SCANDINAVIAN JOURNAL OF UROLOGY
2022, VOL. 56, NO. 2, 149–154
https://doi.org/10.1080/21681805.2022.2028897

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ARTICLE

Risk of recurrence and long-term mortality following radical cystectomy for bladder cancer

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ABSTRACT

Purpose: To investigate the risk of recurrence and long-term mortality after radical cystectomy (RC) for bladder cancer (BC) at a high-volume tertiary referral center in Denmark over 19 years.

Materials and methods: Patients undergoing RC between the 1st of January 2000 to 31st of December 2018 were included. Patient data were manually retrieved from electronic patient files. Follow-up ended 18th of May 2020. Cumulative incidences were used to assess risk of recurrence and mortality using competing risk modelling. Cause-specific Cox regression models were used for multivariable analysis.

Results: A total of 1267 patients underwent RC of which 1042 were eligible for analysis. Overall mortality was 40% and 56% after 5 and 10 years, respectively. The cumulative incidence of recurrence and BC specific mortality was high within the first 2 years. Only 3.2% of the patients with recurrence were alive at the end of follow-up. The cumulative incidence of BC mortality after 5 years was 6.7% (95% CI 3.6–9.9) and 10% (95% CI 6.8–14) for patients with $\leq$ pT1bN0 and pT2N0, respectively. For patients with lymph node positive disease the cumulative incidence of BC mortality after 5 years was 65% (95% CI 58–71).

Conclusions: We found a significant risk of recurrence and disease-specific mortality following RC for BC, especially within the first 2 years following surgery. Our data seem comparable to other large cohorts. The chance of long-term survival following recurrence is low and there is a continuous need to improve adjuvant or salvage strategies following RC.

ARTICLE HISTORY
Received 20 August 2021
Revised 29 December 2021
Accepted 10 January 2022

KEYWORDS
Bladder cancer; radical cystectomy; mortality; recurrence

Introduction

Muscle-invasive bladder cancer (BC) is an aggressive disease with a 5-year cumulative incidence of cancer specific mortality of at least 85% if left untreated [1]. The recommended treatment for high-risk non-muscle-invasive and muscle-invasive BC is radical cystectomy (RC) for patients fit for major surgery [2]. However, RC is a procedure associated with high risk of complications and estimated 5-year survival of approximately 60% [3, 4]. There is a close relationship between stage of the disease at RC and expected survival [5].

In Denmark as well as in the rest of the Nordic countries life expectancy is increasing [6]. Due to the fact, that bladder cancer is more common among elderly, the burden of this cancer may increase in the future. Hence, valid Nordic long-term mortality data after cystectomy brings value to the literature. We aimed to investigate the risk of recurrence and the long-term mortality following RC for BC at a high-volume tertiary referral center in Denmark over a 19-year period. The complications following RC for the same cohort has been described elsewhere [7].

Materials and method

All patients who underwent RC for bladder cancer with intent to cure at the Department of Urology, Copenhagen University Hospital, Rigshospitalet, Denmark, from 1st of January 2000 to 31st of December 2018 were included in the study. Patient data were analyzed from an institutional database, which has been updated through a manual review of the patient file. BC specific mortality was defined as death with diagnosed metastatic recurrence of BC. Recurrence was diagnosed pathologically and/or by imaging using RECIST criteria [8].

A total of 1267 cystectomies were performed in the time frame. Of these, 225 were excluded: 111 patients underwent RC for other malignancies such as vaginal or cervical cancer or benign disease, 36 patients were from Greenland or Faroe Islands and were lost to follow-up, three patients were lost to follow-up for other reasons, 17 patients had unknown T- or N-stage, 17 patients had a concomitant nephroureterectomy, and 41 patients underwent RC as a salvage procedure. The 17 patients, who underwent concomitant nephroureterectomy, were excluded due to malignancy in the upper

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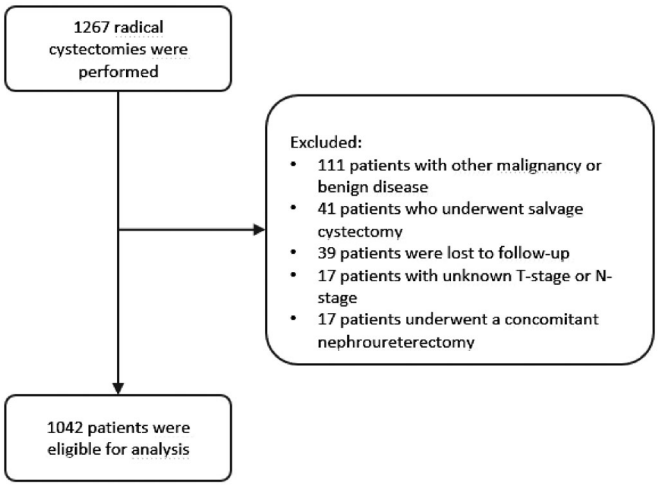

Figure 1. Flowchart that describes the selection of patients.

urinary tracts. Therefore, a total of 1042 patients were eligible for analysis. A flowchart is shown in Figure 1.

The standard procedure of RC included removal of the bladder, internal genitalia/prostate and pelvic lymph node dissection with the aortic bifurcation as the upper limit. RC was performed as open procedure only until January 2012 where robot-assisted laparoscopic radical cystectomy (RARC) was introduced and performed parallel to the open procedure. The choice of procedure was based on the patient's preference, the choice of urinary diversion (only ileal conduits were performed with RARC) and any conditions contraindicating prolonged Trendelenburg position for RARC.

From 1st of January 2013 patients eligible for RC with $\geq$ cT2N0M0 stage, urothelial carcinoma, age $\leq$ 75 years and glomerular filtration rate $\geq$ 60 ml/min were referred for neoadjuvant chemotherapy (four series of cisplatin + gemcitabine). Patients with clinical node-positive non-metastatic disease on preoperative computed tomography (CT) scan were referred for induction chemotherapy (six series of cisplatin-based chemotherapy).

The Charlson Comorbidity Index (CCI) without age adjustment was used to appraise comorbidity [9]. CCI was retrieved manually from review of the individual patient file. Unfortunately, CCI was not part of original database and could not be retrospectively retrieved for patients who were entered into the database at the time where only paper files were available as this is now stored in a facility outside the hospital and access to those paper files was not possible (41% missing). Pathologic data included stage according to the tumor-node-metastasis (TNM) classification and grade according to the World Health Organisation [10].

The postoperative follow-up for all patients consisted of a thoracoabdominal CT scan usually at 4, 12 and 24 months postoperatively. In patients with carcinoma *in situ* in the bladder or ureters a supplementary CT scan at 36 months operatively were performed and each CT scan was with excretion phase. In patients with $\geq$ pT3N0 or pTxN + disease, a CT scan was also performed at 8 and 18 months postoperatively.

The oncological treatment for all patients were performed at another department, hence data have not been gathered due to GDPR.

Statistics

Descriptive analyses of continuous variables were reported with median and interquartile range (IQR) and categorical values in numbers and concurrent percentages. Risk of BC mortality was described using cumulative incidences with the Aalen-Johansen method for competing risks with death of other cause as the competing risk and tested with Gray's test. The Cox regression model was used to identify risk factors for BC death. In the multivariable analysis we adjusted for pre-specified predictors: age (continuous), gender, and TNM stage (grouped into: $\leq$pT1bN0M0, pT2N0M0, $\geq$pT3N0M0 and pTanyN+/M+). CCI was excluded from analysis due to missing variables. Status on survival was set on the 18th of May 2020. Median follow-up time was calculated using the reverse Kaplan-Meier Method [11].

Risk of recurrence was described using a competing risk model with other cause death before recurrence as a competing risk. Recurrence was defined as the date of biopsy/imaging establishing recurrence (whichever came first). Also, a few patients died shortly after cystectomy with clinically suspected recurrence of the disease without histological confirmation. These patients were also registered as recurrence of the disease. The impact of different prognostic factors on the overall risk of death was assessed using competing risk Cox regression analysis. Sensitivity analysis included impact on year of surgery. Statistical analyses were performed using SPSS software version 25; (IBM) and R (R Development Core Team, Vienna, Austria).

Ethics

This study was approved in accordance with Danish regulations by The Legal Department at Rigshospitalet, Copenhagen University Hospital, Denmark and authorized by the Danish Data Protection Agency.

Results

Patient characteristics are summarized in Table 1. Median follow-up time was 8.3 years (95% CI 7.7–8.8). The median age at surgery was 66 years (IQR 60–71), most were male (73%), and the median BMI was 26 (IQR 23–29). A total of 53.6% of the patients had a CCI of $\leq$2. We found a correlation between ASA and CCI with both Spearman rank sum test (rho = 0.38, $p < .0001$) and Cramer's V test (0.29, $p < .001$), indicating a good correlation. Neoadjuvant chemotherapy was administered to 10% of the patients, and 2.4% of the patients received induction chemotherapy. Urothelial carcinoma was the most frequent morphology (94%). At final pathology, a non-muscle-invasive tumor was found in 28% of the patients, pT2 tumor in 36% of the patients and pT3 or pT4 in 36% of the patients. A total of 21% of patients had lymph node positive disease. The risk of having N+/M + disease increased significantly ($p < .001$) with increasing pT-stage; no patients with < pT1, 0.5% of patients with pT1, 15% of patients with pT2, 36% of patients with pT3 and 49% of

Table 1. Patient characteristics from a single center cohort study of cystectomy between 2000 and 2018, Rigshospitalet, Copenhagen, Denmark.

Variable	Cystectomy ($N = 1042$)
Age at surgery (years), Median (IQR)	66 (60–71)
Male, *N* (%)	765 (73.4)
BMI (kg/m^2), Median (IQR)	26 (23–29)
Missing, *N* (%)	78 (7.5)
Smoking, *N* (%)	
Never	190 (18.2)
Ever	832 (79.8)
Missing data	20 (1.9)
CCI, *N* (%)	
CCI 0	230 (22.1)
CCI 1	217 (20.8)
CCI 2	111 (10.7)
CCI 3	43 (4.1)
CCI 4	12 (1.2)
CCI 5	5 (0.5)
Missing data	424 (40.7)
ASA score, *N* (%)	
ASA 1	139 (13.3)
ASA 2	596 (57.2)
ASA 3	283 (27.2)
ASA 4	4 (0.4)
Missing data	20 (1.9)
Preoperative chemotherapy, *N* (%)	
Neoadjuvant chemotherapy[a]	107 (10.3)
Downstaging chemotherapy	25 (2.4)
Missing data	3 (0.3)
Preoperative hemoglobin, Median (IQR)	8.3 (7.5–9.1)
Missing data, *N* (%)	35 (3.4)
Preoperative creatinine (μmol/L), Median (IQR)	84 (70–102)
Missing data, *N* (%)	37 (3.6)
Type of surgery, *N* (%)	
ORC	899 (86.3)
RARC	134 (12.9)
Converted from RARC to ORC	9 (0.9)
Concomitant urethrectomy, *N* (%)	53 (5.1)
Missing data	2 (0.2)
Lymph node dissection, *N* (%)	
Local	158 (15.2)
Extended[b]	836 (80.2)
Missing data	48 (4.6)
Nerve-sparing technique, *N* (%)	38 (3.6)
Missing data	3 (0.29)
Morphology, *N* (%)	
Urothelial carcinoma	981 (94.1)
Squamous cell carcinoma	22 (2.1)
Adenocarcinoma	14 (1.3)
Sarcomatoid	14 (1.3)
Neuroendocrine	4 (0.4)
Small cell carcinoma	2 (0.2)
Other[c]	5 (0.5)
pT category[d], *N* (%)	
pTis	30 (2.9)
pTa	7 (0.7)
pT1	254 (24.4)
pT2	374 (35.9)
pT3	288 (27.6)
pT4	89 (8.5)
pN category, *N* (%)	
N0	824 (79.1)
N1	99 (9.5)
N2	105 (10.1)
N3	11 (1.1)
N+	3 (0.3)
Positive soft tissue margins, N (%)	43 (4.1)

ASA: American Society of Anaesthesiology; BMI: Body Mass Index; CCI: Charlson Comorbidity Index; N: Number of patients; ORC: Open Radical Cystectomy; pN: pathological lymph node category; pT: pathological tumor category; RARC: Robot Assisted laparoscopic Radical Cystectomy.

[a]Neoadjuvant chemotherapy: defined as at least one series completed. 4 patients received neoadjuvant chemotherapy before 2013, and 103 patients received neoadjuvant chemotherapy from 2013.

[b]Extended lymph node dissection: defined as the local pelvic lymph node dissection including obturator fossa and external iliac vessels with the aortic bifurcation as the upper limit.

[c]Other: Leiomyosarcoma, Metaplastic carcinoma, Langerhans cell sarcoma, Paraganglioma.

[d]pT stage: defined as the highest stage found in TURB or cystectomy.

patients with pT4 stage disease had lymph node positive disease.

Overall mortality was 17% (95% CI: 15–19), 40% (95% CI: 37–44) and 56% (95% CI: 53–60) after 1, 5 and 10 years, respectively. The cumulative incidence of recurrence was 20% (95% CI 17–22) after 1 year, 32% (95% CI 29–34) after 5 years, and 35% (95% CI 32–38) after 10 years (Figure 2(a)). The cumulative incidence of BC mortality increased rapidly within the first two years after RC and was 11% (95% CI: 9.3–13), 27% (95% CI: 24–30), and 30% (95% CI: 27–33) after 1, 5 and 10 years, respectively (Figure 2(b)). We found a close univariate relationship between stage of disease and the risk of BC mortality. The cumulative incidence of BC mortality stratified by TNM stage is demonstrated in Figure 3. In the multivariable analysis, TNM stage $\geq$ pT3N0M0 and pTanyN+/M+ were significantly ($p < .001$) associated with the risk of death from BC with an HR of 6.28 (95% CI: 3.92;10.1) and 16 (95% CI: 10.5;25.8), respectively, compared to patients with < pT2N0M0 (Table 2). Gender and age were not found to be associated with BC mortality. We did not find a significant difference in the cumulative incidence of BC specific mortality between patients with or without carcinoma *in situ* in the TNM subgroups (data not shown). Sensitivity analysis showed no impact on year of surgery.

Discussion

This study included a large cohort of patients who underwent RC for BC with long-term follow-up. The study demonstrated that patients after RC are at high risk of disease-specific mortality despite the curative intent of RC. We demonstrated a close relationship between recurrence after RC and disease-specific mortality with only 3.2% of patients experiencing recurrence still being alive in our cohort at the end of follow-up.

RC remains the gold standard for treatment of non-metastatic, muscle-invasive BC in international guidelines [2, 12]. Bladder preserving treatment in muscle-invasive BC with trimodal treatment (TURB followed by radiosensitizing chemotherapy and external beam radiotherapy) is a good alternative option for selected patients with overall survival (OS) comparable to RC [13]. External beam radiotherapy or chemotherapy alone after TURB have been studied as other treatment options to RC but with inferior survival outcomes [14, 15]. However, in this cohort undergoing surgical treatment we still find that 30% succumb to BC; the majority within the first 2 years after RC. According to the Danish Bladder Cancer Database the cancer-specific mortality 1 year after cystectomy for the year 2013 was 24% using Kaplan-Meier analysis [16]. Our study demonstrated a cumulative incidence of BC death of 11% after 1 year, rapidly increasing within the first two years, whereafter the mortality stagnated. This indicates that our results are aligned with the general trends in Denmark and that all five uro-oncological centers in Denmark have uniform results. However, it must be recognized that two different methods were used for risk analysis which may explain the small differences. Compared to Scandinavia, our results seem comparable. Häggström et al.

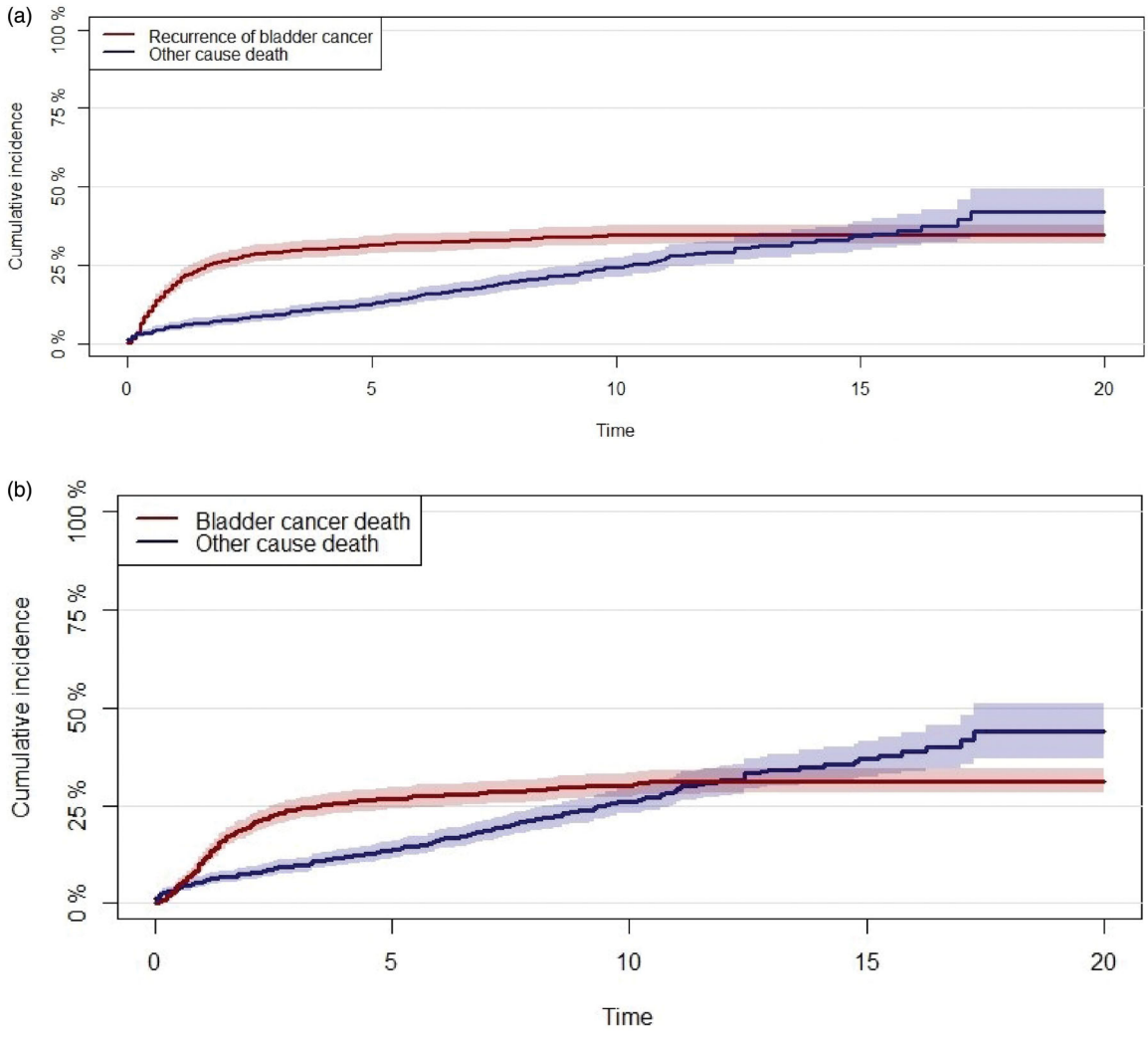

Figure 2. (a) Cumulative incidence of recurrence of bladder cancer or death of other cause over time after cystectomy. (b) Cumulative incidence of bladder cancer death or death of other cause over time ofter cystectomy.

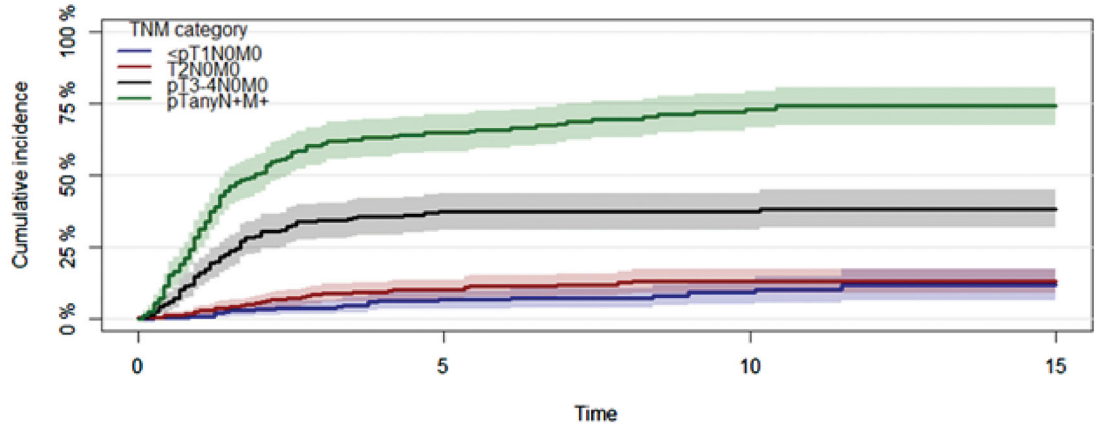

Figure 3. Cumulative incidence of bladder cancer death over time ofter cystectomy stratified by TNM stage.

[17] used the Bladder Cancer Data Base Sweden and found that the absolute risk of BC death 5 years after RC was 39%. Daehlin et al. [18] found the disease-specific survival rates 5 years after RC to be 88% and 56% for Ta-T1 and T2-T3, respectively. Compared to countries outside Scandinavia our results are consistent as well with the described survival for other cohorts following RC. Stein et al. [5] reported an OS of 66% and 43% after 5 and 10 years, respectively, based on a cohort of 1054 patients with a median age of 66 years and with 40% non-muscle invasive tumors, 11% pT2 tumors, and 49% pT3 or pT4 tumors. A total of 23% of patients had lymph node positive disease. Although more patients had pT2 tumors in our cohort, the results from Stein et al. seem comparable to our study. Hautmann et al. [19] reported an

Table 2. Multivariate Cox regression analysis of death of bladder cancer and other cause death.

	Death of bladder cancer		Other cause Death	
Covariates	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Age, per 5-year increase	0.94 [0.88–1.01]	.08	1.27 [1.16–1.39]	<.001
Gender (Ref. Male)	1.00 [0.78–1.29]	.98	0.99 [0.74–1.32]	.94
TNM stage				
≤pT1bN0M0	Ref.		Ref.	
pT2N0M0	1.51 [0.89–2.56]	.13	1.03 [0.74–1.45]	.85
≥ pT3N0M0	6.28 [3.92–10.1]	<.001	1.65 [1.16–2.34]	.006
pTanyN+/M+	16.5 [10.5–25.8]	<.001	1.37 [0.89–2.12]	.15

HR: Hazard Ratio; 95%CI: 95% Confidence Interval; M: Metastatic category; N: Lymph node category; pT: pathological Tumor category; Ref. – Reference.

OS of 58% and 44% after 5 and 10 years, respectively. Hautmann et al. also reported ASA score as a good surrogate marker for the overall health of the patients and their distribution was similar to our study with most patients being classified as ASA 2.

We found that the pathologic stage is an important determinant for the risk of disease-specific mortality. In previous studies they found that pathologic stage was determinant for the survival probability. Ghoneim et al. [20] reported that the 5-year disease-free survival for BC patients with ≤ pT1 was 82%. For patients with stage pT2a, pT2b, pT3 and pT4 the 5-year survival probability was 75%, 53%, 40% and 29%, respectively. Similar to a previous study [5], we observed no significant difference in the risk of BC mortality between patients with ≤ pT1bN0 and pT2N0 stage disease. A previous study [21] reported disease-specific survival for > pT2N0 of 59% 3 years after RC and 50% 7 years after RC. In the study by Stein et al. [5], the OS after 5 years based on T-stage was 74%, 72%, 58%, 38% and 33% for pT1, pT2a, pT2b, pT3 and pT4, respectively.

A total of 21% of the patients in our cohort had positive lymph node disease. We found that the cumulative incidence of BC specific death 5 years after RC for patients with lymph node positive disease was 65%. Similar results have been documented by others [5, 20–22]. In a study by Madersbacher et al. [23] the 5-year OS after RC for lymph node positive disease was 26%.

Our sensitivity analysis showed no impact on year of surgery, thus no apparent improvement in survival over time. This is in line with a Swedish study from 2016 [24] that showed no increase in the survival over time. This underlines the need for improving treatment option for patients with an adverse pathological stage and recurrence.

It has long been debated how patients should be followed up after RC. Although a strategy based on risk relying on histology, patient assessment, and time since RC seem warranted, imaging studies seem to constitute the largest financial burden [25], with no proof of positive impact on survival. This is substantiated by the finding from this and other studies that recurrence and BC specific death are closely linked. There is a continuous need to address if adjuvant or salvage therapies can improve survival in patients with high risk of recurrence after RC. Recent developments in oncological treatment increase the interest for early detection of recurrence after RC in the hope of improving long-term survival recurrence. Measurable circulating tumor cells seem to be a promising marker of disease activity that precedes tumor presence in imaging studies [26] and may be a useful marker for designing early intervention studies following RC. Recently, a novel study [27] using circulating tumor DNA has described the genomic heterogeneity of metastatic urothelial carcinoma. We must take advantage of these new methods, also in earlier stages of the disease, to better understand the tumor in the individual patient. This could impact the use of neoadjuvant or induction chemotherapy before or after RC in a personalized medicine approach.

Our study has limitations related to the retrospective nature of the analysis, especially regarding the CCI, that was not registered at the time when the original database was created. Patients that only had a paper file could not be retrospectively reviewed for CCI as the files are stored in a facility outside Copenhagen and access to the files are very difficult. The number of patients with CCI of 0 is lower than reported in national registries from Sweden [28] and the US [29] where patients with CCI = 0 before RC has been reported to be 56–78%. Whereas CCI was accessed through Medicare and a National Patient Registry of hospital contacts, we also captured comorbidity that was treated and handled by general practitioners and not registered in a hospital registry, e.g. mild chronic obstructive pulmonary disease. This could explain why there were fewer patients with CCI = 0 in our cohort compared to registry-data. Denmark has one of highest prevalence's of smokers in people > 15 years of age in Europe which could contribute to the fact that Danish patient are unhealthier than other cohorts [30]. Smoking is also a known risk factor adverse outcome in surgery, but our data did not allow to separate previous smokers and active smokers and the number of pack years and thus we decided not to include it in the analysis here. The single-center design may limit the generalizability, and comparison with other cohort studies may be hampered by heterogeneity in the study cohorts. Lastly, our pathological data did not contain detailed information on urothelial carcinoma divergent differentiation and variant histology which could have been interesting for a deeper insight into the mortality analysis, including data on the treatment administrated in case of recurrence. The strengths include the use of competing risk analysis, which is more accurate than previously used Kaplan-Meier estimation, the long-term follow-up and the low number of patients lost to follow-up.

Conclusion

In this study, we demonstrated that the risk of recurrence and BC mortality is high following RC for non-metastatic BC. One in three patients die of the disease during long-term follow-up, but the risk of mortality is highest within the first two years following surgery. The prognosis after recurrence of BC after RC is dismal, with only 3.2% of patients with recurrence being alive at the end of follow-up. There is a continuous need to reduce risk of recurrence and improve treatment of recurrence after RC.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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