.; Freitas, R.; Correia, T.; Cerqueira, M.; et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: Does variant histology matter? *Int. Urol. Nephrol.* **2022**, *54*, 3163–3169. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Lin-Brande, M.; Zainfeld, D.; Ghodoussipour, S.; Cai, J.; Miranda, G.; Djaladat, H.; Schuckman, A.; Sadeghi, S.; Dorff, T.; Quinn, D.; et al. MP47-06 Impact of Variant Histology on Response to Neoadjuvant Chemotherapy for Urothelial Bladder Cancer. *J. Urol.* **2018**, *199*, e617. [\[CrossRef\]](#)
27. Babjuk, M.; Burger, M.; Capoun, O.; Cohen, D.; Compérat, E.M.; Escrig, J.L.D.; Gontero, P.; Liedberg, F.; Masson-Lecomte, A.; Mostafid, A.H.; et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *Eur. Urol.* **2022**, *81*, 75–94. [\[CrossRef\]](#)
28. D’Andrea, D.; Black, P.C.; Zargar, H.; Zargar-Shoshtari, K.; Zehetmayer, S.; Fairey, A.S.; Mertens, L.S.; Dinney, C.P.; Mir, M.C.; Krabbe, L.-M.; et al. Impact of sex on response to neoadjuvant chemotherapy in patients with bladder cancer. *Urol. Oncol. Semin. Orig. Investig.* **2020**, *38*, 639.e1–639.e9. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Kimura, S.; Iwata, T.; Abufaraj, M.; Janisch, F.; D’Andrea, D.; Moschini, M.; Al-Rawashdeh, B.; Fajkovic, H.; Seebacher, V.; Egawa, S.; et al. Impact of Gender on Chemotherapeutic Response and Oncologic Outcomes in Patients Treated with Radical Cystectomy and Perioperative Chemotherapy for Bladder Cancer: A Systematic Review and Meta-Analysis. *Clin. Genitourin. Cancer* **2020**, *18*, 78–87. [\[CrossRef\]](#)
30. Fajkovic, H.; Halpern, J.A.; Cha, E.K.; Bahadori, A.; Chromecki, T.F.; Karakiewicz, P.I.; Breinl, E.; Merseburger, A.S.; Shariat, S.F. Impact of gender on bladder cancer incidence, staging, and prognosis. *World J. Urol.* **2011**, *29*, 457–463. [\[CrossRef\]](#)
31. Bahlburg, H.; Reicherz, A.; Reike, M.; Bach, P.; Butea-Bocu, M.C.; Tully, K.H.; Roghmann, F.; Noldus, J.; Müller, G. A prospective evaluation of quality of life, psychosocial distress, and functional outcomes two years after radical cystectomy and urinary diversion in 842 German bladder cancer patients. *J. Cancer Surviv.* **2024**, *19*, 1102–1110. [\[CrossRef\]](#)
32. Proietti, F.; Flammia, R.S.; Licari, L.C.; Bologna, E.; Bove, A.M.; Brassetti, A.; Tuderti, G.; Mastroianni, R.; Tufano, A.; Simone, G.; et al. Impacts of Neoadjuvant Chemotherapy on Perioperative Outcomes in Patients with Bladder Cancer Treated with Radical Cystectomy: A Single High-Volume Center Experience. *J. Pers. Med.* **2024**, *14*, 212. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Park, J.H.; Lee, S.; Jeong, S.-H.; Ku, J.H.; Kim, K.H.; Kil Nam, J.; Lim, B.; Hong, B.S.; Nam, W.; Kang, S.G.; et al. The effect of neoadjuvant chemotherapy on survival outcomes subsequent to radical cystectomy in pathological T0 bladder cancer patients: A multicenter large-scale analysis. *Investig. Clin. Urol.* **2025**, *66*, 395–404. [\[CrossRef\]](#) [\[PubMed\]](#)

34. Lee, F.C.; Harris, W.; Cheng, H.H.; Sheno, J.; Zhao, S.; Wang, J.; Champion, T.; Izard, J.; Gore, J.L.; Porter, M.; et al. Pathologic Response Rates of Gemcitabine/Cisplatin versus Methotrexate/Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. *Adv. Urol.* **2013**, *2013*, 317190. [[CrossRef](#)]
35. Miyagi, H.; Kwenda, E.; Ramnarain, B.H.; Chatzkel, J.A.; Brisbane, W.G.; O'malley, P.; Crispen, P.L. Predicting Complete Response to Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer. *Cancers* **2022**, *15*, 168. [[CrossRef](#)] [[PubMed](#)]
36. Robertson, A.G.; Meghani, K.; Cooley, L.F.; McLaughlin, K.A.; Fall, L.A.; Yu, Y.; Castro, M.A.A.; Groeneveld, C.S.; de Reyniès, A.; Nazarov, V.I.; et al. Expression-based subtypes define pathologic response to neoadjuvant immune-checkpoint inhibitors in muscle-invasive bladder cancer. *Nat. Commun.* **2023**, *14*, 2126. [[CrossRef](#)]
37. García-Rayó, C.; Juste-Álvarez, S.; Gómez-Cañizo, C.; Hernández-Arroyo, M.; Velasco, G.; Castellano, D.; Rodríguez-Antolín, A.; Guerrero-Ramos, F. The Dynamic Field of Perioperative Treatment for Localized Muscle-Invasive Bladder Cancer: A Review of the Current Research Landscape. *J. Clin. Med.* **2025**, *14*, 5653. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.