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ARTICLE

Prognostic significance of previous tonsillectomy after radical cystectomy for bladder cancer

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ABSTRACT

Introduction: To examine whether previous tonsillectomy (TE) impacts on survival after radical cystectomy (RC) for bladder cancer (BC).

Patients and Methods: A total of 320 patients were staged cM0 and underwent RC for BC between 2002 and 2013. We retrospectively investigated whether patients had undergone TE prior to RC. Chi-square/Fisher-Exact test was carried out to compare clinicopathological features between the TE- and non-TE-group. Kaplan–Meier analysis with log-rank test was used to estimate recurrence-free survival (RFS) and multivariable Cox-regression analysis of risk factors of recurrence. The median follow-up was 31 months (interquartile range: 9–54).

Results: A history of TE was present in 18 of the 320 patients (5.6%). All TEs were performed for benign conditions. TE prior to RC was associated with a history of appendectomy ($p = 0.045$), lower age at RC ($p = 0.029$), tumor unifocality ($p < 0.001$), advanced histopathological tumor stage ($p = 0.015$), non-pure urothelial carcinoma ($p = 0.025$), lymphovascular invasion ($p = 0.035$) and receipt of palliative chemotherapy ($p = 0.004$). The 3-year RFS was 39.2% for patients with previous TE and 62.4% for those without ($p = 0.008$). In multivariable analysis, adjusted for all significant parameters of univariable analysis, lymph-node tumor involvement ($p = 0.017$), positive surgical margins ($p = 0.047$), tumor grade ($p = 0.032$), advanced tumor stage ($\geq$pT3a; $p = 0.049$) and a history of TE ($p = 0.021$) remained independent prognosticators of recurrence.

Conclusion: In this series, previous TE was an independent predictor of recurrence after RC for BC. Further studies are needed to assess whether TE induces immunological alterations that might exert adverse effects on cancer progression of patients with invasive BC.

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Bladder cancer; radical cystectomy; recurrence; survival; tonsillectomy

1. Introduction

Invasive bladder cancer (BC) is a highly immunogenic cancer, which expresses high levels of neoantigens and ligands that can inhibit effective T-cell function and activation [1,2]. The ability of urothelial cancer cells to evade the immune system by inhibiting its cytotoxic function and maintaining an immunosuppressive microenvironment contributes to its aggressive nature and high recurrence rates [1]. Cytokine-induced imbalances in the distribution and differentiation of tumor-infiltrating cytotoxic cells can boost cancer cell proliferation and drive metastasis formation [3,4]. Therefore, an intact immune system is essential for effective cancer control.

The tonsils are one of the most important secondary lymphoid organs of the immune system. They contain both B- and T-lymphocytes which implies that both the cell-mediated and humoral immune axes are regulated [5]. One of the earliest interventions to the human immune system is in the context of a tonsillectomy (TE). Traditionally, TE has been performed for recurrent acute tonsillitis and related complications. Yet, in recent times, sleep-disordered breathing and obstructive sleep apnea have emerged as primary indications [6]. Therefore, TE remains one of the most common pediatric surgical procedures worldwide [6]. However, little is known about the long-term health consequences of this procedure. It can be hypothesized that early removal of these lymphatic organs may exert a negative effect on the development and function of the immune system. The fact that this procedure is associated with an increased long-term risk of respiratory, infectious and allergic diseases supports this assumption [7]. It has been also shown that TE is associated with an increased risk of cancer for different entities [8,9]. Therefore, we aimed to examine whether previous TE impacts on the oncological outcomes of patients with invasive bladder cancer (BC).

2. Material and methods

2.1. Patients

This retrospective study was conducted in accordance to the declaration of Helsinki and the provisions of the local ethics committee Tuebingen (approval number: 417/2010 A).

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We searched our prospectively maintained database consisting of a total of 329 consecutive patients who underwent RC for stage cM0 BC between 2002 and 2013. In order to provide a homogenous cohort, a total of 9 patients who were treated with neoadjuvant chemotherapy were excluded from analysis. During this time period, indications for radical cystectomy (RC) were histologically confirmed muscle-invasive BC, primary non-muscle invasive bladder cancer (NMIBC) at high to highest risk of progression, high-risk NMIBC after failure of intravesical therapy and extensive NMIBC not amenable to endoscopic control. Records were reviewed for clinical and histopathological characteristics as well as individual treatment response. RC consisted of the removal of the bladder, prostate and seminal vesicles in men and bladder and with anterior vaginal wall, uterus and adnexes in women as well as bilateral pelvic lymph node dissection [10].

2.2. Clinical and histologic assessment

We assessed the following clinical and histopathological parameters: TE at any time before RC and its indication (benign vs. malignant condition), age at RC, gender, smoking status, history of appendectomy (AE), history of previous malignancy before diagnosis of BC, Eastern Cooperative Oncology Group (ECOG) performance status (PS), number of TUR-BT prior to RC, median time between last TUR-BT and RC, tumor grade, tumor size, multifocality, hydronephrosis at RC, clinical and histopathological tumor stage, clinical and histopathological nodal stage, soft-tissue surgical margin status (STSM), lymphovascular invasion, histological entity of BC (pure vs. non-pure urothelial BC), preoperative administration of intravesical immuno- and/or chemotherapy, type of diversion, hydronephrosis at RC and receipt of postoperative systemic chemotherapy. In addition, precystectomy levels of serum creatinine, serum C-reactive protein, hemoglobin, platelets and the neutrophile-to-lymphocyte ratio were recorded. Lab values were assessed 1–3 days prior to RC [11–15]. The histologic assessment was based on the WHO grading system of 1973 and TNM classification as approved by the AJCC [16,17].

Cystectomy specimens were macro- and microscopically assessed according to standardized protocols based on H&E and immunohistochemical staining to identify the presence of urothelial and non-urothelial histology. Lymphovascular invasion was defined as the presence of malignant cells within an endothelial lining. Surgical margins were considered positive in case of malignant cells at any soft-tissue margin of the specimen [18].

In terms of postoperative chemotherapy, any administration of chemotherapy for $\geq$ pT3a and/or pN + disease up to four months after RC was defined as adjuvant chemotherapy [19]. By contrast, any chemotherapy delivered for any recurrent disease (either in the lymph nodes, local recurrence or in case of systemic disease) after RC was defined as palliative chemotherapy.

2.3. Follow-up

For follow-up, we reviewed our electronic hospital charts and institutional tumor registry to determine recurrence and vital status of the patients. Given the retrospective nature of this analysis and lack of prospective data [20], a standardized follow-up protocol was precluded in all patients. Generally, in our institution, follow-up examinations after RC are recommended at least every three to four months for the first year, semiannually for the second and third years, and annually thereafter. Oncological evaluation for recurrence included cross-sectional imaging with computed tomography or magnetic resonance imaging at regular intervals. In addition, physical examination with cystoscopy, urine cytology, urethral washings, laboratory testing, intravenous pyelography and bone scintigraphy were carried out if indicated [20]. Recurrence was defined as any tumor recurrence in the surgical bed, lymph nodes, distant organs or in the remnant urothelium [21]. Location of tumor recurrence (local and/or lymphonodal vs. distant vs. urothelial) was recorded in all patients. Patients who did not experience recurrence (RFS), death from progressive BC disease (CSS) or death from any cause (OS) were censored at last follow-up. The median follow-up for recurrence was 31 months (interquartile range, IQR: 5–48) and 36 months (IQR: 9–54) for death.

2.4. Statistics

Pearson χ2-test and Fisher Exact Test (in case of sample size <5 in contingency tables) were conducted to correlate various parameters with a history of TE. The Kaplan–Meier method with log-rank testing was utilized to estimate the impact of previous TE and AE on recurrence-free (RFS), cancer-specific (CSS) and overall survival (OS). RFS, CSS and OS data were calculated from the date of RC to the date of documented recurrence or death. Univariable Cox-proportional regression models were built to evaluate risk factors of recurrence, cancer-specific death and death. A multivariable Cox-proportional model was constructed for risk factors of recurrence encompassing established clinical and histopathological parameters which were significantly associated with a history of TE. For scaled variables, values are given as mean, median and interquartile range (IQR). All tests were two-sided. A $p < 0.05$ was considered significant. Analyses were done using JMP® 12.2 software package (Cary, NC, USA).

3. Results

Of the 329 patients, 18 (5.5%) had a positive history of TE. All TEs were conducted for benign conditions during childor early adulthood. In univariable analysis, TE prior to RC was associated with a positive history of AE ($p = 0.045$), lower age at RC ($p = 0.029$), tumor unifocality ($p < 0.001$), advanced histopathological tumor stage ($p = 0.015$), non-pure urothelial carcinoma ($p = 0.025$), lymphovascular invasion ($p = 0.035$) and receipt of palliative chemotherapy ($p = 0.004$; see Table 1).

Table 1. Clinical and histopathological characteristics of patients treated with radical cystectomy for bladder cancer subanalyzed for history of tonsillectomy.

Parameter	Previous tonsillectomy	No tonsillectomy	*p* Value
Number of patients (%)	18 (5.6)	302 (94.4)	
Duration of follow-up [mo.]			
Median	23	32	0.48
Mean	32	37	
IQR	5–45	10–55	
Gender			
Male	11 (61.1)	227 (75.2)	0.26
Female	7 (38.9)	75 (24.8)	
Mean age at RC [a]	62	68	**0.029**
Median	63	70	
IQR	53–70	61–75	
Smoking			
Never	5 (27.8)	127 (42.1)	0.32
Ever	13 (72.2)	175 (57.9)	
History of appendectomy			
Present	8 (44.4)	68 (21.0)	**0.045**
Absent	10 (55.6)	234 (73.6)	
History of previous malignancy before BC diagnosis			
Present	1 (5.6)	35 (11.6)	0.70
Absent	17 (94.4)	267 (88.4)	
Mean time between last TUR-BT and RC [d]	71	49	0.35
Median	28	32	
IQR	22–52	20–49	
Mean number of TUR-BTs before RC	2	2.0	0.98
Median	1	2	
IQR	1–3	1–2	
ECOG PS at RC			0.65
0	17 (94.4)	252 (83.4)	
1	1 (5.6)	42 (13.9)	
2	0	6 (2.0)	
3	0	2 (0.7)	
Clinical tumor stage			
≥cT3	6 (33.3)	83 (27.5)	0.59
≤cT2	12 (66.7)	214 (70.9)	
cTX	0 (0)	5 (1.7)	
Clinical nodal stage			
cN0	14 (77.8)	252 (83.4)	0.23
cN1	0 (0)	17 (5.6)	
cN2	4 (22.2)	28 (9.3)	
cN3	0 (0)	5 (1.7)	
pT-stage			
≥pT3a	14 (77.8)	145 (48.0)	**0.015**
≤pT2b	4 (22.2)	157 (52.0)	
pT0	1 (5.6)	13 (4.3)	
pTis	0 (0)	22 (7.3)	
pTa	0 (0)	12 (4.0)	
pT1	2 (11.1)	27 (8.9)	
pT2a	1 (5.6)	37 (12.3)	
pT2b	0 (0)	44 (14.6)	
pT3a	6 (33.3)	52 (17.2)	
pT3b	5 (27.8)	56 (18.5)	
pT4a	1 (5.6)	31 (10.3)	
pT4b	2 (11.2)	8 (2.7)	
Histopathological nodal stage			
pN+	8 (44.4)	74 (24.5)	0.16
pN0	9 (50.0)	212 (70.2)	
pNX	1 (5.6)	16 (5.3)	
STSM status			
Positive	2 (11.1)	41 (13.6)	0.91
Negative	16 (88.9)	255 (84.4)	
Not assessible	0 (0)	6 (2.0)	
Lymphovascular invasion			
LVI	10 (55.6)	101 (33.4)	**0.035**
LV0	6 (33.3)	183 (60.6)	
LVX	2 (11.1)	18 (6.0)	
Tumor multifocality			
Present	0 (0)	108 (35.8)	**<0.001**
Absent	18 (100)	194 (64.2)	
Estimated tumor size at RC [cm]			
Mean	3.9	3.0	0.061
Median	3.4	2.8	
IQR	2.4–5.1	2.0–4.0	

(*continued*)

Table 1. Continued.

Parameter	Previous tonsillectomy	No tonsillectomy	*p* Value
Tumor grade at RC			
G1	0 (0)	2 (0.7)	0.90
G2	6 (33.3)	82 (27.2)	
G3	12 (66.7)	197 (65.2)	
GX	0 (0)	21 (7.0)	
Hydronephrosis at RC			
Present	6 (33.3)	57 (18.9)	0.11
Absent	11 (61.1)	245 (81.1)	
Data not available	1 (5.6)	0 (0)	
Non-pure UC pathology at RC			
Present	7 (38.9)	50 (16.6)	**0.025**
Absent	11 (61.1)	252 (83.4)	
Preop. serum creatinine [mg/dl]			
Mean	1.1	1.0	0.60
Median	0.9	1	
IQR	0.8–1.3	0.8–1.2	
Preop. serum C-reactive protein [mg/dl]			
Mean	1.8	1.3	0.45
Median	0.8	0.4	
IQR	0.3–1.4	0.1–1.3	
Preop. hemoglobin [mg/dl]			
Mean	13.1	13.2	0.96
Median	13.3	13.5	
IQR	12.3–13.9	12.0–14.6	
Preop. Neutrophile-to-Lymphocyte Ratio			
Mean	3.4	4.4	0.61
Median	3.6	3.0	
IQR	2.6–3.9	2.3–3.9	
Preop. thrombocytes ($x10^3/\mu l$)			
Mean	316	308	0.77
Median	275	287	
IQR	209–420	231–362	
Intravesical BCG and/or chemotherapy			
Performed	5 (27.8)	85 (28.2)	1.0
Not performed	13 (72.2)	217 (71.8)	
Type of diversion			
Orthotopic neobladder	14 (77.8)	180 (59.6)	0.14
Ileal Conduit	122 (40.4)	122 (40.4)	
	4 (22.2)		
Location of recurrences			
Solitary lymph nodes and/or local	8 (44.4)	77 (25.5)	0.09
Solitary or concomitant distant	9 (50.0)	75 (24.8)	**0.026**
Urothelial	0	17 (5.6)	0.61
Receipt of postoperative systemic chemotherapy			
Total	8 (44.4)	58 (19.2)	**0.013**
Adjuvant	0 (0)	12 (4.0)	1.0
Palliative	8 (44.4)	46 (15.2)	**0.004**

a: year; BCG: Bacille-Calmette-Guerin; d: days; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; MIBC: muscle-invasive bladder cancer; mo: months; PD: primary diagnosis; preop.: preoperative; RC: radical cystectomy; STSM: soft tissue surgical margin; TUR-BT: transurethral bladder tumor resection; UC: urothelial carcinoma; bold values indicate statistically significant difference.

Of the 320 patients, 108 (33.8%) experienced recurrence after RC. Recurrence was present in 10 of the 18 patients (55.6%) with a history of TE and in 98 of the 302 (32.5%) patients without a history of TE. Solitary or concomitant distant recurrences were significantly more frequent among TE-patients (50.0% vs. 24.8%; $p = 0.026$). Of a total of 58 cancer-specific deaths, 5 (29.4%) were noted in the group of patients with previous TE and 53 (17.6%) in the group without TE ($p = 0.33$). Mortality events were registered in a total of 122 patients with 8 (44.4%) events in patients with previous TE and 114 (37.8%) in patients without TE ($p = 0.62$).

The 3-year RFS was 39.2% for patients with previous TE and 62.0% for those without ($p = 0.009$; see Figure 1). The 3-year CSS/OS was 63.1/58.2% in patients with previous TE and 80.3/66.2% in patients without TE ($p = 0.17/p = 0.36$). A history of AE was not associated with RFS ($p = 0.72$), CSS ($p = 0.92$) and OS ($p = 0.93$).

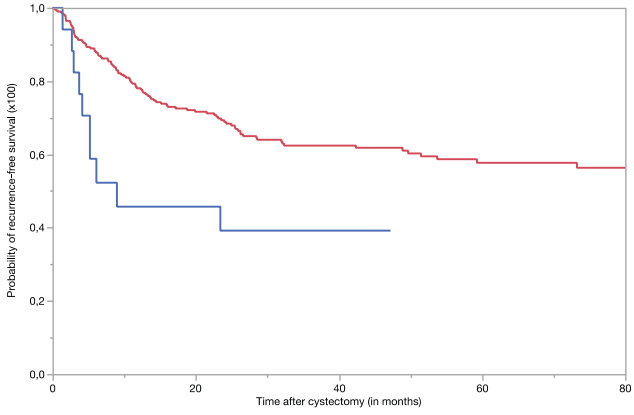
In univariable analysis, RFS was associated with advanced tumor stage (≥pT3a; $p < 0.001$), lymph-node tumor involvement ($p < 0.001$), positive surgical margins ($p < 0.001$), non-pure urothelial histology ($p < 0.001$), tumor grade ($p = 0.002$), and a history of previous TE ($p = 0.023$).

In multivariable analysis, adjusted for all significant parameters of univariable analysis, recurrence was independently associated with lymph-node tumor involvement ($p = 0.017$), positive surgical margins ($p = 0.047$), tumor grade ($p = 0.032$), advanced tumor stage (≥pT3a; $p = 0.035$) and a history of previous TE ($p = 0.021$; see Table 2).

4. Discussion

In the present study, a history of TE was associated with advanced histopathological features of BC and inferior RFS after RC. In detail, we found TE to be significantly associated

with advanced histopathological tumor stage, lymphovascular invasion, non-pure urothelial histology and administration of palliative chemotherapy. All these risk factors have been repeatedly found to be associated with inferior survival after RC [22–25]. These concordances underline the reproducibility and validity of our results compared with larger cystectomy series. We also observed that patients with previous TE were more likely to have a positive history for AE. Yet, we did not find AE to be associated with survival after RC. Similarly, AE has not been found to be associated with cancer development in various studies [26,27]. These data strengthen the oncological importance of our findings. Interestingly, we observed higher rates of non-pure urothelial carcinoma and a clear trend towards higher local recurrence rates in the TE cohort. In this regard, it is well known that rates of local recurrence are higher in BC patients with non-urothelial histology [28]. Therefore, TE may represent a risk factor or even driver for dedifferentiation of urothelial carcinoma.



Number of patients at risk of recurrence at given time intervals after radical cystectomy						
Variable/Time	**0**	**12**	**24**	**36**	**48**	**60**
Previous tonsillectomy	18	7	6	4	1	1
No tonsillectomy	302	187	145	109	83	59

Figure 1. Recurrence-free survial in patients with (blue line) and without (red line) history of tonsillectomy prior to radical cystectomy for stage cM0 bladder cancer ($p = 0.008$).

The tonsils belong to the mucosa-associated lymphatic tissue system which is important for T- and B-cell maturation of the adaptive immune system. The tonsils contribute to the innate immune system by expressing alpha- and beta-defensins [29]. Due to its exposed location in the oral cavity the tonsils are in intense contact with the oropharyngeal flora. This circumstance may lead to chronic inflammatory processes within the tonsils which may eventually necessitate their removal due to recurrent acute infections, chronic pharyngitis or peritonsillar abscess formation. The incidence of TE peaks twice at the age of 4 and 16 years with a cumulative incidence of ≈8–9% in the first 20 years and a female-to male ratio of 1.2:1 [30].

The majority of published series support the assumption that TE in children does not exert adverse effects on humoral and cellular immunological parameters [31]. Yet, it was shown that patients with a history of TE exhibit a higher risk for developing autoimmune diseases at a later point which may be related to post-TE immune dysfunction [32]. In terms of TE and cancer risk, there are equivocal findings. While conflicting results were reported on the risk of developing hematological malignancies, i.e. leukemia and Hodgkin's disease, TE was found to be strongly associated with an increased risk for pre- or postmenopausal breast cancer [33,34]. For urological malignancies, data exists with regard to prostate cancer. A twofold increased risk for prostate cancer was reported among patients who had TE in their early adulthood [8].

The possible scenarios for the underlying molecular mechanisms that may drive bladder carcinogenesis and progression in the absence of the tonsils are rather hypothetical due to the lack of specific research data. Generally, in literature, the necessity of TE is regarded as a proxy for an increased susceptibility to infections during child- and early adulthood. Clinical and subclinical infections can invoke strong inflammatory responses. As the tonsils function to produce mature

Table 2. Uni- and multivariable Cox-regression analysis for survival of risk factors in patients with bladder cancer treated with radical cystectomy.

	Univariable						Multivariable	
	RFS		CSS		OS		RFS	
Parameter	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR	*p* Value
History of tonsillectomy Present vs. absent	2.36 (1.23–4.54)	**0.010**	1.86 (0.74–4.67)	0.22	1.39 (0.68–2.85)	0.38	2.36 (1.14–4.91)	**0.021**
≥pT3a vs. ≤pT2b	3.32 (2.22–4.98)	**<0.001**	3.98 (2.25–7.04)	**<0.001**	3.00 (2.06–4.38)	**<0.001**	1.64 (1.00–2.70)	**0.049**
pN + vs. pN0	3.72 (2.51–5.52)	**<0.001**	7.90 (4.40–14.21)	**<0.001**	3.35 (2.29–4.91)	**<0.001**	2.10 (1.25–3.51)	**0.017**
Pos. vs. neg. surgical margins	3.35 (2.06–5.45)	**<0.001**	5.38 (3.02–9.59)	**<0.001**	3.97 (2.57–6.13)	**<0.001**	2.02 (1.15–3.55)	**0.047**
Tumor grade G1/G2 vs. G3	1.89 (1.19–3.01)	**0.006**	3.28 (1.55–6.91)	**0.001**	1.88 (1.21–2.93)	**0.004**	1.71 (1.05–2.79)	**0.032**
LVI vs. LV0	2.76 (1.88–4.04)	**<0.001**	4.64 (2.68–8.04)	**<0.001**	2.30 (1.60–3.30)	**<0.001**	1.25 (0.78–2.02)	0.35
Non-pure vs. pure vs. UC	2.24 (1.45–3.45)	**<0.001**	2.64 (1.51–4.62)	**<0.001**	1.78 (1.17–2.72)	**0.007**	1.46 (0.91–2.36)	0.12
Age at RC (cont. per unit [a])	1.01 (0.99–1.02)	0.61	1.02 (0.99–1.04)	0.26	1.03 (1.01–1.05)	**0.001**	1.01 (0.99–1.03)	0.09
Gender male vs. female	1.05 (0.68–1.63)	0.82	0.83 (0.47–1.48)	0.54	1.23 (0.83–1.82)	0.30	1.44 (0.87–2.39)	0.15
Tumor multifocality Present vs. absent	1.25 (0.85–1.84)	0.25	1.27 (0.76–2.15)	0.36	1.17 (0.81–1.68)	0.31	1.50 (0.98–2.29)	0.06

a: year; CI: confidence interval; CRP: C-reactive protein; CSS: cancer-specific survival; HR: hazard ratio; LV0: lymphovascular invasion absent; LVI: lymphovascular invasion present; OS: overall survival; RFS: recurrence-free survival; TARCs: tumor-associated round cells.
Bold values indicate a statistically significant difference ($p < 0.05$).

lymphocytes, their removal may impair immunosurveillance [35]. Importantly, it is well known that impaired immunosurveillance is a driver for BC progression. Conversely, restoration of immunosurveillance *via* PD-(L)1-inhibitors can result in improved outcomes of patients with metastatic BC [2,36].

Another hypothesis of how TE may induce adverse long-term effects on the immune system is linked to its role in the context of the microbiome. The tonsils are important organs for the development of the oral microbiome [35]. Resident microbiota are essential in activating, training, and modulating the host immune system. These microbiota are also actively involved in drug metabolism. Dysbiosis in the commensal flora may induce dysbalances between microbiota and the immune system which eventually may result in immunologic dysregulation and cancer progression [37]. Interestingly, microbes are capable of migrating to other locations in the human body and induce tumor development [37]. There is also increasing evidence that the various microbiota mediate the pathogenesis of genitourinary malignancies, including bladder, kidney, and prostate cancer [38].

There are some limitations to our study that have to be taken into account in the interpretation of the results. First, the results have to be interpreted cautiously with regard to the retrospective setting and the relatively low number of patients with a history of TE. Therefore, larger studies, preferably on a population-based level would be recommendable to investigate further this association. Though patient records were screened for history of TE very thoroughly, the rate of TE in our cohort was 5.6% which is lower compared with a rate of 8–9% in population-based studies [9,30]. We found RFS, but not CSS and OS was associated with TE which is puzzling. This may be related to the low number of patients in the TE-group and subsequent low number of events for CSS and OS. Another possible explanation for this finding may be that distant but not local recurrence patterns were significantly more frequently in the TE-group. In this regard, distant recurrences have been reported to occur later and respond better to palliative treatment compared to local ones [22,39]. In addition, urothelial recurrences which were exclusively present in the non-TE cohort are considered to occur lately (24–48 months after RC) with a better prognosis compared to distant or local ones [21,40]. We could not adjust for confounders, i.e. exact age of TE which is due to the fact that TEs were performed decades before RC during child- or early adulthood and therefore difficult to be exactly assessed during history taking. In addition, TE status may have been misclassified as reliability studies which compared self-reported TE to a physical exam showed only a 76% sensitivity for correct classification [41]. From a current perspective, the use of neoadjuvant chemotherapy in this cohort was low, but at that time, it was not well accepted compared with adjuvant chemotherapy in the uro-oncological community [42]. For this reason, we excluded the nine cases a priori.

To the best of our knowledge, this is the first study reporting on an association of TE and oncological outcomes in invasive bladder cancer and should therefore be considered as hypothesis-generating. Nonetheless, these findings add to the current evidence that TE may influence on cancer development and progression. Further research is needed to corroborate whether TE on BC exerts adversely on BC progression and elucidate possible molecular mechanisms.

In summary, in this analysis, previous TE was an independent risk factor of recurrence after RC for BC. Further studies are needed to assess whether TE induces immunological alterations that might exert long-term adverse effects on cancer progression of patients with invasive BC.

Ethics approval

This study was conducted in accordance to the declaration of Helsinki and the provisions of the local ethics committee Tuebingen (approval number: 417/2010 A).

Disclosure statement

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

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