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ARTICLE

Do repeated transurethral procedures under general anesthesia influence mortality in patients with non-invasive urothelial bladder cancer? A Danish national cohort study

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ABSTRACT

Purpose: To investigate the effect of repeated transurethral procedures under general anesthesia on overall mortality in patients with non-invasive bladder cancer.

Materials and methods: All Danish residents with non-invasive papillary urothelial carcinoma or primary urothelial carcinoma *in situ* diagnosed between 1 January 2000 and 1 January 2011 were included and followed until death or 31 March 2017. All transurethral procedures under general anesthesia, intravesical instillation therapy, recurrences and progression to invasive disease or cystectomy were recorded during follow-up. Associations between treatments and overall mortality were evaluated using multivariable regression analysis adjusted for age, gender, comorbidities and socioeconomic status. The effect of disease progression on mortality was removed by censoring patients at the time of progression or cystectomy.

Results: Risk of death increased with the number of transurethral procedures under general anesthesia for Ta low- and high-grade tumors compared to patients who had only one procedure; after eight or more procedures the risk of death increased by 28% and 83%, respectively. There was no similar relationship for carcinomas *in situ*. In total, 36–52% of procedures under general anesthesia did not identify urothelial neoplasia.

Conclusions: Repeated transurethral procedures under general anesthesia appear to be associated with increased risk of death in patients with primary non-invasive papillary urothelial carcinoma. Furthermore, a substantial number of procedures were without findings of neoplasia, indicating that too many patients are admitted for transurethral procedures under GA. Attempts should be taken to reduce unnecessary transurethral procedures under GA, e.g. by improved outpatient diagnosis of urothelial neoplasia.

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Introduction

A Danish national cohort study showed increased mortality and lower survival in patients with non-invasive bladder cancer compared to a matched background population [1]. After adjusting for age, gender, comorbidities and socioeconomic status, there was a 28% and 79% increased risk of death in low-grade (LG) and high-grade (HG) non-invasive papillary urothelial carcinoma (Ta), respectively. Studies evaluating long-term outcomes in patients with primary TaLG tumors showed that 2.0–6.3% progressed to muscle invasive bladder cancer, 1.2–2.4% died of bladder cancer, and 5 year cancer-specific survival was ~98% [2–4]. Therefore, the observed 28% and 79% increased risks of death in patients with primary Ta bladder tumors may not be due to stage progression and disease-specific mortality alone.

Approximately 50% of patients diagnosed with primary Ta tumors experience recurrence [4,5]. These patients have repeated transurethral resections of bladder tumors (TUR-BTs) under general anesthesia (GA). Overall complication rates at 30 days range from 4.3–16%, and 30-day mortality rates range from 0.8–1.3% following TUR-BT [6–10]. Furthermore, there is a greater risk of postoperative morbidity and mortality in older patients with non-invasive bladder cancer [11]. Therefore, repeated transurethral procedures under GA with possible postoperative complications and subsequent intravesical instillation therapy for patients with non-invasive bladder cancer may affect mortality in the long-term, which was not detected in 30-day postoperative mortality. This may explain some of the decreased survival among Danish patients with non-invasive urothelial bladder cancer compared to a matched background population.

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Supplemental data for this article can be accessed here

To our knowledge, no follow-up study has evaluated the relationship between repeated transurethral procedures in GA and overall mortality risk among subgroups of patients with non-invasive bladder cancer in a national population. National prospective collected data since 1 January 2000, including surgical procedures, histopathology, use of intravesical bacillus Calmette-Guerin (BCG) and mitomycin and survival from all Danish patients, were included in this study to investigate whether bladder tumor treatment is associated with mortality in patients with non-invasive bladder cancer.

Materials and methods

Source of data

All Danish residents are provided with a unique Civil Personal Registration (CPR) number [12], which links data from the following national registries that were used in this study:

Danish Pathology Data Bank (DPDB) [13]: The DPDB was established in 1999 and records all histological and cytological examinations of normal and abnormal specimens performed in Denmark. Pathologists' evaluations are described using the Danish SNOMED for Pathology [14], based on College of American Pathologists second edition of Systematized Nomenclature of Medicine (SNOMED) [15]. The system includes codes for the source organ, morphology, tumor grading, tumor stage, and procedure for obtaining the tissue. The bladder cancer registration of tumor stage and grade is continually revised in accordance with the latest versions of the Union for International Cancer Control's (UICC) TNM classification [16] and the World Health Organization's (WHO) classification systems [17].

Danish Bladder Cancer Cohort (DBCC) [1]: On 1 January 2000, the DBCC began prospectively collecting data on all histological bladder tissue examinations registered in the DPDB. Software was developed, using algorithms to translate DPDB data into clinical data prepared for analysis. Neoplasia data obtained before 2017 were translated into UICC's 2017 TNM and WHO's 2016 classification nomenclature. Non-neoplasia data are also retained in the register to include every histological examination performed on patients.

Danish National Patient Register (DNPR) [18]: In 1976, the DNPR was established to record all patient-related activity in public and private Danish hospitals. Every patient contact is registered by date, type of contact (inpatient, acute, or outpatient), hospital, department (ward, outpatient or day-surgery), WHO's International Statistical Classification of Diseases (ICD-10), the Danish version of the Nordic NOMESCO Classification of Surgical Procedures (NCSP) and the Danish healthcare classification of non-surgical procedures (SKS).

Study design

This observational national cohort study includes all Danish patients with a primary diagnosis of urothelial TaLG, TaHG or primary carcinoma *in situ* (CIS) between 1 January 2000 and 1 January 2011. Patients were followed from their first diagnosis until death, emigration or 31 March 2017, whichever came first. Age, gender, civil status, education, income and Charlson Comorbidity Index (CCI) data were recorded at study inclusion. During follow-up, all transurethral procedures under GA, intravesical instillations with either mitomycin or BCG, recurrences, progression to invasive bladder cancer and cystectomies were recorded. Patients who experienced progression or had a cystectomy were censored at the time of the event.

Patients and baseline characteristics

All patients diagnosed with primary non-invasive urothelial carcinoma during the inclusion period were identified from the DBCC. To minimize under staging, the primary diagnosis was defined as the worst diagnosis within a period of 6 months from the patient's first evaluation. Primary urothelial papilloma ($n = 88$) and urothelial dysplasia ($n = 55$) were excluded. Papillary urothelial neoplasms of low malignant potential ($n = 985$) were categorized as TaLG. Papillary tumors with concomitant CIS ($n = 236$) were categorized as TaHG. In total, 10,197 patients with primary TaLG, TaHG, or CIS were included at the time of diagnosis for statistical analysis. Variables known to be associated with risk of death were included at baseline: civil status (CPR), income and educational level (Statistics Denmark) [19] and CCI (calculated from DNPR data).

Transurethral procedures under GA, intravesical installation therapy and outcomes

Transurethral procedures performed under GA were identified from DNPR. Procedures coded as inpatient or performed in the urology ward or day-surgery were defined as being done under GA. In Danish registry coding, day-surgery comprises surgery under GA. Outpatient cystoscopy with biopsy or fulguration is uncommon in Denmark and not included as GA procedures. Histological evaluation of bladder tissue without simultaneous coding of TUR-B or cystoscopy/cystoscopy with biopsy was recorded in 4,280 procedures and interpreted as procedures under GA. Data on intravesical instillation with mitomycin or BCG were obtained from the DNPR. Recurrences were identified from the DBCC as histological examinations with neoplasia, and progression was defined as a stage T1 diagnosis or greater. Cystectomies were defined using DPDB procedure codes.

Approval for data collection was obtained from the Danish National Data Protection Agency (file number: 2013-41-2509).

Statistical methods

Transurethral procedures under GA, treatment with mitomycin or BCG, recurrences and progression were recorded over time and are presented for the cohort as totals, medians and interquartile ranges (IQRs). These variables are visualized as mean cumulative counts or incidence on a time since

Table 1. Characteristics of the study population in numbers and percentages at the time of inclusion.

	n (%)		
	Ta LG	Ta HG	CIS
Primary diagnosis	7,787 (76.4)	1,904 (18.7)	506 (5.0)
Mean age in years (SD)	68.33 (11.24)	70.94 (10.35)	69.71 (9.21)
Gender			
Male	5,710 (73.3)	1,542 (81.0)	405 (80.0)
Female	2,077 (26.7)	362 (19.0)	101 (20.0)
Year of diagnosis			
2000–2002	2,090 (75.8)	566 (20.5)	102 (3.7)
2003–2005	2,144 (78.0)	459 (16.7)	146 (5.3)
2006–2008	2,237 (78.9)	462 (16.3)	137 (4.8)
2009–2010	1,316 (71.0)	417 (22.5)	121 (6.5)
CCI			
0	4,952 (63.6)	1,108 (58.2)	290 (57.3)
1	1,631 (20.9)	437 (23.0)	132 (26.1)
2	657 (8.4)	196 (10.3)	52 (10.3)
3+	547 (7.0)	163 (8.6)	32 (6.3)
Civil status			
Widower	1,130 (15.9)	306 (18.3)	72 (16.5)
Divorced	849 (12.0)	178 (10.6)	41 (9.4)
Married	4,610 (65.1)	1,101 (65.7)	301 (68.9)
Single	496 (7.0)	91 (5.4)	23 (5.3)
Income in quintiles			
0–20	1,461 (20.6)	380 (22.6)	95 (21.7)
20–40	1,494 (21.1)	348 (20.7)	88 (20.1)
40–60	1,490 (21.0)	327 (19.5)	89 (20.3)
60–80	1,289 (18.2)	311 (18.5)	88 (20.1)
80–100	1,363 (19.2)	314 (18.7)	78 (17.8)
Education			
Higher	1,154 (14.8)	251 (13.2)	73 (14.4)
Medium	3,479 (44.7)	806 (42.4)	244 (48.2)
Short	2,459 (31.6)	623 (32.7)	152 (30.0)
Unknown	689 (8.9)	224 (11.8)	37 (7.3)

diagnosis scale. Progression and cystectomies were used for censoring.

The mortality of patients with recurrent Ta/CIS bladder tumor was compared with the mortality of patients with Ta/CIS bladder tumor who only experience their primary bladder tumor. Thus, two theoretically similar patient cohorts with the same comorbidity and other factors related to mortality were compared and the potential influence of repeated bladder tumor surgeries on mortality were estimated.

The effects of transurethral procedures under GA and of treatment with mitomycin or BCG on mortality were estimated using hazard ratios (HRs) obtained from Cox proportional hazards models. Transurethral procedures under GA were categorized into 1, 2–4, 5–7 and 8+ surgeries with the first TUR-BT used for reference. All analyses were adjusted for baseline characteristics and stratified by TaLG, TaHG and CIS. Risk of progression was estimated using the same Cox model, stratifying the analysis by TaLG, TaHG and CIS and adjusting for baseline characteristics and treatments. The continuous variables, age at index date and calendar year were included as restricted cubic splines. All effect estimates are shown with 95% confidence intervals (CIs). Statistical analyses were performed using R software (ver. 3.1.0; R Development Core Team, 2014) [20] and the significance level was 5%.

Results

In Denmark, between 1 January 2000 and 1 January 2011, 10,197 patients (approximate ratio = 3 males: 1 female) were diagnosed with primary TaLG, TaHG or primary CIS. Characteristics at inclusion such as age, gender, socio-economic status and CCI were evenly distributed among patients with TaLG, TaHG and CIS (Table 1).

During follow-up, 57.5% of patients with TaLG, 69.5% with TaHG and 66.8% with primary CIS experienced recurrence (Table 2). Patients with HG tumors had a higher risk of early recurrence. The 1-year probability of recurrence was 50.0% (95% CI = 47.5–52.4%), 55.8% (95% CI = 50.9–60.6%) and 26.4% (95% CI = 25.4–27.4%) in patients with TaHG, primary CIS and TaLG, respectively. After 3 years, the incidence of recurrence decreased in all groups and the rates for high- and low-grade disease became similar (Figure 1(a)).

Table 2 shows that during follow-up, at least 25% of patients with TaLG or CIS had five or more transurethral procedures under GA and at least 25% of patients with TaHG had six or more procedures. In contrast, at least 25% of patients with TaLG only had the primary procedure and at least 25% of patients with TaHG or CIS had no more than two transurethral procedures under GA.

The number of transurethral procedures under GA was higher than the number of histologically verified recurrences because no neoplasia was identified in DPDB in 35.9% ($n = 8,366$), 44.5% ($n = 2,910$) and 52.9% ($n = 821$) of procedures on patients with TaLG, TaHG and primary CIS, respectively (Table 2 and Figures 2(a) and (b)).

Mitomycin and BCG instillations in the cohort are presented in Table 2. Mitomycin was mainly used to treat patients with TaLG. BCG was mainly used to treat patients with primary CIS. A mean of 4.8 BCG instillations was

Table 2. Numbers of transurethral procedures under GA, mitomycin, BCG and outcomes during the follow-up period.

		Ta LG	Ta HG	CIS
Follow-up time in years	Median (IQR)	8.14 (5.01–11.18)	6.09 (2.23–9.05)	6.15 (2.05–9.01)
Treatments				
Transurethral procedures under GA*	Total	31,076	8,443	2,085
	Median (IQR)	3 (1–5)	4 (2–6)	4 (2–5)
Mitomycin	Total	3,252	584	119
	Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
BCG	Total	6,714	4,812	2,538
	Median (IQR)	0 (0–0)	0 (0–4)	1 (0–7)
Outcomes				
Recurrence	Total	14,923	3,629	758
	Median (IQR)	1 (0–3)	1 (0–3)	1 (0–2)
	n (%)	4,479 (57.5)	1,324 (69.5)	338 (66.8)
Progression	*n* (%)	324 (4.2)	176 (9.2)	53 (10.5)
Cystectomy	*n* (%)	44 (0.6)	54 (2.8)	38 (7.5)
Mortalities	*n* (%)	3,645 (46.9)	1,158 (60.9)	296 (58.5)

*Including primary transurethral resections of the bladder tumor and transurethral procedures under general anesthesia without recurrence.

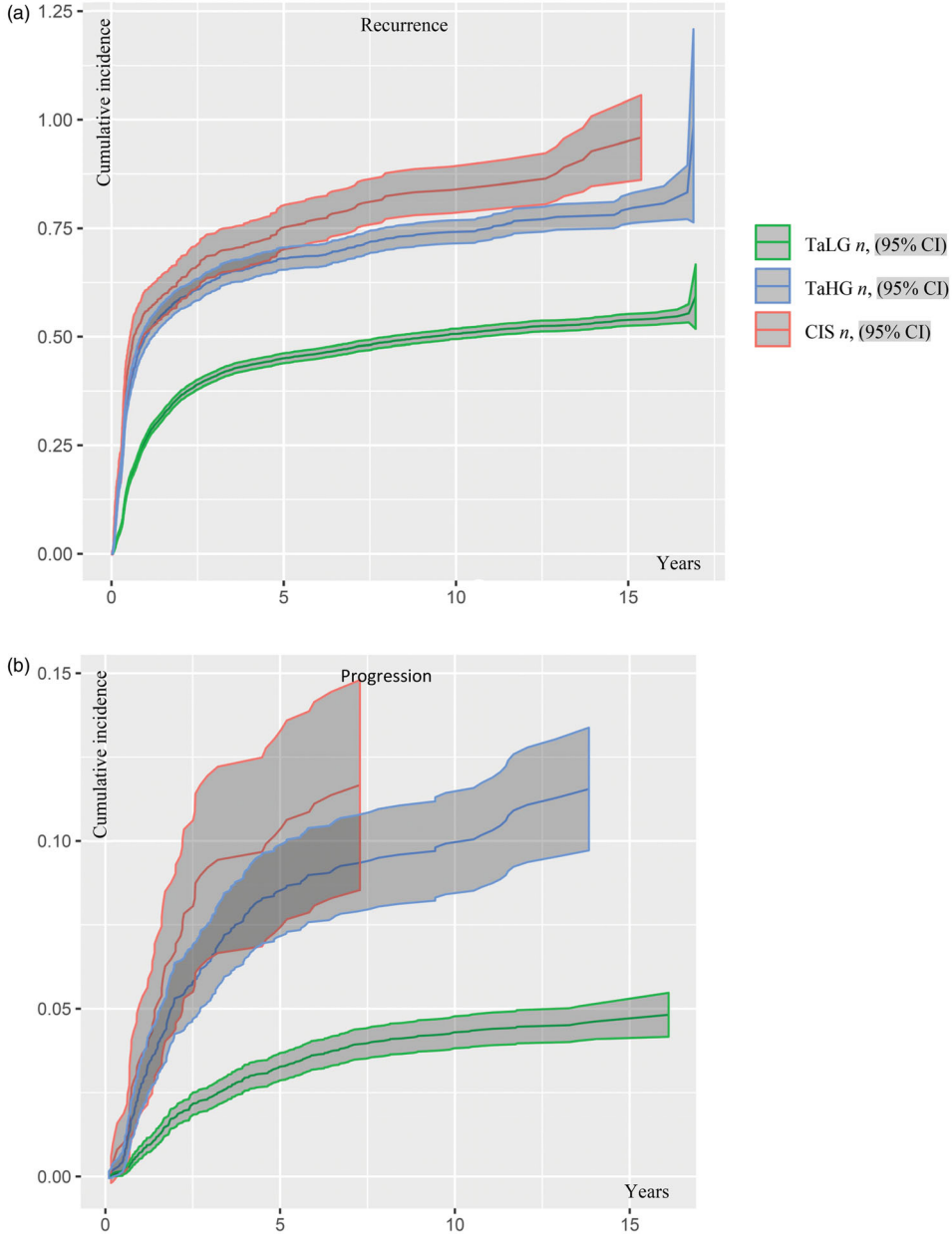

Figure 1. Cumulative incidence of recurrence and progression over time in percentages (1.00 = 100%) with 95% confidence interval (CI).

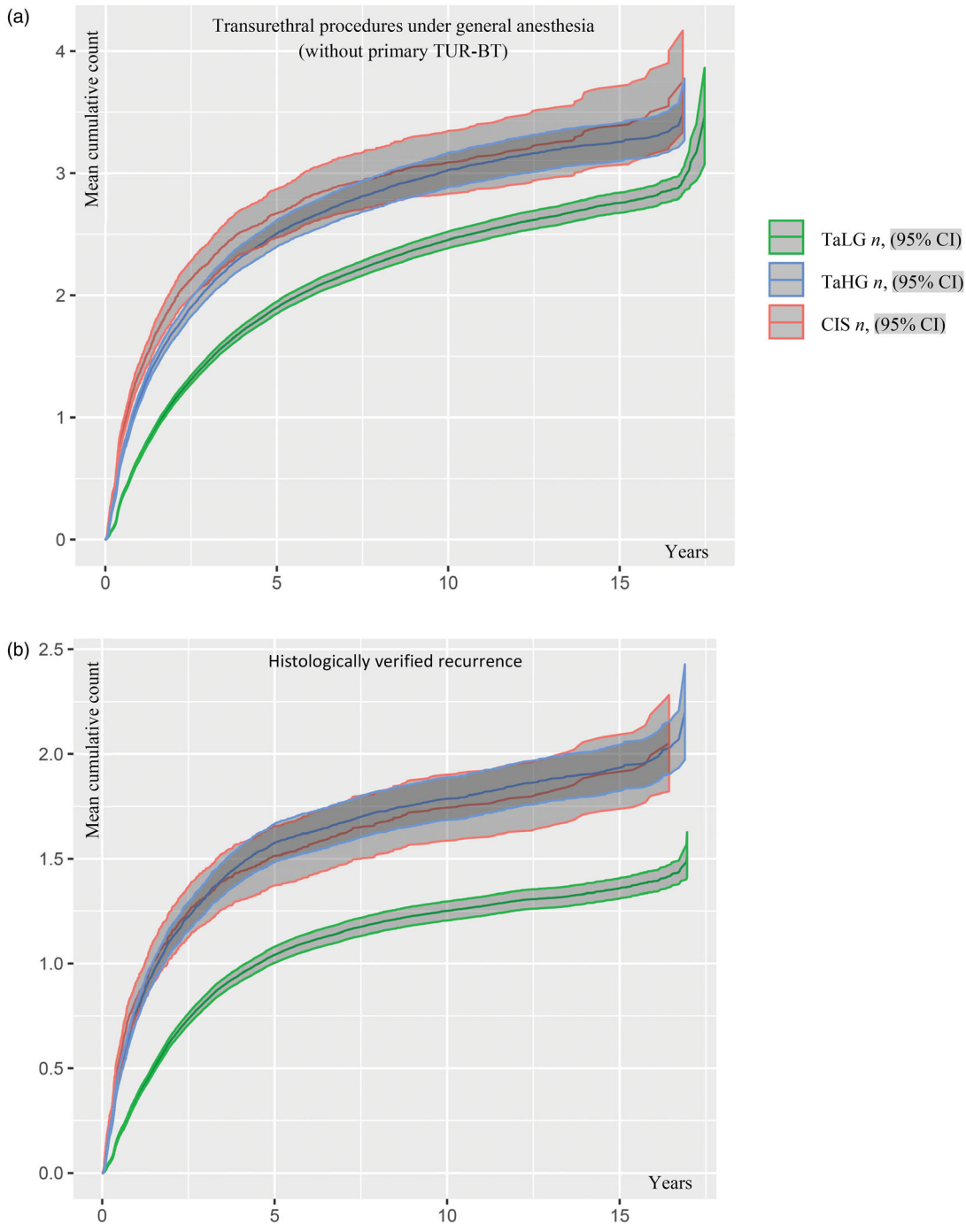

Figure 2. Mean numbers of treatments and recurrences over time with 95% confidence interval (CI).

observed 5 years after the primary diagnosis (Figures 2(c) and (d)).

Among baseline characteristics, CCI had the greatest effect on mortality risk, which increased proportionally with increasing patient comorbidities. Female gender, increasing year of primary diagnosis, marriage, medium income and higher education were associated with a lower risk of death (Table 3). These effects did not differ among patients with TaLG, TaHG or CIS, with the exception of female gender, which benefitted patients with TaLG (HR = 0.79, 95% CI = 0.72–0.86, $p = 0.00$), but not those with TaHG (HR = 1.04, 95% CI = 0.87–1.24, $p = 0.65$) or CIS (HR = 0.97, 95% CI = 0.67–1.41, $p = 0.88$).

Repeated transurethral procedures under GA were associated with an increased risk of death in patients with TaLG or TaHG. Compared to patients who only had the primary TUR-BT, those who had 2–4 procedures had an increased risk of 48.3% (95% CI = 18.2–86.0%, $p < 0.01$) and 14.3% (95% CI = 4.6–24.9%, $p < 0.01$) for TaHG and TaLG, respectively. Eight or more procedures resulted in an increased risk of 82.6% (95%

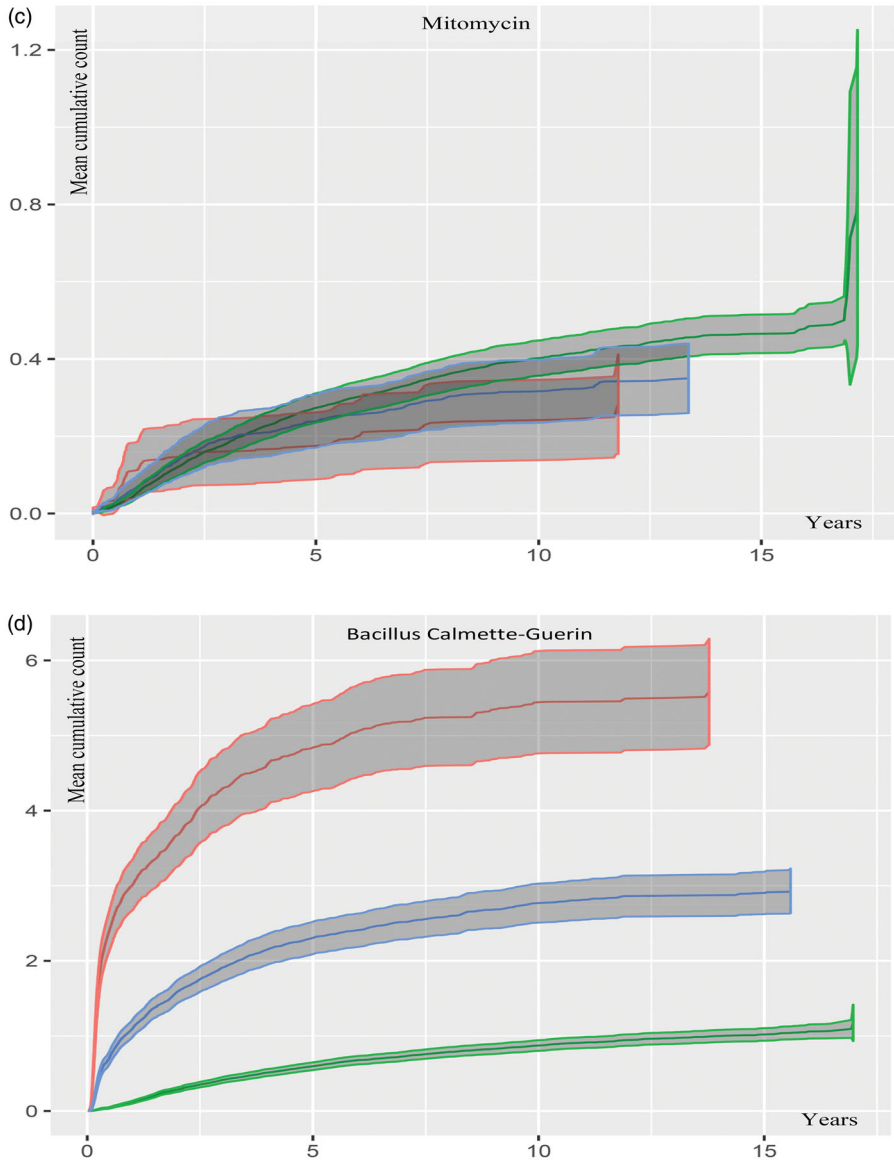

Figure 2. Continued.

CI = 34.3–148.3%, $p < 0.01$) and 27.5% (95% CI = 11.0–46.4%, $p < 0.01$) for TaHG and TaLG, respectively. Repeated procedures had no effect on mortality in patients with CIS and neither did BCG or mitomycin bladder irrigations (Table 4).

For all three groups, the risk of progression was greatest within 3 years after the primary diagnosis and was particularly high in patients with primary CIS and TaHG (Figure 1(b)). The 1–5-year and 10-year risks of recurrence and progression are presented as Supplementary Information.

Patients with TaHG had a 2.45-fold and those with CIS had a 3.48-fold greater risk of progression than patients with TaLG in a multivariable analysis that included baseline variables, tumor stage and grade, BCG and mitomycin treatments and recurrences (Table 5). Recurrence was associated with an increased risk of progression in patients with TaLG, TaHG and especially CIS. Females with TaLG had a lower risk of progression than males.

Discussion

This study shows that repeated transurethral procedures for non-invasive urothelial bladder tumors performed under GA are associated with an increased risk of overall death in patients with TaLG and TaHG tumors. For example, patients who had 2–4 procedures had a 14% greater risk of death than patients who only had one procedure. Approximately half of patients with TaLG tumors had three or more procedures performed. This may explain the previously reported lower survival rate among patients with TaLG bladder tumors compared to background population, even after adjustment for risk factors [1].

The procedure-related risk of death was greater in patients with TaHG tumors (a 48% increased risk for 2–4 procedures) than in TaLG patients. This may be explained by TaLG recurrent tumors often being small, requiring less traumatic TUR-BT and shorter surgeries. Furthermore, the lower recurrence rate of TaLG tumors results in fewer surgeries,

lowering the overall treatment intensity in contrast to patients with HG tumors. This was confirmed in the present study, as treatment frequency was higher in patients with Ta HG, especially in the first 3 years after primary diagnosis.

Table 3. The effect of comorbidity and socioeconomic status at time of primary diagnosis on mortality in hazard ratios (HR) with 95% confidence interval (CI) with the first listed value in each variable as reference.

	Whole cohort	
	HR (95% CI)	*p*-value
Mean age	1.09 (1.08–1.09)	<0.001
Gender		
Male		
Female	0.83 (0.77–0.89)	<0.001
Year of diagnosis		
2000–2002		
2003–2005	0.89 (0.83–0.96)	0.003
2006–2008	0.77 (0.71–0.84)	<0.001
2009–2010	0.74 (0.64–0.85)	<0.001
CCI		
0		
1	1.51 (1.41–1.63)	<0.001
2	1.88 (1.70–2.07)	<0.001
3+	2.76 (2.48–3.07)	<0.001
Civil status		
Widower		
Divorced	1.17 (1.04–1.31)	0.007
Married	0.84 (0.77–0.91)	<0.001
Single	1.28 (1.10–1.48)	0.001
Income in quintiles		
0–20		
20–40	0.96 (0.88–1.05)	0.384
40–60	0.85 (0.77–0.93)	0.001
60–80	0.95 (0.86–1.05)	0.316
80–100	1.02 (0.93–1.12)	0.689
Education		
Higher		
Medium	1.17 (1.05–1.31)	0.005
Short	1.29 (1.16–1.45)	<0.001
Unknown	1.09 (0.95–1.25)	0.208

We found no statistically significant relationship between repeated procedures and mortality in patients with primary CIS. Fewer patients with primary CIS and especially few patients in the reference group (patients with only primary TUR-BT) and a higher rate of censoring due to progression or cystectomy may result in lower statistical precision. Furthermore, patients may be exposed to less straining surgeries as inpatient cystoscopy with biopsy under GA as follow-up after BCG induction therapy is recommended in the Danish national guidelines, which may reduce a surgery induced influence on mortality.

No other studies have to our knowledge investigated the long-term relationship between treatment load and risk of overall mortality in patients with non-invasive bladder cancer. Transurethral procedures under GA for suspected recurrent non-invasive tumors are considered minor procedures, and perioperative mortality related to the procedure or anesthesia is expected to be low. Mortality within 30 days following TUR-BT is reportedly 0.8–1.3% [6,8,10]. However, 30-day postoperative complications are reported in up to 16% of TUR-BTs [6–10]. These studies investigated morbidity and mortality following only one TUR-BT procedure, and tumor stages and grades and long-term treatment data were not included in the analyses. Our study focuses on long term treatment and outcome in 10,197 patients over up to 16-years and in that period a higher association between repeated transurethral procedures in GA and overall mortality were identified than the 30-day postoperative mortality reported elsewhere. This association is not a result of bladder cancer specific mortality, as patients were censored at the time of progression, and death due to cancer progression is thus eliminated from the analyses. Neither can comorbidity, gender, social status or level of income explain the increased

Table 4. The effect of transurethral procedures under GA, BCG and mitomycin on mortality in hazard ratios (HR) with 95% confidence interval (CI).

	TaLG		TaHG		CIS		All	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Transurethral procedure under GA								
1								
2–4	1.14 (1.05–1.25)	0.003	1.48 (1.18–1.86)	0.001	1.13 (0.66–1.93)	0.652	1.20 (1.11–1.30)	<0.001
5–7	1.09 (0.97–1.25)	0.146	1.55 (1.18–2.03)	0.002	1.22 (0.66–2.26)	0.519	1.19 (1.07–1.32)	0.002
8+	1.28 (1.10–1.46)	0.001	1.83 (1.34–2.48)	<0.001	1.62 (0.81–3.26)	0.177	1.40 (1.24–1.58)	<0.001
BCG	0.98 (0.97–1.01)	0.087	0.99 (0.97–1.00)	0.121	0.99 (0.95–1.01)	0.273	0.98 (0.97–0.99)	0.004
Mitomycin	0.98 (0.96–1.01)	0.195	1.00 (0.94–1.05)	0.884	1.13 (0.95–1.35)	0.164	0.99 (0.96–1.01)	0.206

All HRs are adjusted for age, gender, socio-economic status and comorbidity at primary diagnosis.

Table 5. The effect of gender, recurrence, and tumor grade on progression in hazard ratios (HR) with 95% confidence interval (CI).

	TaLG		TaHG		CIS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender						
Male						
Female	0.73 (0.55–0.95)	0.021	1.25 (0.87–1.79)	0.234	1.45 (0.70–2.97)	0.318
Recurrence	1.45 (1.39–1.50)	<0.001	1.39 (1.30–1.48)	<0.001	1.82 (1.54–2.14)	<0.001
Grade*			2.45 (2.02–2.96)	<0.001	3.48 (2.56–4.72)	<0.001

*TaLG is reference.

risk of death as these were adjusted for in the analyses. However, reported combinations of short- and long-term postoperative morbidity as urinary infections, bladder catheterization, immobilization, hematuria or bladder perforation as well as impaired quality-of-life with long-term voiding problems after TUR-B may contribute to mortality [21]. Increasing age and subsequent general fragility of patients also jeopardize patients in their daily living after hospital admittances. The sum of these morbidities after repeated transurethral procedures under GA may influence overall mortality and explain the procedure-related mortality observed in the present study.

Larger tumors and longer surgeries result in increased 30-day postoperative morbidity and mortality rates [6,8,9]. We did not adjust for tumor size, surgery durations, or smoking status because this information is not recorded in the registries. However, because tumor size is associated with risk of recurrence and thus TUR-BT, tumor size and TUR-BT durations were indirectly included in our analyses [5]. Similarly, smoking is related to comorbidities, especially heart and lung diseases, which are part of the CCI and was therefore also indirectly included. It is a limitation to the present study that changes in CCI and socio-economic status over time were not included in the present study. At time of primary diagnosis, socio-economic status and CCI were estimated and included in the analyses. Both may individually change by time and influence mortality. However, study persons and their controls are considered as two identical groups, as patients with repeated procedures are compared to patients with the same tumor characteristics but only experiencing one transurethral procedure under GA. Thus, socio-economic status and CCI are expected to be similar over time and repeated adjustment for socio-economic status and CCI has therefore not been done.

Tumors recurring in patients with TaLG are often small and may be treated in the outpatient department without GA, minimizing the number of inpatient transurethral procedures under GA and the related risk of morbidity and subsequent mortality. Recent advances in outpatient treatments such as diode laser treatment and photodynamic diagnoses during flexible cystoscopy may mean more patients could be treated as outpatients [22,23].

In our population, patients with TaHG tumors and primary CIS had high rates of repeated procedures under GA, especially within 3 years after primary diagnosis. These observations support European Organization for Research and Treatment of Cancer (EORTC) risk scoring models, which suggest that HG tumors, tumor size and prior recurrences are related to greater risk of recurrence and that HG tumors are related to greater risk of recurrence at first follow-up cystoscopy [5,24]. Thus, patients with TaHG tumors and primary CIS are exposed to frequent and potentially high-risk (large tumor) surgeries, increasing the risk of death. These patients may benefit from high-quality TUR-BT using photodynamic diagnoses, narrow-band imaging, or Image1S to reduce the risk of early recurrence [25–28].

The absence of bladder neoplasia in 36–52% ($n = 12,097$) of repeated procedures under GA during 16 years of follow-up is surprisingly high. No previous national study has reported on the false-positive rate of flexible follow-up cystoscopy. A recent retrospective cohort study of 1,042 patients with TaLG found that higher frequency of follow-up flexible cystoscopies were associated with higher numbers of transurethral resections without neoplasia in the specimen [29]. Procedures under GA without neoplasia may be a result of suspicious lesions observed in flexible surveillance cystoscopy, where neoplasia could not be confirmed by the inpatient transurethral procedure. In patients with primary CIS, the present procedures under GA without neoplasia may be explained by rigid cystoscopy with biopsy under GA to evaluate the efficacy of BCG induction therapy as recommended by Danish guidelines. Furthermore, some histological examinations of bladder tissue without simultaneous procedure codes defining GA may originate from an outpatient cystoscopy with biopsy without GA. Such false estimated GA procedures overestimate the number of procedures under GA and may thus reduce the GA procedure related mortality in case our study conclusion is correct. However, cystoscopy with biopsy in the outpatient department is relatively rare in Denmark and the influence on statistical analyses of this systematic bias is expected to be limited. However, it stresses the need for selecting true recurrences for inpatient surgery to prevent patients undergoing unnecessary TUR-BT, e.g. by taking mucosal biopsies during outpatient flexible cystoscopy [23]. In the future advances in optical diagnostics for *in vivo* real-time tumor characterization, such as optical coherence tomography and Raman spectroscopy, may differentiate between bladder neoplasia and healthy tissue during outpatient cystoscopy, minimizing the need for inpatient procedures [30].

Disclosure statement

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

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