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ORIGINAL ARTICLE

Nationwide analysis of survival after radical cystectomy for bladder cancer in Finland

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ABSTRACT

Background: Population-based survival results after radical cystectomy (RC) are limited. Our objective was to report short and long-term survival results after RC for bladder cancer from Finland in a population-based setting.

Materials and methods: The Finnish National Cystectomy Database containing retrospectively collected essential RC data covering the years 2005–2017 was combined with the survival data from the Finnish Cancer Registry. Kaplan-Meier plots were used to estimate survival and the survival graphs were illustrated according to the final pathological staging. Centers were divided according to operational volume, and the results were then compared using Pearsons's Chi-squared test.

Results: A total of 2047 patients were included in the study. 30-, and 90-day mortality was 1.3%, and 3.8%, respectively. The OS of the entire RC population at 5- and 10 years was 66% and 55%, and CSS was 74% and 72%, respectively. Center volume did not significantly associate with surgical mortality or long-term survival. The 5- and 10-year OS according to pT-category was 87% and 74% for pT0, 85% and 69% for pTa-pTis-pT1, 70% and 58% for pT2, 50% and 42% for pT3 and 41% and 30% for pT4. The corresponding 5- and 10-year CSS rates were 96% and 93% for pT0, 91% and 90% for pTa-pTis-pT1, 78% and 75% for pT2, 56% and 55% for pT3 and 47% and 44% for pT4. The 5- and 10-year OS rates in patients with no lymph node metastases (pN-) were 74% and 62%, and CSS 82% and 80%, respectively. If lymph nodes were positive (pN+), the corresponding OS rates were 44% and 34% and CSS 49% and 48%, respectively.

Conclusion: RC survival results have improved in contemporary series and are associated with the pTNM-status. The nationwide results from Finland demonstrate outcome comparable to high volume single-center series.

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Bladder cancer; radical cystectomy; overall survival; cancer-specific survival; muscle-invasive bladder cancer

Background

Muscle-invasive bladder cancer (MIBC), which constitutes approximately 25% of newly diagnosed BCs, is an aggressive disease and radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the gold standard of therapy [1]. According to EAU non-muscle-invasive bladder cancer (NMIBC) guidelines, RC is also recommended immediately for certain patients with pTa- and pT1-staged BC with a high risk for disease progression [2]. In Finland, approximately 1200 new BC cases are diagnosed, and about 180 RCs are performed annually [3]. There has been growing evidence and demand for centralizing the treatment of MIBC to high-volume surgeons and hospitals [4]. In Finland, the Finnish government gave a Government Decree on the centralization of demanding surgery in August 2017 [5]. As a result, the centralization of complex cancer surgery in Finland began in 2018 and 2017 was the last year when low and medium-volume centers performed RCs in Finland.

The tumor-node-metastasis (pTNM) -status is the most important prognostic factor for overall survival (OS) [6,7].

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Neoadjuvant chemotherapy (NAC) has been shown to downstage BC and improve prognosis [8,9]. Only a few national population survival analyses are available with some exclusions, for example, from Nordic countries, Australia, Italy, Austria, and the Netherlands results have been published [10–17]. This has also been the situation in Finland, as only one center has previously reported survival rates [18]. Specialized single-center long-term RC survival data have also been reported before [6,19–21]. These series contain up to 50-100 RCs performed annually, making them comparable to national series.

This study aimed to report short and long-term survival results after RC for bladder cancer from Finland in a population-based setting. A secondary objective was to evaluate perioperative mortality and critically assess if the centralization policy of demanding cancer surgery to high-volume centers is justified. This recommendation is also supported by the EAU MIBC guidelines but has not been investigated on a national level.

Materials and methods

The institutional Medical Ethics Committee of the Hospital District of Southwestern Finland (EMTK: 4/1802/2015) approved this retrospective study.

The Finnish National Cystectomy Database (FNCD) is an online platform, which was established by academic urologists to gather information from all 16 hospitals in Finland where RCs were carried out between 2005 and 2017 to complete the period before the centralization of RCs. The FNCD was designed for research purposes only and it was modeled to be secure and accessible through the Internet. The inclusion criteria for the study was that the RC was performed due to BC. The BC did not need to be of urothelial origin. Cystectomies performed for benign reasons were excluded from the study. The patients were identified using the ICD-10 codes (C67.*= malignant neoplasm of the bladder) and surgical procedure codes in each hospital, as per the Nordic Classification of Surgical Procedures.

The collected data included patient characteristics (age, gender, BMI, ASA class, smoking status, CCI), tumor features (TURB-T and RC specimen histology, stage, grade, concomitant prostate cancer), and treatment details (NAC, surgical modality, diversion method). Comprehensive details about surgery and hospitalization, along with the use of potential adjuvant therapies, were documented. Postoperative complications and mortality were assessed using the Clavien Dindo-grading system [22].

The data was collected retrospectively by urologists dedicated to BC care and each individual medical record was comprehensively examined to ensure accuracy. If possible, a urologist not responsible for performing RCs was selected to collect the data to avoid distortion of the results. In larger centers, the data inserter had a supervisor. In select low-volume centers, the patient files were sent to the main investigator in Turku who was responsible for inputting the data into the database.

The centers were divided into low (< 5 RCs performed annually), medium (5-20 RCs performed annually), and high volume centers (>20 RCs performed annually). By doing this, four university hospitals (Turku, Tampere, Helsinki, and Oulu) were classified as high-volume centers.

We combined the data from the FNCD with survival data from the Finnish Cancer Registry (FCR). The FCR contains information on all diagnosed cancer cases in Finland since 1953, including the unique personal ID number and diagnostic details. The registry covers 96% of solid and 86% of non-solid tumors [23]. The Finnish Cancer Organizations maintain the registry, and data is collected by compulsory notifications of cancer diagnoses made by all Finnish healthcare units. The FCR data includes the site and date of cancer, the basis of diagnosis, TNM stage, histology, and information on treatment. The registry is annually matched with the Cause of Death Registry and the Finnish Central Population Registry. In the latter, the personal identifier digit is also checked annually, and the complete name, vital status, possible date of death, emigration status, and the official place of residence prior to the date of diagnosis are obtained. Patients were identified using the ICD-10-codes and the patients' social security numbers with strict data security policies [23].

Kaplan-Meier plots were used to estimate the OS and CSS for all patients in the database. Survival was calculated from the time of RC and the end of follow-up was 2018. Death from BC was defined from the FCR data when the main cause of death was inserted as C67.*.The survival graphs were illustrated according to the final pathological TNM-classification. The log-rank test was used to compare subgroups of patients in terms of survival, and hazard ratios (HR) were calculated. The Wilcoxon rank sum test and Pearsons's Chi-squared test were used to compare centers.

Results

Basic characteristics of the study population are presented in Table 1. The study population included a total of 2047 patients. Of these, 1648 (81%) were men, and the median age of the patients was 69 (range 62–75) years. Overall, 384 (19%) patients had no smoking history, and the median ASA-score was 3. At the time of RC, 437 (22%) of patients had NMIBC (pTa-Tis-T1), and 356 (18%) had no evidence of tumor (pT0) in the RC specimen. A muscle-invasive (pT2) tumor was present in 372 (19%) patients, and 824 (41%) patients had an invasion beyond the detrusor muscle (pT3-4). Positive LNs were found in 395 (19%) patients. Patients had more advanced tumors and LND was more commonly performed in high and medium-volume centers. In low-volume centers LND was not performed in 20 (11%) of the cases and not reported in 58 (31%). NAC has used in 370 (18%) cases in the entire study population. Figure 1. represents the incidence of BC and RCs performed in Finland during 2005–2017.

The entire population's 30- and 90-day perioperative mortality was 1.3% and 3.8%, respectively. The 30-day mortality in high, medium, and low volume centers was 1.3%, 1.6%, and 0.5%, respectively. The 90-day mortality rates in high,

Table 1. Basic characteristics of the study population.

Characteristic	High[a] volume centers, $N = 1358$	Medium[b] volume centers, $N = 504$	Low[c] volume centers, $N = 185$	Overall, $N = 2047$
Age, median (IQR[d])	68 (62, 74)	70 (64, 76)	69 (63, 75)	69 (62, 75)
BMI[5], median (IQR[d])	25 (22, 29)	26 (23, 28)	24 (20, 27)	25 (22, 29)
Gender, N(%)				
Female	266 (20%)	100 (20%)	33 (18%)	399 (19%)
Male	1092 (80%)	404 (80%)	152 (82%)	1648 (81%)
Smoke, N(%)				
Active	332 (24%)	88 (17%)	38 (20%)	458 (22%)
Never	232 (17%)	111 (22%)	41 (22%)	384 (19%)
Stopped	321 (24%)	79 (16%)	24 (13%)	424 (21%)
Not available	473(35%)	226 (45%)	82 (44%)	781 (38%)
ASA[f]-class, N(%)				
1	40 (3%)	36 (7%)	8 (4%)	84 (4%)
2	428 (32%)	193 (38%)	74 (40%)	695 (34%)
3	645 (48%)	241 (48%)	73 (39%)	959 (47%)
4	62 (5%)	27 (5%)	8 (4%)	97 (4%)
Not available	183 (13%)	7 (1%)	22 (12%)	212 (10%)
TUR-BT[g] T-category, N(%)				
T0	11 (1%)	6 (1%)	1 (1%)	18 (1%)
Ta-Tis-T1	330 (28%)	184 (39%)	45 (26%)	559 (31%)
T2	696 (60%)	269 (57%)	103 (59%)	1068 (59%)
T3	92 (8%)	11 (2%)	22 (13%)	125 (7%)
T4	35 (3%)	5 (1%)	3 (2%)	43 (2%)
pT-category, N(%)				
T0	241 (18%)	98 (20%)	17 (10%)	356 (18%)
Ta-Tis-T1	287 (21%)	103 (21%)	47 (27%)	437 (22%)
T2	242 (18%)	81 (16%)	49 (28%)	372 (19%)
T3	351 (26%)	164 (33%)	44 (25%)	559 (28%)
T4	198 (15%)	47 (10%)	20 (11%)	265 (13%)
pN-category, N(%)				
N-	902 (66%)	313 (62%)	79 (43%)	1294 (63%)
N+	286 (21%)	81 (16%)	28 (15%)	395 (19%)
Not performed	71 (5%)	5 (1%)	20 (11%)	96 (5%)
Not available	99 (7%)	105 (21%)	58 (31%)	262 (13%)
NAC[h], N(%)				
Yes	261 (19%)	75 (15%)	34 (18%)	370 (18%)
No	1097(81%)	429 (85%)	151 (82%)	1677 (82%)

[a]High volume: over 20 radical cystectomies per year.
[b]Medium volume: 5–20 radical cystectomies per year.
[c]Low volume: less than 5 radical cystectomies per year.
[d]IQR: inter quartile range.
[e]BMI: body mass index (kg/m^2).
[f]ASA: American society of anesthesiologists classification.
[g]TUR-BT: transurethral resection of bladder tumor.
[h]NAC: Neoadjuvant chemotherapy.

Figure 1. The incidence of BC and RCs performed in Finland during 2005–2017.

medium, and low-volume centers were 3.4%, 4.4%, and 4.9%, respectively. There was no statistically significant difference concerning mortality between high, medium, and low-volume centers.

Tables 2 and 3 summarize the survival results. The OS of the entire RC population at 5- and 10 years was 66% and 55%, and CSS was 74% and 72%, respectively. There was no statistically significant difference between the OS or CSS rates in low, medium, and high-volume centers. The 5- and 10-year OS according to pT-category was 87% and 74% for pT0, 85% and 69% for pTa-pTis-pT1, 70% and 58% for pT2, 50% and 42% for pT3 and 41% and 30% for pT4. The corresponding 5- and 10- year CSS rates were 96% and 93% for pT0, 91% and 90% for pTa-pTis-pT1, 78% and 75% for pT2, 56% and 55% for pT3 and 47% and 44% for pT4. The 5- and 10-year OS rates in patients with no lymph node metastases (pN-) were 74% and 62%, and CSS 82% and 80%, respectively. In node-positive cases (pN+) the corresponding OS rates were 44% and 34% and CSS 49% and 48%, respectively. The OS and CSS Kaplan-Meier curves according to the pT-category are presented in Figures 2(A,B), respectively.

Table 2. Survival rates of the study population according to center volume.

	Overall Survival		Cancer Specific Survival	
	5-y.	10-y.	5-y.	10-y.
High[a] volume centers	67%	56%	74%	73%
Medium[b] volume centers	65%	53%	73%	72%
Low[c] volume centers	66%	55%	70%	68%
Overall	66%	55%	74%	72%

[a]High volume: over 20 radical cystectomies per year.
[b]Medium volume: 5–20 radical cystectomies per year.
[c]Low volume: less than 5 radical cystectomies per year.

Table 3. Survival rates of the study population according to pT- and pN-category.

	Overall Survival			Cancer Specific Survival		
	5-y.	10-y.	HR[1] (95% CI[2])	5-y.	10-y.	HR[a] (95% CI[b])
pT-category						
pT0	87%	74%		96%	93%	
pTa-Tis-T1	85%	69%	1.2 (0.9–1.6)	91%	90%	1.4 (0.8–2.4)
pT2	70%	58%	1.9 (1.5–2.5)	78%	75%	4.1 (2.6–6.5)
pT3	50%	42%	3.3 (2.6–4.2)	56%	55%	9.0 (5.8–13.9)
pT4	41%	30%	4.7 (3.6–6.1)	47%	44%	12.9 (8.2–20.2)
pN-category						
pN-	74%	62%		82%	80%	
pN+	44%	34%	2.3 (1.9–2.7)	49%	48%	3.4 (2.8–4.1)
pNx	64%	54%	1.2 (1.0–1.5)	70%	69%	1.7 (1.4–2.2)

[a]HR: Hazard Ratio.
[b]CI: Confidence Interval.

Discussion

Our study reports the survival results for patients treated with RC in Finland in 2005–2017. The five-year OS and CSS for patients with pTa, pT1, or pTis were 85% and 91%, and the corresponding results for patients with pT2 were 70% and 78%. When extravesical tumor growth is present, survival decreases dramatically as patients with pT3 staged disease had 5-year OS and CSS rates of 50% and 56%, respectively. Patients with positive LNs had the worst OS and CSS, with 5-year results of 44% and 49%.

In the 2012 study by Hautmann et al. the five-year CSS for patients with pTa,pT1, pTis and pT2, pT3, pT4 was 93%, 74%, 66%, and 46%, respectively [6]. This study is regarded as one of the landmark papers reporting 'surgery only' survival. Selection biases and treatment approach differences make direct comparisons difficult, but survival results are

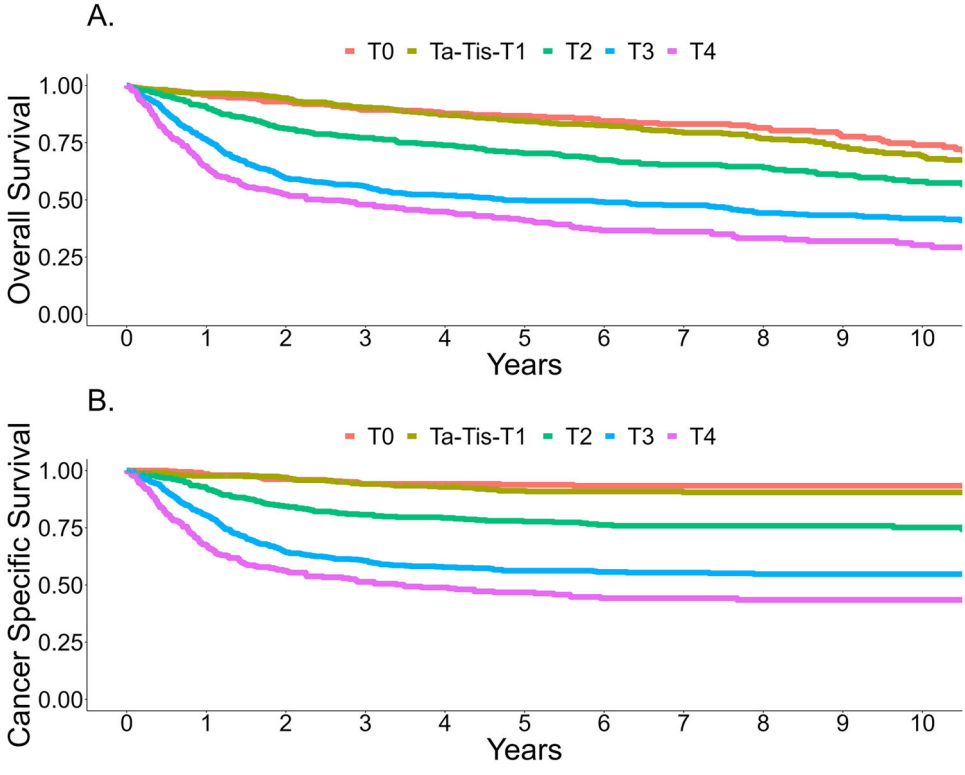

Figure 2. **A.** Overall survival according to pT-category **B.** Cancer specific survival according to pT-category.

comparable. Similar results have been reported by research groups lead by Shariat, Madersbacher, and Stein [19–21]. Our study's national results were similar or better in some aspects. The most notable difference is in patients with positive LNs as in the aforementioned studies the 5-year CSS ranges from 22–34% and is an impressive 49% in our study. One can only speculate the reasons for the difference. Firstly, our study period is more modern as all patients were operated on in the twenty-first century in comparison to patients operated on in the 70s in the study by Stein et al [21]. RC survival results in general seem to have improved in the more modern studies even though no major breakthroughs in MIBC treatment have appeared. Similar to our results in a study published in 2016 (patients operated 2007–2009) a 3-year CSS of 46% in patients with positive regional LNs was reported [24]. There are likely several factors that may contribute to the improvements in survival after RC, including earlier detection of BC, the adaptation of national cancer management protocols, the use of consistent cancer care guidelines across the country, and the establishment of standardized patient pathways [25]. An interesting study by Palumbo et al. in 2019 reported that the HR for cancer-specific mortality decreased to non-significant levels at three years of follow-up for patients with positive LNs after surgery [26]. A study by Bruins et al. showed that a considerable number of patients with low-volume lymph node metastasis (2–3 positive nodes) remained free of recurrence during follow-up. They concluded that LN density was associated with higher recurrence risk than merely positive nodes [27]. This is also seen in our results as the 5- and 10-year CSS for pN + patients are nearly alike. Thus, it seems that patients who survive the first two to three years after surgery are unlikely to die due to BC. It can be argued that these patients most likely have a low LN density and a clinical N0 –status after surgery, and oncological follow-up could be stopped around 3–5 years after RC. Secondly, the difference in survival rates observed in our study may also be attributed to patient selection. Although our study included cN + patients, cM + patients were mostly excluded, and these patients were more likely to receive NAC. NAC was introduced as standard treatment for patients with cT2 disease in 2008 in the Turku University Hospital and gained interest nationally from there-on. Our entire population had a NAC utilization rate of 18%, but this is prior to any national cancer care guidelines and national acceptance later on. In the reports by Stein et al. and Shariat et al. patients receiving NAC were also included [20,21]. The survival results are more comparable with our results, and the survival for patients with a positive LN status is also improved compared to the results by Hautmann. A comparison of our results with previous large RC series and other large RC studies is presented in the Supplementary material.

National RC survival studies have been published from Australia, England, the Netherlands, Italy, Sweden, Denmark, and Iceland with an approximately 50% 5-year OS for all RC patients [10–16,28]. Mainly survival results of the entire study population have been reported, and survival according to pT-category is lacking. Our study reports the survival rates according to pT-category. It shows that a tumor growing beyond the bladder wall at the time of surgery, or positive lymph nodes, is the leading cause for poorer survival rates. A Swedish study focusing on patients with clinically suspected LN metastases reported a 5-year CSS and OS of 37% and 29%, respectively [29]. The national results from Iceland showed a 5-year OS of 54% for patients with a positive LN status [10]. Our results are consistent with these studies.

The importance of hospital volume as a major determinant of peri-operative morbidity and mortality has been shown in a large systematic review [4] and is also supported by the EAU guidelines [1]. As 2017 was the last year medium and low-volume centers performed RCs in Finland, we now have an excellent view on RC survival prior to centralization. In the comparison between centers, there was no significant difference in the long-term survival results. Centralization may, however, be advocated with a broader spectrum of diversion methods which are introduced to more advanced staged patients. In the comparison between centers, patient characteristics are different which may unjustify the direct comparison of survival results concerning center volume. High-volume centers had more patients with extravesical tumor growth and positive LNs. In the systematic review by Bruins et al. the LND rate was significantly higher in high volume centers [4] and in our study, information whether or not a LND was even performed was missing in 20–30% of patients in medium and low-volume centers. However, all available pathological reports were evaluated and while the quantity of removed LNs was missing in the aforementioned cases, LN positivity is in line with that reported in BC literature [21]. Therefore, we consider that our data concerning LN metastases and LN positivity can be in general considered reliable.

The study population had 30- and 90-day perioperative mortality of 1.3% and 3.8%, respectively. Center volume did not affect mortality statistically significantly. However, there seems to be a tendency to favor larger operational volumes as the 90-day mortality was 3.4% in high-volume centers and 4.9% in low-volume centers. These results compare favorably with international standards and studies. In unselected series 30-day mortality up to 4.5% has been reported, although there is variation in the literature of 0–9% with the highest mortality rates in patients with many comorbidities [4]. It is also notable that 4% of the patient population had an ASA-class of 4, defined as a patient with severe systemic disease that is a constant threat to life. This is reflected in the peri-operative mortality rate, which is nearly the same at 90 days.

This study has several limitations common to retrospective studies, such as selection and misclassification bias, and patients being lost to follow-up. However, the FNCD data covers every RC performed due to BC during the study period. In addition, the risk of underreporting mortality or cause of death is tolerable as follow-up data from different centers was verified when combined with the FCR-data. Also, during the follow-up period, there may have been a shift from local institutions toward tertiary centers with the most demanding patients, which was impossible to adjust. This may hinder the potentially existing difference in survival and

perioperative mortality between centers with different operational volumes.

In conclusion, the Finnish national RC results demonstrate that long-term survival is associated with pTNM- status at the time of surgery. We report promising survival outcomes after RC for BC from a nationwide population. This comprehensive national series also suggests that operational volume is not as important as the pTNM – status at the time of surgery and that RC survival results have improved in contemporary series.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Ilkka Nikulainen, upon reasonable request.

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