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RESEARCH

Health Related Quality of Life in Patients with Bladder Cancer: A Cross-Sectional Survey and Validation Study of the Hungarian Version of the Bladder Cancer Index

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Abstract Health-related quality of life (HRQoL) is an important outcome in oncology care although an underexplored area in bladder cancer (BC). Our aims were to assess HRQoL of patients with BC, analyse relationships between diverse HRQoL measures and validate the Hungarian version of the Bladder Cancer Index (BCI) questionnaire. A cross-sectional survey was performed among patients with BC (N=151). Validated Hungarian versions of the FACT-Bl, SF-36 and EQ-5D were applied and SF-6D was derived. Psychometric analysis of the Hungarian BCI was performed. Pearson correlations between the five measures were analysed. Deterioration in SF-36 Physical Functioning was detected among patients aged 45–64 years. The EQ-5D score did not differ significantly from the age-matched population norm. Correlations between the FACT-Bl, EQ-5D and SF-6D utility measures were strong (r>0.6). Cronbach alpha coefficients of the Hungarian BCI ranged from 0.75 to 0.97 and factor analysis confirmed that data fit to the six predefined subdomains. Test-retest correlations (reliability, N=50) ranged from 0.67 to 0.87 and interscale correlations between urinary, bowel and sexual BCI domains were weak or moderate (r=0.29 to 0.49). Convergent validity revealed a stronger correlation with FACT-Bl (r=0.126 to 0.719) than with generic health state scores (r=0.096 to 0.584). Results of divergent validity of the Hungarian BCI by treatment groups by Kruskal Wallis test were promising although limited by low sample sizes in cystectomy subgroups. Generic health state measures have limited capacity to capture HRQoL impact of BC. Validity tests yielded favourable results for the Hungarian BCI. Mapping studies to estimate utility scores from FACT-Bl are encouraged but less recommendable with the BCI.

Keywords Bladder cancer · Quality of life · EQ-5D · FACT-Bl · Bladder Cancer Index · Validation

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Introduction

Bladder cancer (BC) ranks 9th in worldwide cancer incidence as it is the 7th most common cancer in men and the 17th most common cancer in women [1]. Both the disease itself and the therapies applied (e.g. transurethral surgery, intravesical chemotherapy, radical cystectomy with urinary diversion) might have influence on health-related quality of life (HRQoL) of individuals with BC. However, not much is known in the international medical literature regarding the burden imposed by BC cancer upon patients [2]. Evidences on the HRQoL effects of different urinary diversions are weak [3]. Moreover,

there are only a few BC-specific instruments to explore and measure HRQoL outcomes in depth [3]. For the Central and Eastern European (CEE) countries, lack of validated language versions is an additional obstacle for the comparison of outcomes of care and participation in international multicentre trials. The Bladder Cancer Index (BCI) questionnaire was developed and validated in the US to assess HRQoL of patients with BC [4]. It has been applied in an increasing number of studies [5–8] and was validated for a few languages (US English, Spanish and partially in French) but not for the CEE countries [4, 9, 10].

Due to the large financial impact of managing BC, economic considerations have come into focus in the past decades [11]. HRQoL measures that provide utility scores for quality adjusted life year (QALY) calculations in cost-effectiveness analyses gained special importance [12, 13]. However, epidemiological cohorts and clinical trials that generate evidence on disease-specific HRQoL changes rarely incorporate utility measures. In health economic analyses, therefore, disease-specific HRQoL data of cancer patients are often converted to utility scores or used as a proxy to calculate QALYs [14]. According to our knowledge, the most widely used utility measure, the EQ-5D questionnaire has been reported only in two BC studies so far [15, 16]. Extrapolated utility scores from other conditions with similar health states have been used to estimate QALY gains as little is known on the link between disease-specific HRQoL and preference based health state measures in the field of BC [17, 18].

The aims of our study were, therefore, to assess the HRQoL of patients with BC and analyse the relations between diverse HRQoL tools, including utility measures. We aimed to validate the Hungarian language version of the BCI questionnaire as well. The unique feature of this study is that we applied four instruments alongside the BCI, namely the disease-specific Functional Assessment of Cancer Therapy for patients with bladder cancer (FACT-Bl), the Short-Form-36 (SF-36) generic health state measure and the EQ-5D and Short-Form-6D (SF-6D) utility assessments. In this paper we report results of a multicentre cross-sectional survey in a convenience sample patients with BC in Hungary.

Materials and Methods

Study Design and Patients

Patients' data were collected through a cross-sectional survey at three hospital based urology centres in Hungary. Consecutive patients diagnosed with BC and aged 18 or over who attended routine medical care were invited to participate in the study. The target number of participants was 150. The recruitment was pursued between May 2012 and September 2013. All participants provided informed consent prior to their inclusion in the study. The study was approved by the appropriate ethics committee (Scientific and Research Ethics Committee of the Medical Research Council, Hungary; 7794-1I2012/EKU) and have therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Questionnaire Survey and Health Related Quality of Life Assessment

Main clinical parameters including disease history, type of urinary diversion, type and stage of cancer, the distinct interventions applied and co-morbidities were provided by the urologists. Patients filled in a set of questions regarding their demographics and completed the validated Hungarian versions of BC-specific FACT-Bl questionnaire, and of two generic health state measures, namely the EQ-5D and SF-36 [19–21]. SF-6D utility scores were derived from SF-36 by ordinal, standard gamble, Bayesian and parametric approach [22]. Due to lack of local value sets in Hungary, the UK tariffs were used to calculate EQ-5D and SF-6D utility scores. The Hungarian language version of the BCI was developed and applied also in the survey (details are provided below). Higher scores indicate better HRQoL regarding each of the applied instruments.

The Bladder Cancer Index (BCI) Questionnaire

The BCI is a disease-specific HRQoL questionnaire that involves two introductory questions and 3 primary domains, namely urinary, bowel and sexual functions, containing 14, 10 and 12 items, respectively [4]. Each primary domain consists of two subdomains (function and bother). Item responses are based on four and five-point Likert scales. To calculate domain summary and subscale scores, items are standardized to a 0–100 point scale and an average is calculated for each. Higher values indicate better HRQoL. The minimum number of non-missing items needed to compute the score is defined for each score.

Translation of the BCI Questionnaire into Hungarian

The language of the original BCI is United States English [4]. Three Hungarian translations of the questionnaire were carried out independently by three researchers, qualified in health economics, native speakers of Hungarian who were fluent in English. Subsequently, the forward Hungarian translations were reconciled and a blind back-translation into English was performed by an independent professional translator. The backward translation was compared to the original BCI and discussed, involving two urologists and a Hungarian consensus version was formed. Cognitive debriefing interviews and pilot testing were performed involving five patients

with BC (age: 56–74; males: 2; 3 patients with native bladder, 1–1 with neobladder and ileal conduit). Based on the experiences of the pilot the final consensus version was shaped and formatted as the original BCI.

Statistics and Psychometric Testing of the Hungarian BCI

SPSS 20.0 programme package was used to record and analyse questionnaire data. Descriptive statistics of the variables were calculated. Correlations (Pearson coefficients) between the FACT-Bl, SF-36 Physical / Mental Component Summary score, SF-6D, EQ-5D score and EQ VAS were analysed. Correlations of >0.5, 0.30–0.49, and 0.1–0.29 were considered as strong, moderate, and weak relationships, respectively. Comparison across treatment subgroups (transurethral resection - TUR, TUR with intravesical therapy, cystectomy with ileal conduit, cystectomy with neobladder) was analysed by Kruskal-Wallis test. Level of significance was set at $p<0.05$.

Psychometric analysis of the Hungarian BCI was performed following the quality criteria proposed by Terwee and colleagues [23]. Internal consistency (the extent to which items of a questionnaire are correlated) was estimated applying Cronbach's alpha coefficient for each domain and subdomain of the Hungarian BCI. To determine dimensionality, an exploratory factor analysis was used. Our predefined hypothesis was that data related to the Hungarian BCI fit to the 3 primary and 6 subdomains of the original BCI. A scale is usually considered consistent if factor analysis is performed (confirms dimensionality of the questionnaire) and the value of Cronbach's alpha is between 0.70 and 0.95 [23]. Criterion validity was not feasible due to lack of a well-established gold standard measure in BC. To assess construct validity, interscale correlations (Pearson coefficients) between BCI domains and subscales were analysed, as well as with FACT-Bl, EQ-5D, SF-36 and SF-6D scores. Our prespecified hypothesis were that: 1) correlations between urinary, sexual, and bowel BCI domains are weak as these three are supposed to measure different impacts; 2) correlations between function and bother subscales within each domain are moderate as the alteration of a function can, but not necessarily bothers the patient; 3) correlations are moderate or strong with the disease-specific FACT-Bl but weaker correlations are expected with the generic instruments (EQ-5D, SF-36 and SF-6D). Correlations of >0.5, 0.30–0.49, and 0.1–0.29 were regarded as strong, moderate, and weak, respectively [24]. To qualify construct validity as appropriate, usually ≥75 % of the results should be in accordance with the predefined hypotheses [23]. Discriminating ability between four treatment subgroups (TUR without and with intravesical therapy, cystectomy with ileal conduit or with neobladder) was analysed by Kruskal-Wallis test. To assess reproducibility (reliability) 50 patients were asked at the end of the visit to fill in a second piece of BCI at home and mail back. Relations between the results of the two rounds were analysed by Pearson correlation considering a correlation ≥0.70 between (sub)domains as sufficient level of reliability. Floor or ceiling effects were considered if more than 15 % of the respondents had the lowest or highest possible score, respectively [23].

Results

Patient Characteristics and BC Histology

Altogether 151 patients (males N=98, 65 %) were involved in the study with a mean age of 66.3 (SD 9.6) years and disease duration of 4.2 (SD 3.8) years (<1 year: 4 %, 1–5 years: 66 %, >5 years: 30 %). The majority (N=114, 76 %) was married while the others were living alone. The average Body Mass Index (BMI) was 27.8 (SD 5.1). Urothelial carcinoma was the most frequent BC type (N=89, 82 %) other types occurred in 7 (6 %) patients and the specific type of malignancy was not available in 12 (11 %) cases at the time of the survey (missing response: N=43).

Non-invasive tumour was more common than muscle invasive disease. Distribution by cancer stages was as follows — T1: N=43 (28 %), T2: N=14 (9 %), T3: N=6 (4 %), T4: N=1 (1 %), Ta: N=57 (38 %), Tis: N=4 (3 %), Tx: N=4 (3 %), missing data N=22 (14 %); and by cancer grades as G1: N=35 (23 %), G2: N=54 (36 %), G3: N=34 (23 %), Gx: N=2 (1 %) missing data N=26 (17 %) patients. TUR with intravesical therapy was applied in 68 (45 %) patients, 60 (40 %) had solely TUR and 20 (13 %) underwent cystectomy (among them 14 patients had ileal conduit diversion and 6 had neobladder). Three patients (2 %) with muscle invasive tumour received palliative therapy but did not undergo cystectomy.

Health Related Quality of Life of the BC Patients

Main results on HRQoL scores are presented in Table 1. The mean EQ-5D score of the sample did not differ significantly from the age-matched general population norm (by age groups 45–54 years: 0.751 vs. 0.808; 55–64 years: 0.794 vs. 0.765; 65–74 years 0.808 vs. 0.756; 74–85 years: 0.728 vs. 0.634;, $p>0.05$) [25]. The SF-36 domain scores were (mean, SD): Physical Functioning 67.8 (27.0); Role Physical 56.8 (42.8); Bodily Pain 73.4 (27.6); General Health 50.9 (23.2); Vitality 65.4 (25.3); Social Functioning 78.6 (25.1); Role Emotional 63.4 (44.1) and Mental Health 69.6 (24.2). These average scores are comparable to the Hungarian population norm of age-group >65 years [26]. In the age-group of 45–54 BC patients had lower (worse) average scores in the Physical Functioning, Role Physical and Role Emotional domains than the respective population norm in Hungary (72 vs. 85, 56 vs.

Table 1 Health related quality of life of patients with bladder cancer

Summary scores, score range (Number of respondents, %)	Mean (S.D.)
FACT-Bl Physical well-being (PWB), 0–28 (*N*=146, 96.7 %)	23.1 (5.4)
FACT-Bl Social/family well-being (SWB), 0–28 (*N*=148, 98.0 %)	21.6 (5.5)
FACT-Bl Emotional well-being (EWB), 0–24 (*N*=150, 99.3 %)	17.9 (4.9)
FACT-Bl Functional well-being (FWB), 0–28 (*N*=149, 98.7 %)	19.2 (6.6)
FACT-Bl Bladder Cancer Subscale (BlCS), 0–48 (*N*=150, 99.3 %)	32.9 (7.1)
FACT-Bl Trial Outcome Index (TOI), 0–104 (*N*=150, 99.3 %)	74.1 (17.8)
FACT-Bl, 0–156 (*N*=150, 99.3 %)	113.3 (25.1)
FACT-G, 0–108 (*N*=150, 99.3 %)	80.6 (19.5)
EQ-5D score, −0.594–1 (*N*=148, 98.0 %)	0.784 (0.242)
EQ VAS, 0–100 (*N*=141, 93.4 %)	67.8 (19.3)
SF-36 Physical component summary (PCS)*, 0–100 (*N*=149, 98.7 %)	45.6 (10.4)
SF-36 Mental component summary (MCS)*, 0–100 (*N*=148, 98.0 %)	48.4 (12.7)
SF-6D Ordinal v2 – SG health state valuation, 0–1 (*N*=121, 80.1 %)	0.717 (0.141)
SF-6D Ordinal v2 – Ordinal health state valuation, 0–1 (*N*=125, 82.8 %)	0.738 (0.155)
SF-6D Bayesian v2 – Parametric Mean, 0–1 (*N*=121, 80.1 %)	0.717 (0.141)
SF-6D Bayesian v2 – Posterior Mean, 0–1 (*N*=125, 82.8 %)	0.683 (0.136)

SG=standard gamble *QualityMetric Health Outcomes Scoring Software was used applying maximum data recovery method for missing data estimation. Number of respondents with no missing responses for the 36 items was 116 (77 %)

Note: The FACT-Bl Trial Outcome Index (TOI) comprises the sum of scores of PWB, FWB and BICS; FACT-G is calculated by adding the scores PWB, SWB, EWB, FWB; while FACT-Bl includes the sum of the scores of FACT-G and BICS

71, and 53 vs. 73, respectively). Deterioration in Physical Functioning was detectable also in age-group 55–64 (69 vs. 79). BC patients aged ≥65 years had similar SF-36 scores as the general Hungarian population of the same age. (Levels of significance cannot be calculated as S.D. was not provided in the publication of SF-36 population norms [26].) Results of SF-6D scored by the four distinctive methods did not differ considerably.

The difference of FACT-Bl, EQ-5D, SF-36 (Physical component summary) and SF-6D scores across the four treatment subgroups was not significant. (Table 2) We find important to note, however, that the sample size was small in the cystectomy with neobladder subgroup (*N*=6) that hampers the reliability of this result.

Relationship Between FACT-Bl, SF-36, SF-6D and EQ-5D

Results are presented in Table 3. Correlations between FACT-Bl, EQ-5D, EQ Visual Analogue Scale (EQ VAS), SF-36 and SF-6D were moderate or strong ($r \geq 0.467$). The association of the FACT-Bl and the two utility measures, namely the EQ-5D score and SF-6D, was strong. SF-36 Physical component summary score correlated weakly with SF-36 Mental component summary score.

In Table 4, descriptive statistics of the Hungarian BCI are presented. Cronbach's alpha was in the required range of 0.70–0.95 indicating high internal consistency, only the sexual function was slightly higher (0.97). In factor analysis (applying principal axis factoring method) when 3 factors were fixed in accordance with the 3 primary domains of the BCI, data did not fit. In case of 6 factors analogue with the 6 subdomains, responses to the 36 items fit to the 6 subdomains with the exception of 5 items. (The outlier items were item number 24, 25 in urinary function; 36, 42 in bowel bother; and 52 in sexual bother subdomains.)

Interscale correlations between urinary and bowel/sexual domains were moderate ($r=0.489$ and $r=0.311$, respectively) and between bowel and sexual domains was weak ($r=0.289$). Interscale correlations between BCI domain subscales are presented in Table 5. Correlations between urinary, sexual, and bowel BCI subdomains were low or moderate but bordering to low, in accordance with our hypothesis, only the urinary bother and bowel bother scores presented moderate but bordering to strong correlation ($r=0.484$). Strong correlations were found between function and bother scores within the urinary and bowel domains ($r=0.499$ and 0.547, respectively), as expected, however, it was low but bordering to moderate in the sexual domain ($r=0.263$).

Correlations with other HRQoL measures applied in the study are indicated in Table 5. Correlations of the BCI subscales and the other disease-specific measure, the FACT-Bl were moderate or strong, only the sexual bother subdomain presented weak relationship ($r=0.126$). Regarding the correlations between the BCI and generic HRQoL measures, these were weaker than with the FACT-Bl (except one: bowel bother and EQ-5D score) which is in line with our predefined hypothesis. In the urinary and bowel domains, correlations of the generic HRQoL measures with the bother subdomains were stronger than with the functional subdomains. Correlations with the sexual bother subdomain were not significant.

An analysis of the Hungarian BCI by treatment subgroups is presented in Table 2. Mean scores across the four subgroups differed significantly in five domains. Although results in sexual summary, sexual function, sexual bother and bowel bother were not significant, differences in scores manifested among groups undergone cystectomy and without cystectomy, respectively. Accordingly, urinary, bowel and sexual scores were consistently lower in cystectomy groups

Table 2 Comparison by treatment subgroups

Domains	Native bladder		Cystectomy		Comparison of the four subgroups*, *p* value
	TUR (*N*=63) Mean (S.D.)	TUR with intravesical therapy (*N*=68) Mean (S.D.)	Ileal conduit (*N*=14) Mean (S.D.)	Neobladder (*N*=6) Mean (S.D.)	
Age, years	66.4 (10.0)	66.9 (9.9)	64.1 (7.5)	63.7 (7.2)	0.591
Disease duration, years	3.8 (4.4)	4.3 (2.9)	5.2 (3.4)	6.5 (4.6)	0.032
FACT-Bl	112.1 (28.7)	115.8 (21.8)	108.6 (24.7)	109.2 (22.2)	0.648
EQ-5D	0.788 (0.264)	0.815 (0.179)	0.617 (0.354)	0.810 (0.193)	0.229
EQ VAS	68.5 (20.3)	68.7 (16.2)	62.4 (26.9)	64.2 (21.7)	0.858
SF-36 Physical Component score	46.6 (10.4)	45.4 (10.3)	43.3 (11.0)	40.9 (10.7)	0.496
SF-36 Mental Component score	49.0 (12.7)	48.5 (12.1)	40.5 (12.5)	63.2 (4.4)	0.002
SF-6D†	0.739 (0.137)	0.720 (0.143)	0.623 (0.113)	0.702 (0.193)	0.101
BCI Urinary:	80.1 (20.7)	85.9 (16.5)	74.1 (17.0)	52.2 (23.6)	0.006
– function	72.6 (28.3)	77.8 (27.4)	64.4 (32.5)	20.8 (10.9)	0.005
– bother	86.3 (19.8)	89.8 (14.6)	76.9 (16.9)	68.9 (22.0)	0.007
BCI Bowel:	84.6 (16.2)	85.0 (14.5)	75.5 (19.1)	65.8 (23.6)	0.046
– function	84.9 (15.1)	84.1 (18.3)	82.9 (15.6)	56.3 (29.4)	0.257
– bother	84.4 (19.4)	85.7 (15.8)	71.1 (24.4)	72.2 (15.8)	0.043
BCI Sexual:	50.9 (26.3)	52.7 (21.0)	39.9 (21.0)	37.3 (41.1)	0.343
– function	35.9 (32.5)	40.1 (27.3)	24.0 (27.6)	28.2 (39.9)	0.448
– bother	73.5 (30.6)	70.0 (26.9)	62.3 (29.8)	50.0 (43.6)	0.442

*Kruskal-Wallis test was performed. TUR=transurethral resection. †Results with SF-6D Bayesian parametric mean scores are presented

than in native bladder, i.e. endoscopically managed (TUR) groups of BC patients. Mean scores by disease stages (Ta, T1/Tis, T2, T3 and T4) did not indicate statistically significant differences ($p>0.05$).

Among the subdomains of urinary, bowel and sexual function the test-retest correlation was strong (between 0.805 and 0.871) while in the bother subdomains the coefficient was strong but slightly under the required 0.70 cut-off (between 0.665 and 0.698). Rate of participants reporting maximum score was the highest in both urinary and bowel primary domains (28.6 and 13.1 %, respectively), consequently, ceiling effects were relatively strong regarding these domains.

Table 3 Correlations between the disease-specific FACT-Bl and generic health state measures

	FACT-Bl	SF-36 physical component summary score	SF-36 mental component summary score	SF-6D score†	EQ-5D score	EQ-VAS
FACT-Bl	1	0.590*	0.578*	0.643*	0.693*	0.620*
SF-36 physical component summary score	–	1	0.263*	0.695*	0.643*	0.567*
SF-36 mental component summary score	–	–	1	0.730*	0.592*	0.467*
SF-6D score†	–	–	–	1	0.676*	0.572*
EQ-5D score	–	–	–	–	1	0.634*
EQ-VAS	–	–	–	–		1

*Correlation is significant at the 0.01 level. †Results with SF-6D Bayesian parametric mean scores are presented. Results with the other three SD-6D score variants were similar (data not shown)

Table 4 Domain specific summary and subscale characteristics of the Hungarian BCI questionnaire

BCI domains	Number of items	Missing items[a]	Missing score[b]	Observed range	Mean (SD)	Cronbach's alpha	Test-retest correlation[c]
Urinary:	14	44 (28.5)	18 (11.9)	31.6–100	81.1 (19.7)	0.86	0.85*
- function	6	23 (15.2)	24 (15.9)	8.3–100	72.6 (29.5)	0.79	0.84*
- bother	8	35 (23.2)	23 (15.2)	39.3–100	86.4 (17.9)	0.85	0.70*
Bowel:	10	24 (15.9)	21 (13.9)	28.3–100	83.4 (16.2)	0.82	0.67*
- function	4	22 (14.6)	22 (14.6)	25.0–100	83.6 (17.4)	0.79	0.81*
- bother	6	23 (15.2)	21 (13.9)	16.7–100	83.3 (18.8)	0.75	0.69*
Sexual:	12	43 (28.5)	34 (22.5)	4.6–100	50.5 (23.9)	0.91	0.78*
- function	7	38 (25.2)	30 (19.9)	0.0–100	36.7 (29.9)	0.97	0.87*
- bother	5	38 (25.2)	28 (18.5)	10.0–100	97.4 (9.5)	0.88	0.67 *

*$p<0.01$

[a] Number and percentage of patients with any missing item

[b] Number and percentage of patients with missing score

[c] $N=50$ patients

Minimal ceiling effect was observed in the sexual domain (0.9 %). Floor effects were no relevant at all since none of the patients had minimum score.

Discussion

In this cross-sectional study we assessed the HRQoL of patients with BC in three hospital based urology centres in Hungary. The average general health status of the BC patients was similar to the Hungarian population norm [26]. The rate of patients with native bladder was dominant (87 %) in our sample, that can account for the rather favourable results with the SF-36 and EQ-5D general health state tools.

Alongside the advances in urology surgery reconstructive aspects gained greater importance and the need to assess and compare the HRQoL impact of different treatment strategies is increasing [5]. According to a recent systematic literature review by Ali and colleagues, the difference between patients with ileal conduit and neobladder was not significant with the SF-36 in most of the studies [3]. Their overall conclusion was, based on the available results including studies with disease-specific tools as well, that neobladder urinary diversion shows

Table 5 Interscale correlations between BCI function and bother subscales and other health related quality of life scores

Measures	BCI Urinary		BCI Bowel		BCI Sexual	
	function	bother	function	bother	function	bother
BCI urinary function	1	–	–	–	–	–
BCI urinary bother	0.499*	1	–	–	–	–
BCI bowel function	0.276*	0.383*	1	–	–	–
BCI bowel bother	0.343*	0.484*	0.547*	1	–	–
BCI sexual function	0.290*	0.349*	0.188**	0.258*	1	–
BCI sexual bother	−0.130	0.133	0.132	0.162	0.263*	1
FACT-Bl	0.423*	0.719*	0.363*	0.521*	0.467*	0.126
EQ-5D score	0.251*	0.569*	0.307*	0.584*	0.327*	0.084
EQ VAS	0.276*	0.469*	0.234*	0.364*	0.439*	0.163
SF-36 Physical Component score	0.317*	0.488*	0.280*	0.354*	0.417*	0.096
SF-36 Mental Component score	0.222**	0.495*	0.317*	0.435*	0.282*	0.138
SF-6D	0.286*	0.570*	0.297*	0.368*	0.319*	0.153

*Correlation is significant at the 0.01 level;**Correlation is significant at the 0.05 level

Note: Numbers in bold are the interscale correlation coefficients comparing function and bother scores within each domain of the Hungarian BCI

only marginally better HRQoL compared to ileal conduit diversion, especially when considering younger and fitter patients. Our study seems to confirm these observations however, our results by treatment types might be biased by the small sample sizes in the cystectomy subgroups. (Table 2) Further studies involving larger samples with cystectomy are needed.

The criterion of cost-effectiveness has become crucial in reimbursement decisions in most of the countries of the European Union. For the evaluation of new health technologies (e.g. drugs, devices), these are compared with the available ones in terms of incremental costs and incremental benefits. This latter includes both the quality and the quantity of life years gained and is expressed in quality-adjusted life-years (QALYs) [12]. To measure the 'Q' of the QALY, a range of preference-based measures (also called utility measures) has been developed. The key point is whether results of cost per QALY analyses using diverse utility measures can be matched. In our study, mean utility scores assessed by the EQ-5D and SF-6D were similar and their correlation was strong, indicating that the two instruments perform similarly in BC. (Table 3) Thus comparison of EQ-5D and SF-6D based cost-utility studies seems to be reliable in BC, nevertheless, further research investigating their equivalency especially in terms of responsiveness to changes, is encouraged. Estimation of EQ-5D and SF-6D utility scores from FACT-Bl seems to be promising as well. Mapping studies across various settings of patients with BC might provide clear evidences.

The Hungarian BCI proved to be satisfactory regarding survey characteristics in validation analysis involving 151 patients with BC. Internal consistency was excellent as marked by Cronbach's alpha [23] (Table 4). Psychometric experts disagree on the minimum number of subjects needed for assessment of internal consistency of a questionnaire by factor analysis [23, 27]. Rules-of-thumb vary from four to 10 candidates per variable, with a minimum number of 100 subjects, accordingly, our sample including 151 participants fulfilled this criteria. Responses given to the Hungarian BCI questionnaire, with the exception of five outlier items of the 36, fit to the six subdomains of the original BCI, but not to the three primary domains. This result indicates that the relations between subdomains (function and bother) within each primary domain are not stronger than relations between primary domains themselves. Respectively, function and bother subdomains are closer to each other than function and bother pairs within a primary domain. Interscale correlations between BCI subdomains revealed good construct validity, referring adequate measurement independence among urinary, bowel and sexual domains (Table 5). The association between BCI and the other disease-specific measure (FACT-Bl) was stronger than with the generic health state measures, that supports the disease-specific character of the questionnaire. Response rate across BCI domains (78 and 88 %) was comparable to the generic SF-36 and SF-6D measures indicating good feasibility of the Hungarian BCI, although not as excellent as the EQ-5D and FACT-Bl questionnaires had. The difference across treatment subgroups was significant in the urinary and bowel summary scores and also in the urinary function and bother subdomains of the BCI (Table 4). Seems that the BCI is more sensitive to capture treatment effects, nevertheless the discriminating capacity of the Hungarian BCI between therapeutic subgroups have to be confirmed in larger studies involving more patients with cystectomy.

Comparison of our results with the original BCI validation study by Gilbert and colleagues revealed similarities that support the appropriateness of the Hungarian version of the BCI questionnaire [4]. A minor difference to note is that the relationship between sexual function and bother was weak in our survey whilst it was moderate in the original BCI study. There might be, in the background, cultural differences between populations towards reporting about sexual life and certainly, we cannot exclude translation bias either. However, during cognitive debriefing interviews patients who did not respond the sexuality related items said that those questions were clear but 'irrelevant' as they had no sexual life. Thus their 'Never' response on the pain related intercourse question did not mean a painless intercourse but simply the lack of activity. This shortcoming of the original BCI questionnaire may weaken its feasibility and sensibility to demonstrate HRQoL effects in the sexual domain. Another point to consider is that only participants who completed the questionnaire were included in the original BCI analyses (response rate 45 %) [4]. This patient selection can also have positive impact on psychometric results. Nevertheless, findings by Schmidt and colleagues seem to strengthen our observations as they also found weak correlation between sexual function and bother subdomains in the validation study of the Spanish version of the BCI [10]. Overall, we encourage new multi-country studies to get a better insight into cross-cultural differences, as well as on the impact of age, gender and disease stage on the performance of the BCI, with special focus on the sexual domain.

Relations between the BCI and generic health state and utility measures deserve further attention. The moderate and weak association between BCI and EQ-5D, SF-36 and SF-6D indicates, on the one hand, that the BCI captures HRQoL aspects that are not detectable with generic questionnaires, particularly in urinary and bowel functioning and sexual areas. On the other hand, estimation of EQ-5D or SF-6D utility scores from BCI results is very limited. Thus, we suggest applying preference-based measures alongside the condition-specific BCI questionnaire in studies that aim to provide QALYs for economic evaluations.

Some limitations of our study have to be taken into account. The sample was not representative and the rate of patients with cystectomy was quite low thus the generizability

of our results to this subgroup of patients is limited. For the same reason, evidences on discriminating ability of the Hungarian BCI between treatment groups are promising but have to be confirmed in further studies. Responsiveness to changes was not assessed due to the cross-sectional design of our study. Further studies should focus specifically on these points. Among the pros, we find important to highlight that according to our knowledge we were the first to analyze the relations between BCI, FACT-Bl and the EQ-5D and SF-6D preference-based measures in parallel.

Finally, we would like to point out that understanding disease-related quality of life issues and measuring HRQoL outcomes are crucial in the management of BC. HRQoL assessment supports shared decision making. On the one hand, it helps physicians to explore patients' health problems, needs and preferences in depth. On the other hand, the more cumulative data on HRQoL outcomes are available, the better clinicians can inform patients on the expected HRQoL gains. However, that requires validated assessment tools across countries. In everyday practice, assessment of HRQoL in the follow-up of an individual patient helps to evaluate the achieved health benefits considering the patient's perspective. On the health care level, HRQoL assessment adds valuable information for the comparison of the performance of different health services both on the national and international level. From the health economics and health policy point of view, cost per QALY results are usually taken into account in resource allocation decisions. Therefore, it is crucial to provide utility data for QALY calculations also in the field of urological oncology. Our study generated evidences on the HRQoL of patients with BC in Hungary, analysed the validity of the Hungarian version of the BCI questionnaire and revealed the relationship across various disease-specific and preference-based utility measures in BC. We believe that health technologies for the treatment of BC will successively improve and the significance of measuring and incorporating HRQoL outcomes in everyday practice, patient registries, clinical trials and health economic evaluations will increase as well. This study aimed to contribute to that goal.

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Conflict of Interest Authors declare that they have no conflict of interest.

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