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Original Article

The impact of positive surgical margins after cystectomy on oncological outcomes: a nationwide study

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Objective

To evaluate whether surgical margin status, alongside existing postoperative risk indicators, improves the identification of bladder cancer patients who may benefit from adjuvant therapy following radical cystectomy (RC).

Methods

In this nationwide cohort study, patients aged ≥18 years diagnosed with muscle-invasive bladder cancer (MIBC) without nodal or distant metastasis (cT2-4aN0/xM0) between November 2017 and December 2020 who underwent RC were selected from the Netherlands Cancer Registry. Detailed information on surgical margin status was obtained through linkage with the Dutch central pathology database, Palga. Overall survival (OS) and progression-free survival (PFS) were assessed using the Kaplan–Meier method. Multivariable Cox regression analysis was performed to assess the independent prognostic effect of positive surgical margins (carcinoma *in situ* (CIS)] only or invasive carcinoma) on PFS and OS.

Results

We identified 1445 MIBC patients treated by RC (53% open, 47% robot-assisted), of whom 135 (9.3%) had positive surgical margins (10.7% in the open and 7.7% in the robot-assisted cohort). In the entire cohort, OS was 79% and 60% at 12 and 48 months after RC, respectively. PFS was 70% and 61% at 12 and 24 months, respectively. Multivariable Cox regression showed worse PFS (hazard ratio (HR) 2.13, 95% confidence interval (CI) 1.67–2.72) and OS (HR 2.02, 95% CI 1.58–2.58) in patients with surgical margins with invasive carcinoma vs patients with negative margins. Patients with only CIS in the margins also appeared to have worse PFS (HR 1.60, 95% CI 1.00–2.58) but these results were not statistically significant. No difference was found for OS (HR 1.30, 95% CI 0.80–2.12).

Conclusion

Positive margins should be considered a 'high risk feature, as they result in increased risk of disease progression and impaired survival outcomes. These findings support further investigation of the potential efficacy of adjuvant therapy (i.e., radiotherapy and systemic therapy) among patients with positive surgical margins.

Keywords

adjuvant therapy, muscle-invasive bladder cancer, overall survival, radical cystectomy, surgical margins

Introduction

Localised muscle-invasive bladder cancer (MIBC) only yields 5-year survival rates of approximately 50% after treatment with curative intent [1,2]. Radical cystectomy (RC) is recommended as the preferred curative treatment option for MIBC, with trimodal treatment as a bladder-sparing alternative. The European Association of Urology (EAU) guidelines provide clear recommendations for the use of neoadjuvant treatment for patients undergoing RC [3].

Neoadjuvant chemotherapy (NAC) is recommended for cisplatin-eligible patients, providing an 8% survival benefit [4]. Nevertheless, survival rates after RC are still poor.

Adjuvant treatment provides another opportunity to improve survival outcomes. While EAU guidelines on adjuvant treatment are limited by the availability of strong evidence, there is a strong recommendation for offering adjuvant cisplatin-based combination chemotherapy when patients are diagnosed with pT3-4 and or pN+ disease and NAC has not been given. Nevertheless, current evidence on adjuvant radiotherapy is insufficient despite randomised studies [3]. Adjuvant immune checkpoint inhibition with nivolumab has shown a progression-free survival (PFS) benefit [5]. However, only interim overall survival (OS) data have been reported thus far, suggesting a benefit for patients treated with nivolumab, while mature OS data remain pending [6].

The current era with emergence of new therapeutic agents warrants reevaluation of the identification of patients who might benefit from adjuvant treatment. Pending availability of accurate biomarkers, pathological features remain crucial. Therefore, the aim of this study was to assess whether incorporating surgical margin status alongside existing postoperative risk indicators (i.e., pT3-4 and/or pN+) improves classification of patients at high risk for recurrent disease.

Patients and Methods

Cohort and Data

Patients aged ≥18 years, who received a first diagnosis of bladder cancer with localised, muscle-invasive disease (cT2-4aN0/xM0) between 1 November 2017 and 31 December 2020, were identified from the Netherlands Cancer Registry (NCR). Those who underwent RC as primary treatment, with or without neoadjuvant treatment, were included in this nationwide prospective cohort study. Patients who received simultaneous treatment for other cancers in the pelvic region, patients with missing data on margin status, patients with <30 days of follow-up and patients with pathological M1 disease were excluded.

The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and data are collected by trained IKNL data managers on all newly diagnosed cancers in the Netherlands, covering patient and tumour characteristics, disease stage, treatment, and vital status. Data on vital status are updated annually by linkage to the Dutch personal records database. In addition to the standard NCR data, more detailed data were collected concerning the surgical procedure and oncological follow-up (at least 2 years since diagnosis). This additional data collection was performed as part of the Dutch Cancer Society-funded BlaZIB project (*BlaaskankerZorg in Beeld*; Dutch for 'Insight into bladder cancer care') for patients diagnosed in 2017–2019, and the ProBCI initiative (Prospective Bladder Cancer Infrastructure) regarding patients diagnosed in 2020 [7,8].

Subsequent linkage to the nationwide network and registry of histo- and cytopathology (Palga) was performed to obtain the pathology reports for all RCs. From these reports, additional data on surgical margins were retrieved.

This study was approved by the Privacy Review Board of the NCR (ref. no. K23.262) and by the Palga review board (ref. no. LZV2023-108).

Clinical, Pathological Data and Definitions

Patient characteristics included patient's sex, age at diagnosis, performance status, comorbidities and laboratory values (haemoglobin levels and renal function) at baseline. Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) performance status scale (or alternatively the Karnofsky performance scale converted to ECOG) and categorised as 0, 1, 2 and 3/4. If ECOG performance status was reported in the medical record as a range between two values, it was categorised as the most favourable value (e.g., ECOG score 0-1 becomes ECOG score 0).

Tumour staging was defined in accordance with TNM Classification of Malignant Tumours (eighth edition) [9]. Morphology was documented and categorised into urothelial cell carcinoma (UCC) in case of pure or predominant UCC, or otherwise as non-UCC.

Neoadjuvant treatment was categorised as chemotherapy or immuno(chemo)therapy directly prior to RC. Adjuvant therapy was defined as administration of radiotherapy, chemotherapy or immunotherapy initiated within 3 months of RC and prior to evidence of disease recurrence or progression.

The postoperative pathological determinants evaluated in this study included pathological T and N stages, lymphovascular invasion and surgical margin characteristics (e.g., location and invasiveness). Pathological stages pT3-4 and/or pN+ without NAC or ypT2-4 and/or ypN+ following NAC were defined as high risk for disease recurrence (abbreviated to (y)pTN high-risk), whereas all other stages were considered low risk ((y)pTN low-risk). Lymphovascular invasion was reported as positive, negative, or unknown, if not documented in the pathology report. The surgical margin status was determined based on the final findings in the pathology reports of the RC and lymph node dissection, not including frozen sections, and classified as negative, positive for carcinoma *in situ* (CIS) only (non-invasive margins) or positive for invasive carcinoma at the perivesical, ureter/urethra and uterus/prostate sites.

The oncological outcomes assessed in this study were PFS and OS. Progression was determined as local or distant evidence of disease after RC (including occurrence of metastases after RC), based on imaging, or death. Time to progression was calculated as time from RC until progression or death. Time to death was calculated as time from RC until death. Patients were censored if no event occurred at the time of last clinical follow-up date without an event, or at 2 years after RC for PFS and 4 years after RC for OS, whichever came first.

Statistical Analysis

Baseline characteristics were described with frequencies and percentages, or median and interquartile range (IQR) for continuous variables. The Kaplan–Meier method was used to evaluate 2-year PFS and 4-year OS, and the log-rank test was used to evaluate survival differences. Kaplan–Meier curves were stratified by surgical margin status and (y)pTN stages.

Finally, a multivariable Cox proportional hazard regression was performed to assess the adjusted prognostic effect of positive surgical margins (CIS only or invasive carcinoma) on PFS and OS, taking into account other prognostic variables including pathological TNM stage, lymphovascular invasion and neoadjuvant therapy.

All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). *P* values <0.05 were taken to indicate statistical significance.

Results

A total of 1531 patients with newly diagnosed MIBC without clinical nodal or distant metastasis (cT2-4aN0/xM0) and RC as primary treatment were identified from the NCR. A total of 55 patients were excluded for insufficient follow-up, including 35 patients who died within 30 days of RC. A total of 12 patients with pathological stage M1 were excluded and data on margin status could not be retrieved for 19 patients, leaving 1445 patients in the final cohort for analysis. The flowchart is shown in Fig. 1.

Patient and tumour characteristics stratified by margin status are summarised in Table 1. Positive surgical margins were

Fig. 1 Flowchart of cohort selection. Neoadjuvant radiotherapy for the following reasons: previous chemotherapy for another malignancy, histological variant, treatment of haematuria while cystectomy postponed due to COVID-19 limitations. NMIBC, non-muscle-invasive bladder cancer.

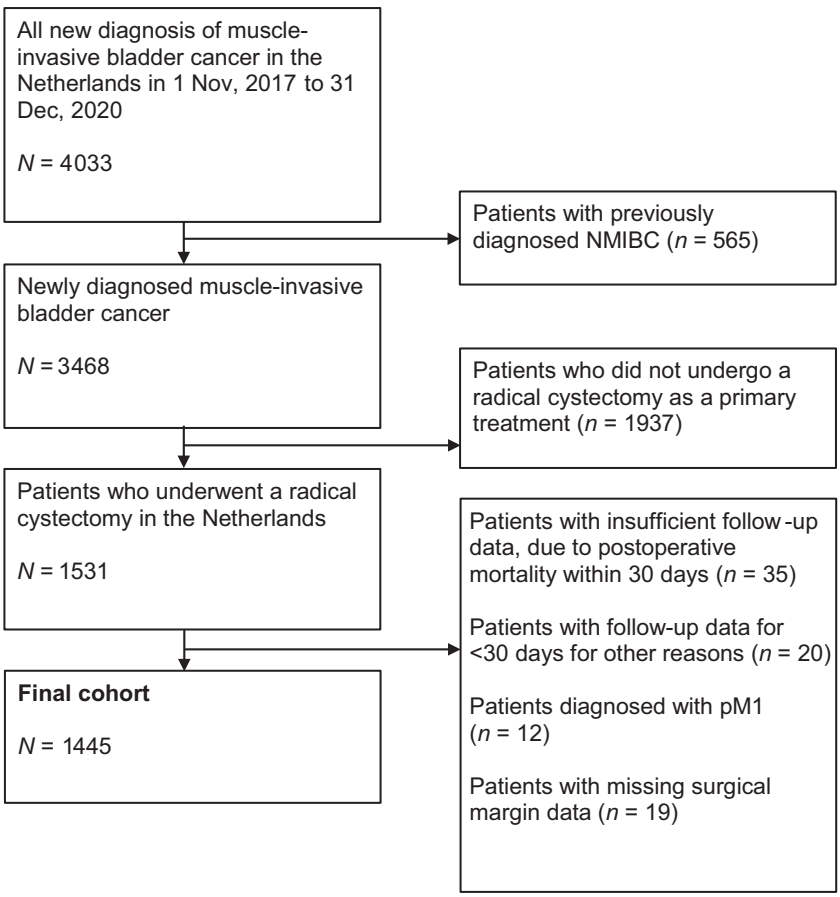


Table 1 Baseline data of patients and tumour characteristics for patients with localised, muscle-invasive bladder cancer treated with radical cystectomy.

	All		Surgical margin status			
			Negative surgical margins		Positive surgical margins	
	N	%	*N*	%	*N*	%
Total	1445	100	1302	90.7	135	9.3
Sex						
Male	1039	71.9	953	72.7	86	63.7
Female	406	28.1	357	27.3	49	36.3
Age at diagnosis						
0–60 years	260	18.0	239	18.2	21	15.6
61–70 years	538	37.2	493	37.6	45	33.3
71–80 years	578	40.0	514	39.2	64	47.4
≥ 81 years	69	4.8	64	4.9	5	3.7
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age at diagnosis, years	70	63–75	69	63–74	71	64–76
	N	**%**	***N***	**%**	***N***	**%**
Performance status						
ECOG 0	733	50.7	676	51.6	57	42.2
ECOG 1	166	11.5	145	11.1	21	15.6
ECOG 2–4	15	1.0	11	0.8	4	3.0
Unknown	531	36.7	478	36.5	53	39.3
Charlson comorbidity index						
0	666	46.1	623	47.6	43	31.9
1	380	26.3	340	26.0	40	29.6
≥2	281	19.4	243	18.5	38	28.1
Unknown	118	8.2	104	7.9	14	10.4
Haemoglobin						
≥8.5 (M)/≥7.5 (F) mmol/L	749	51.8	700	53.4	49	36.3
<8.5 (M)/<7.5 (F) mmol/L	578	40.0	500	38.2	78	57.8
Unknown	118	8.2	110	8.4	8	5.9
Renal function						
0–30 mL/min/1.73 m^2	37	2.6	26	2.0	11	8.1
30–60 mL/min/1.73 m^2	363	25.1	304	23.2	59	43.7
≥60 mL/min/1.73 m^2	941	65.1	882	67.3	59	43.7
Unknown	104	7.2	98	7.5	6	4.4
Clinical TNM stage						
cT2	1004	69.5	932	71.1	72	53.3
cT3	358	24.8	319	24.4	39	28.9
cT4a	83	5.7	59	4.5	24	17.8
Morphology						
UCC	1381	95.6	1252	95.6	129	95.6
Non-UCC	64	4.4	58	4.4	6	4.4

F, female; IQR, interquartile range; M, male; UCC, urothelial cell carcinoma.

observed in 135 patients (9.3%). Patients with positive margins more often were female, more often had advanced clinical tumour stage (cT3-4, N+) and more often had low haemoglobin levels and worse renal function.

Neoadjuvant treatment was administered to approximately one third of the patients (30.8%; Table 2). Just over half (52.8%) of patients underwent an open RC with an ileal conduit urinary deviation (Bricker). The vast majority (77.0%) of patients with positive surgical margins had invasive tumour cells in the margins. The most common location of invasive surgical margins was the perivesical area, followed by the ureters. Among patients with only CIS in the surgical margins, this was most often located in (one of) the ureters.

The median (IQR) follow-up time among patients without events was 23.0 (19.3–28.3) months for PFS, and 539 events (progression or death) occurred within 24 months. The median (IQR) follow-up time among patients without events was 52.7 (42.9–61.9) months for OS and 566 events (death) occurred within 48 months.

Observed OS was 79% (95% CI 77%–81%), 68% (95% CI 66%–71%), 64% (95% CI 62–67%) and 60% (95% CI 57–62%) at 12, 24, 36 and 48 months after RC, respectively. PFS was 70% (95% CI 68%–73%) and 61% (95% CI 58%–63%) at 12 and 24 months after RC, respectively. Patients with negative margins had the best PFS and OS, followed by patients with only CIS in margins, and patients with invasive positive margins had the worst PFS and OS (Fig. 2A,B).

When surgical margin status was considered alongside the pathological T and N stage, patients with (y)pTN high-risk and invasive surgical margins had a worse PFS and OS

Table 2 Characteristics of radical cystectomy, neoadjuvant and adjuvant treatments, and postoperative outcomes.

	All		Surgical margin status			
			Negative surgical margins		Positive surgical margins	
	N	%	*N*	%	*N*	%
Neoadjuvant treatment						
None	995	68.9	883	67.4	112	83.0
Cisplatin-based chemotherapy	387	26.8	368	28.1	19	14.1
Immunotherapy	23	1.6	21	1.6	2	1.5
Other	34	2.4	33	2.5	1	0.7
Surgical approach						
Open	763	52.8	681	52.0	82	60.7
Robot-assisted laparoscopic	675	46.7	623	47.6	52	38.5
Other/unknown	7	0.5	6	0.5	1	0.7
Sexual sparing						
No	1414	97.9	1284	98.0	130	96.3
Yes	31	2.1	26	2.0	5	3.7
Urinary diversion						
Ileal conduit (Bricker)	1336	92.5	1213	92.6	123	91.1
Neobladder	72	5.0	70	5.3	2	1.5
Other/unknown	37	2.6	27	2.1	10	7.4
Adjuvant treatment						
Radiotherapy	9	0.6	–	–	9	6.7
Chemotherapy	14	1.0	13	1.0	1	0.7
Immunotherapy	5	0.3	5	0.4	–	–
None	1417	98.1	1292	98.6	125	92.6
Pathological TNM stage						
(y)pT≤1N0M0	461	31.9	454	34.7	7	5.2
(y)pT2N0M0	234	16.2	224	17.1	10	7.4
(y)pT3N0M0	344	23.8	314	24.0	30	22.2
(y)pT4N0M0	84	5.8	51	3.9	33	24.4
(y)pTanyN+M0	322	22.3	267	20.4	55	40.7
Lymphovascular invasion						
Yes	333	23.0	280	21.4	53	39.3
No	419	29.0	397	30.3	22	16.3
Not reported	693	48.0	633	48.3	60	44.4
Surgical margin status*						
Negative	1310	90.7	1310	100.0	–	-
Positive, CIS only	31	2.1	–	–	31	23.0
Perivesical/serosa	5	0.3	–	–	5	3.7
Ureter/urethra	26	1.8	–	–	26	19.3
Prostate/uterus/other	–	–	–	–	–	–
Positive, invasive tumour tissue	104	7.2	–	–	104	77.0
Perivesical/serosa*	80	5.5	–	–	80	59.3
Ureter/urethra*	30	2.1	–	–	30	22.2
Prostate/uterus/other*	22	1.5	–	–	22	16.3

*CIS, carcinoma in situ. *Non-mutually exclusive categories, patients may have positive margins in more than one location.*

compared to patients with (y)pTN high-risk without invasive margins (Fig. 2C,D).

The multivariable analyses taking into account the (y)pT stage, (y)pN stage, presence of lymphovascular invasion of the primary tumour and neoadjuvant therapy showed that patients with surgical margins with invasive carcinoma had worse PFS (HR 2.13, 95% CI 1.67–2.72) and OS (HR 2.02, 95% CI 1.58–2.58) compared to patients with negative margins (Table 3). Patients with only CIS in the margins also appeared to have worse PFS (HR 1.60, 95% CI 1.00–2.58) but results were not statistically significant. No difference was found for OS (HR 1.30, 95% CI 0.80–2.12).

Discussion

In this nationwide cohort, 9.3% of MIBC patients treated with RC had positive surgical margins, and 7.2% had invasive tumour tissue in the margins. The presence of invasive surgical margins was associated with poorer PFS and OS, also after taking into account established prognosticators including pT and pN stage, presence of lymphovascular invasion and neoadjuvant therapy.

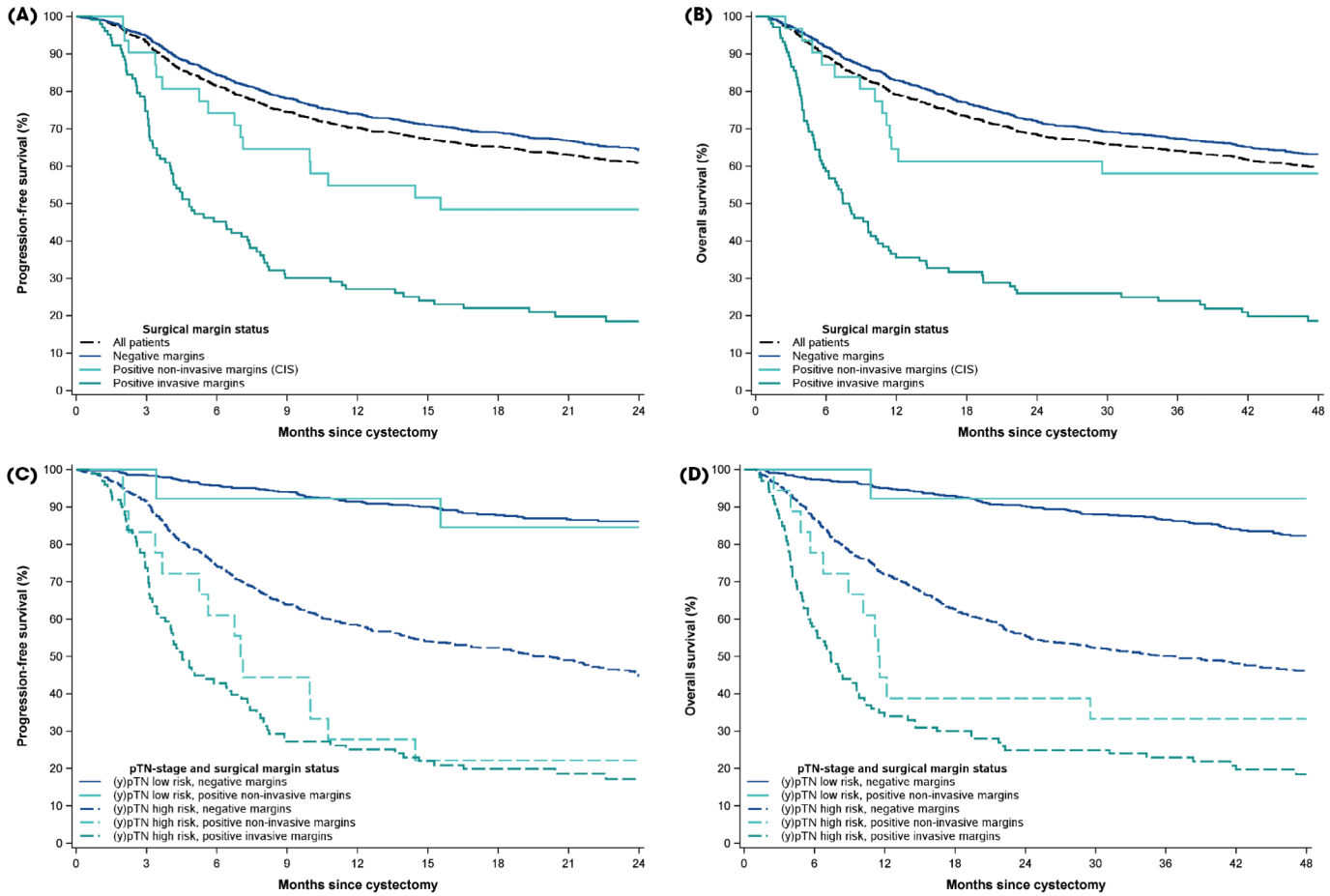
The proportion of patients with positive surgical margins in this Dutch cohort was similar to that reported in cohorts from Italy, France, the United States, and a worldwide cohort [10–13]. The cohorts from France, the United States, and the worldwide cohort only included patients without NAC. Since NAC impacts the (y)pT stage at surgery, it may also affect the risk of positive surgical margins. Within the Italian cohort, only 2.8% of patients received NAC, while in our cohort, 26.8% received NAC. Patients in all cohorts were free of metastatic disease at time of RC. In a US-based cohort of only patients with ≥pT3b, a higher percentage had positive margins (23.5%) [14].

Consistent with our cohort, similar cohorts showed shorter PFS and OS in patients with positive margins compared to those with negative margins [15]. While most studies reported surgical margins as a binary determinant, our detailed data allowed classification of non-invasive positive surgical margins as well, demonstrating that invasive surgical margins are the main driver of prognostically worse outcomes.

Despite RC being a radical treatment, only approximately 50% of patients are alive 5 years post-surgery [1,2]. To improve survival outcomes, current EAU guidelines recommend NAC for cisplatin-eligible patients with non-metastatic MIBC and adjuvant chemotherapy for patients with pT3-4 and/or pN+ disease who have not been treated with NAC and have no contraindications [3].

In the current cohort, only 26.8% of patients received NAC. A recent Dutch study evaluating guideline adherence regarding NAC demonstrated that only a quarter of patients with cT2-disease received NAC and application was also low among cisplatin-eligible patients, possibly due to limited perceived benefit in this cT2 stage group [16]. The indication for NAC is stronger for cT3/4 patients [17], among whom only just over half received NAC, due

Fig. 2 Observed progression-free and overall survival of patients stratified by pathological TNM and surgical margin status after radical cystectomy. (**A**) Observed 24-month progression-free survival and (**B**) 48-month overall survival stratified by surgical margin status. (**C**) Observed 24-month progression-free survival and (**D**) 48-month overall survival stratified by (y)pTN-stage* and surgical margin status. Four patients had the combination of (y)pTN low risk and positive invasive margins and were omitted from parts C and D because of small group size. *(y)pTN high-risk: pT3-4 and/or pN+ without neoadjuvant chemotherapy (NAC) or ypT2-4 and/or ypN+ following NAC; (y)pTN low-risk: all other stages. CIS, carcinoma *in situ*.



to ineligibility or patient preference in the remaining patients.

The absolute 5-year survival benefit of adjuvant chemotherapy was estimated to be 6% based on a meta-analysis of 10 trials, which is similar to the survival benefit of NAC, and can be associated with severe toxicity [18]. The infrequent use of adjuvant chemotherapy (only 1% of the total cohort) may be attributed to these factors, underscoring the importance of identifying features for selecting patients associated with improved survival following adjuvant therapy. Patients with positive surgical margins were excluded from some adjuvant immunotherapy studies (CheckMate-274 and IMvigor010), but not all (AMBASSADOR) [5,19,20]. The POUT trial provides convincing evidence supporting the potential benefits of adjuvant chemotherapy for such patients, demonstrating improved disease-free survival in patients having undergone nephroureterectomy for locally advanced upper urinary tract carcinoma, including those with positive surgical margins. Given the similar clinicopathological characteristics of upper tract and bladder tumours, the findings from the POUT trial might also apply to patients treated with RC who have positive margins [21].

Based on the CheckMate-274 trial, the EAU guidelines recommend the use of adjuvant nivolumab for selected patients with pT3-4 and/or pN+ disease who are not eligible for or have rejected adjuvant chemotherapy, while mature OS data remain pending [3]. These patients are at high risk for adverse outcomes after RC. However, patients with positive surgical margins were not included in this trial, nor in the IMvigor010 trial investigating adjuvant atezolizumab [5,19]. The AMBASSADOR trial, investigating adjuvant pembrolizumab, did include patients with positive surgical margins and demonstrated a significant improvement in

Table 3 Multivariable associations between pathological results of radical cystectomy and progression-free and overall survival.

	Progression-free survival		Overall survival	
	HR	95% CI	HR	95% CI
Pathological TNM stage				
(y)pT≤1N0M0	0.45	0.31–0.65	0.58	0.41–0.82
(y)pT2N0M0	Ref.	–	Ref.	–
(y)pT3N0M0	2.14	1.59–2.88	2.21	1.65–2.96
(y)pT4N0M0	3.50	2.40–5.10	4.03	2.78–5.83
(y)pTanyN+M0	4.17	3.12–5.59	3.83	2.87–5.11
Lymphovascular invasion				
No	Ref.	–	Ref.	–
Yes	1.45	1.16–1.82	1.39	1.11–1.74
Not reported	1.14	0.92–1.42	1.11	0.90–1.36
Surgical margin status				
Negative	Ref.	–	Ref.	–
Positive, CIS only	1.60	1.00–2.58	1.30	0.80–2.12
Positive, invasive tumour tissue	2.13	1.67–2.72	2.02	1.58–2.58
Neoadjuvant therapy				
No	Ref.	–	Ref.	–
Yes	1.12	0.92–1.36	0.92	0.76–1.11

CIS, carcinoma in situ; HR, hazard ratio; Ref., reference.

disease-free survival for patients with high-risk MIBC, and a potentially very strong subgroup effect for those with positive surgical margins, but not on OS [22]. Lack of OS benefit may have been influenced by a high rate of patients in the observation arm receiving subsequent immune checkpoint inhibition.

Thus, the data on definitive efficacy of adjuvant immunotherapy in this particular subgroup are insufficient. However, the results of the current study indicate that positive surgical margins may identify additional patients prone to poor survival outcomes after RC, but who are not clearly in the palliative phase, who might benefit from adjuvant therapy.

The use of biomarkers may be another way to select patients potentially suitable for adjuvant therapy. Accumulating data indicate circulating tumour DNA (ctDNA) as a potential biomarker for residual disease and relapse, demonstrating improved oncological outcomes with atezolizumab in ctDNA-positive patients [23]. Several prospective studies are currently ongoing [24,25]. Combining both positive surgical margins and emerging biomarkers, such as ctDNA, could allow for more precise risk stratification in the future.

The present study has several strengths. Firstly, its nationwide population-based design including a large number of patients over a recent period, provides a contemporary reflection of MIBC care in the Netherlands. In addition, the highly detailed data allow for robust comparisons. Furthermore, the prognostic effect of positive margins is well studied in the absence of adjuvant therapy, with only 1.9% of the total cohort receiving adjuvant therapy.

Nevertheless, two limitations of this study warrant consideration. First, in this observational study design, follow-up procedure data were collected according to routine clinical scheduling, without any changes to their timing for the research protocol. It is possible that patients with positive margins were scanned more often. However, we expect this to have had a minimal effect on the outcomes as the EAU guidelines recommend a CT scan every 6 months for the first 3 years after RC for all patients and most hospitals have predetermined follow-up routines that do not take into account margin status [3]. Second, follow-up data on PFS were only available for all patients up to 2 years after RC. Late local recurrences can occur up to 5 years after RC and late distant recurrences have been found after more than 10 years [26]. However, the first 2 years following RC are critical, as local recurrence usually occurs during the initial 24 months and 90% of distant recurrences occur within the first 3 years after RC, and mainly in the first 2 years [27].

In conclusion, approximately 10% of the patients in this nationwide Dutch cohort had positive surgical margins following RC for MIBC. Patients with positive surgical margins showed worse PFS and OS compared to patients with negative surgical margins, even when stratified by (y)pTN stage. Positive surgical margins provided relevant prognostic information on OS and PFS in addition to commonly used postoperative risk factors, particularly if invasive tumour tissue was observed in the margins. Despite markedly adverse outcomes among patients with invasive surgical margins, a substantial proportion survived past 12 (44%) and 24 (32%) months. These findings support further investigation of the potential efficacy of adjuvant therapy (i.e.,

radiotherapy and systemic therapy) among patients with positive surgical margins.

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Disclosure of Interests

None declared.

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Data Availability Statement

All data used for this study can be requested from the NCR and ProBCI. All data requests are reviewed by the supervisory committee of the NCR for compliance with the NCR objectives and (inter)national (privacy) regulation and legislation and by the ProBCI Steering Committee (https://iknl.nl/en/ncr/apply-for-data).

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Abbreviations: CI, confidence interval; CIS, carcinoma *in situ*; ctDNA, circulating tumour DNA; EAU, European Association of Urology; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IKNL, Netherlands Comprehensive Cancer Organisation; IQR, interquartile range; MIBC, carcinoma invading bladder muscle; NAC, neoadjuvant chemotherapy; NCR, Netherlands Cancer Registry; OS, overall survival; PFS, progression-free survival; RC, radical cystectomy; UCC, urothelial cell carcinoma.