



Quality of life following urinary diversion: Orthotopic ileal neobladder versus ileal conduit. A multicentre study among long-term, female bladder cancer survivors



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ABSTRACT

Introduction: Women undergoing radical cystectomy (RC) followed by urinary diversion (UD) for bladder cancer experience a substantial reduction in health-related quality of life (HRQOL). At present, studies comparing long-term QOL outcomes for different UD methods, needed to inform evidence-based choices of bladder reconstruction for female patients, are sparse. Our objective was to compare two common UD methods in terms of their HRQOL outcomes in women.

Materials and methods: We retrospectively analysed HRQOL in 73 consecutive female bladder cancer patients having undergone orthotopic ileal neobladder (IONB, N = 24) or ileal conduit (IC, N = 49) following RC between 2007 and 2013 in six Italian academic urological centres. Patients had no evidence of tumour recurrence and were actively followed up. Validated Italian versions of the European Organisation for Research and Treatment of Cancer (EORTC) generic (QLQ-C30) and bladder-cancer-specific (QLQ-BLM30) questionnaires were used to evaluate HRQOL.

Results: Patients in the IONB group were significantly younger than those in the IC group (median age: 67 and 73 years, respectively, $p = 0.02$). Barring that, the two groups did not present statistically significant differences in median length of follow-up (43 vs 54 months), pathological stage, grading of the neoplasm, or adjuvant chemo - or radiotherapy. No significant differences in QOL were found between the groups, with the exception of financial difficulties, affecting IONB patients significantly more than IC patients (mean score on a scale of 0–100: 33.3 ± 29.5 vs 18.4 ± 19.3 , respectively; $p = 0.05$).

Conclusion: Financial difficulties was the only HRQOL item to differ between the two UD groups.

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Introduction

Bladder cancer (BC) is the sixth most common cancer in both sexes in the US, with 81,190 estimated new cases in 2018 [1]. According to the European Association of Urology (EAU) guidelines, radical cystectomy (RC) with lymph node dissection represents the standard treatment for localized muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer [2]. This procedure is a traumatic and invasive event for the patients, that deeply affects daily, social, sex and working life. The two most commonly performed kinds of urinary diversion methods are ileal conduit (IC) and orthotopic neobladder (ONB). Nevertheless, data regarding health-related quality of life (HRQOL) after RC are inconclusive, and a urinary diversion (UD) method of choice has yet to be established.

Unfortunately, published results present several problems. Most studies are not randomised, and comparability is compromised by the use of generic versus cancer-specific questionnaires.

Ali et al. performed a systematic review of 21 studies, non-randomised, most of which reported similar QOLs between continent UD methods such as ONB and incontinent ones such as IC [3].

Cerruto et al. found no significant differences between ONB versus IC patients using generic HRQOL questionnaires like the SF 36. However, when evaluating patients using a cancer-specific questionnaire like EORTC QLQ-C30, a significantly better QOL was observed in ONB patients [4].

Moreover, due to the relatively low incidence of bladder cancer in females [1], few studies have evaluated the levels of discomfort in long-term female survivors. In the present study, we used validated Italian versions of the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires to assess generic (QLQ-C30) and bladder-cancer-specific (QLQ-BLM30) long-term HRQOL among female BC patients who had undergone either ileal ONB or IC.

Materials and methods

Study population

This cross-sectional study involved 73 consecutive female patients that had undergone RC and UD for urothelial BC in six Italian academic urological centres between June 2007 and September 2013. All patients were older than 18, and were affected by either muscle-invasive BC or by non-responder high-grade non-muscle-invasive BC, according to EAU Guidelines [2]. They had all undergone pelvic and iliac lymph node dissection with radical en bloc cystectomy as described by Skinner and Lieskovsky [5] followed by UD by either IC or ONB with VIP (Vescica Ileale Padovana) as previously described by Pagano et al. [6]. Ninety-day complications were collected and graded according to the Clavien Dindo classification [7].

To rule out the possible effects of disease-related factors or of the psychological burden of a recent surgical procedure, patients with cancer recurrence or with less than six months of follow-up were excluded from the analysis. Patients unable to understand or fill out the questionnaire due to cognitive impairment or insufficient command of the Italian language (four patients) were also excluded.

All patients provided written informed consent. The study was approved by the Ethics Committees of Verona and Rovigo (protocol number 20097339 KC), and was conducted in accordance with the principles of research involving human subjects as expressed in the Declaration of Helsinki and the Good Clinical Practice guidelines.

HRQOL questionnaires

All patients were evaluated using the EORTC QLQ-C30 and EORTC-QLQ-BLM30 questionnaires. The QLQ-C30 is a modular 30-item questionnaire developed and copyrighted by the EORTC as an integrated tool designed to assess the QOL of cancer patients participating in clinical trials [8]. This tool has been translated into 81 languages and used in more than 3000 studies worldwide. Its cross cultural validity and reliability has been established [9]. The questionnaire is composed of nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, nausea/vomiting), a global health and QOL scale and items assessing the perceived financial burden of cancer and other symptoms frequently reported by cancer patients, such as constipation, diarrhoea, dyspnea, loss of appetite and sleep disturbance [10].

The QLQ-BLM30 is a 30-item questionnaire developed for patients affected by muscle-invasive BC who underwent UD. It was specifically designed to evaluate the burden of UD on HRQOL. This tool includes items concerning urinary function and continence, lower urinary tract symptoms, stoma management, gastrointestinal symptoms, problems regarding body image and sexuality, and concerns about the future. It has not been validated, but has completed phase III of module development.

We used the Italian version of the EORTC QLQ-30 [11]. The majority of questions were assigned a score from one to four (1 = not at all, 2 = a little, 3 = quit a bit, 4 = very much). For two questions were assigned a score from 1 to 7. Also, we used the Italian version of QLQ-BLM30 from EORTC to assess bladder cancer-specific HRQOL [12].

As suggested to the EORTC Manual scoring we linearly transformed all variables to a 0–100 scale. This manual contains scoring procedures for the QLQ-C30, and it also contains summary information about supplementary modules (EORTC Data Center). The principle for scoring these scales is the same in all cases: (1) estimate the average of the items that contribute to the scale; this is the raw score; (2) use a linear transformation to standardize the raw score, so that scores range from 0 to 100. For the functional items, the higher score represents a higher level of functioning. For the symptoms/single items, a higher score means a higher level of symptomatology/problems [13].

Data were collected from each of the patients through an individual interview, conducted in the outpatient clinic in the course of a follow-up evaluation visit.

Statistical analyses

Mean values and standard deviations (\pm SD) were computed for all parametric variables, whereas nonparametric variables were expressed as median and range.

The two groups were compared using Student's T-test and the Wilcoxon two-sample test for continuous variables, while the chi square test with Yates' correction was used for categorical variables. The threshold for statistical significance was set at $p \leq 0.05$ (two-tailed).

Statistical analysis was performed using SPSS v. 20.0 (IBM Corp, Armonk, NY, USA).

Results

Seventy-three female patients undergoing RC and UD were included in the study. Urinary diversion following RC was IC in 67.1% (49/73) of the population and IONB in 32.9% (24/73).

Patients in the IONB group were significantly younger than those in the IC group (median age: 67 and 73 years, respectively, $p = 0.02$). Barring that, the two groups did not present statistically

significant differences with regard to pathological stage, grading of the neoplasm, adjuvant chemo- or radiotherapy, or length of follow-up (Table 1). Minimum follow-up was 6 months and median follow-up was 43 months in IONB patients (range: 16–138) and 54 months in IC patients (range: 6–153).

As far as HRQOL is concerned, only financial difficulties yielded a statistically significant difference, with IONB patients reporting more difficulties than IC patients (33.3 ± 29.5 and 18.4 ± 19.3 , respectively, $p = 0.05$). Other items did not yield statistically significant results (Tables 2 and 3).

Discussion

Treating female patients with BC is a challenge for urologists. This is not only because of the possible mismatch between surgical, oncological and functional outcomes, but also because the female gender represents a risk factor for poor surgical and oncological results following RC.

This was shown by Messer et al. in a large, multicentre, observational, cohort study using retrospectively collected data on 4296 BC patients treated with RC, including 890 women, where female gender was associated with an increased risk for disease recurrence and cancer-specific mortality (HR 1.27; $p = 0.007$) [14].

Similarly, uni- and multivariate analyses conducted on 8102 BC patients treated with RC, of which 1605 were women, indicated the presence of a higher risk of disease recurrence among women, and identified female gender as an independent predictor of cancer-specific mortality ($p = 0.004$) [15].

In the same vein, Novara et al. found female gender to be an independent predictor of major complications after RC in a subgroup of patients who underwent ONB ($p = 0.017$) [16].

This underscores the importance of a careful choice of urinary diversion method for women, so as to minimise complications and preserve HRQOL.

Due to the relatively low incidence of bladder cancer in the female population [1], however, few studies have been published

comparing different methods of UD following RC, in terms of HRQOL outcomes in women.

We interviewed a relatively large study population of all-female long-term survivors ($n = 73$) employing two widely-used, validated HRQOL questionnaires. The two UD groups under study were largely comparable in terms of the length of follow-up, clinical and pathological characteristics. Our analysis yielded a single statistically significant difference in HRQOL, with IONB patients reporting more financial difficulties than IC patients.

As mentioned in the introduction, the literature on this matter is inconclusive. Some studies have documented less favourable results for ONB patients, as we have, but not with regard to financial difficulties. Hedgepeth et al. [17] compared Bladder Cancer Index and EORTC Body Image Scale scores in three groups of patients undergoing RC and IC, RC and ONB, and cystoscopy (used as a control group). Measurements were taken at baseline and at different points in time up to 8 years after the operation. Gender was not associated with either body image or urinary function. Body image scores worsened after the procedure in both treatment groups and then improved over time, although the ONB group did not return to baseline levels. ONB patients also reported worse urinary function, whereas the burden of urinary bother was similar in the two UD groups.

Other studies, on the other hand, found ONB patients to do generally better than IC Patients. In a recent meta-analysis with moderator analysis conducted by Cerruto et al. [4], gender was found to moderate the association between type of urinary diversion and QOL: study populations with over 65% men showed a better HRQOL in the ONB subgroup, suggesting that results concerning men may not apply equally well to female patients. At any rate, in an analysis evaluating all of the QLQ-C30 items, the pooled effect size indicated a better QOL in ONB patients (Hedges' $g = 0.400$; $p = 0.000$). Here too, however, no differences were found in terms of financial burden.

Recently, Gacci et al. [18] concentrated on female patients, evaluating a group of 37 women that had undergone RC and UD by

Table 1

Age, length of follow-up and selected pathological and clinical characteristics of 73 female patients with bladder cancer, by type of urinary diversion.

	Ileal orthotopic neobladder (N = 24)	Ileal conduit (N = 49)	p-value
	N. (%) ^a	N. (%)	
Median age in years (range)	67 (44–86)	73 (51–86)	$p = 0.0182^b$
Median follow-up in months (range)	43 (16–138)	54 (6–153)	$p = 0.7826^b$
Stage (pTNM - UICC)			
0-I	4 (16.7)	17 (34.7)	
II	11 (45.8)	12 (24.5)	
III-IV	9 (37.5)	20 (40.8)	$p = 0.1228^c$
Total	24 (100)	49 (100)	
Grade			
G1-G2	1 (4.2)	5 (10.2)	
G3-G4	23 (95.8)	41 (83.7)	
Unknown	–	3 (6.1)	$p = 0.2929^c$
Total	24 (100)	49 (100)	
Adjuvant chemotherapy			
No	23 (95.8)	41 (83.7)	
Yes	–	8 (16.3)	
Unknown	1 (4.2)	–	$p = 0.0443^c$
Total	24 (100)	49 (100)	
Adjuvant radiotherapy			
No	23 (95.8)	48 (98.0)	
Yes	1 (4.2)	1 (2.0)	$p = 0.6012^c$
Total	24 (100)	49 (100)	

^a Unless otherwise stated.

^b Wilcoxon two-sample test, p-value in comparison to IONB.

^c Chi-square test.

Table 2
Quality of life in bladder cancer patients by type of urinary diversion (EORTC QLQ-C30).

Item	Ileal orthotopic neobladder (N = 24)	Ileal conduit (N = 49)	p-value ^c
	Mean (±SD)	Mean (±SD)	
Physical functioning ^a	51.5 (±20.3)	61.2 (±29.0)	p = 0.1473
Role functioning ^a	47.2 (±27.2)	59.9 (±30.0)	p = 0.2010
Emotional functioning ^a	69.4 (±25.5)	61.3 (±30.2)	p = 0.3341
Cognitive functioning ^a	71.5 (±26.2)	65.0 (±30.5)	p = 0.2978
Social functioning ^a	58.3 (±22.0)	68.3 (±26.6)	p = 0.1941
Fatigue ^b	25.9 (±22.4)	35.6 (±26.3)	p = 0.1239
Nausea and vomiting ^b	17.4 (±16.7)	11.9 (±15.6)	p = 0.1262
Pain ^b	24.3 (±22.5)	21.4 (±21.5)	p = 0.6808
Dyspnea ^b	25.0 (±29.9)	31.3 (±30.7)	p = 0.3805
Insomnia ^b	31.9 (±30.3)	29.9 (±26.6)	p = 0.5719
Loss of appetite ^b	16.7 (±19.7)	19.7 (±24.5)	p = 0.9182
Constipation ^b	33.3 (±34.1)	34.0 (±33.7)	p = 0.8548
Diarrhoea ^b	4.2 (±11.3)	8.2 (±23.1)	p = 0.7607
Financial difficulties ^b	33.3 (±29.5)	18.4 (±19.3)	p = 0.0448
Global quality of life ^b	55.2 (±19.6)	62.2 (±24.5)	p = 0.0984

^a For the functional items, the higher score represents a higher level of functioning.

^b For the symptoms/single items, a higher score means a higher level of symptomatology/problems.

^c Wilcoxon two-sample test, p-value in comparison to IONB.

Table 3
Bladder-cancer-specific quality of life by type of urinary diversion (EORTC QLQ-BLM30).

	Ileal orthotopic neobladder (N = 24)	Ileal conduit (N = 49)	p-value ^b
	Mean (±SD)	Mean (±SD)	
Future perspective ^a	28.2 (±22.0)	43.1 (±30.4)	p = 0.0772
Abdominal bloating/flatulence ^a	25.7 (±25.5)	30.3 (±28.4)	p = 0.6079
Body image ^a	34.3 (±30.9)	38.1 (±31.8)	p = 0.5380
Sexual functioning ^a	13.8 (±13.9)	23.5 (±24.4)	p = 0.2414

^a A higher score indicates a higher level of symptomatology/problems.

^b Wilcoxon two-sample test, p-value in comparison to IONB.

either IC (n = 16), IONB (n = 9) or ureterocutaneostomy (n = 12), all with a minimum follow-up of 36 months and no evidence of disease recurrence. Validated Italian versions of the QLQ-C30, the QLQ-BLM30 and the FACT (BL-VCI) questionnaires were used. This study resembles our series not only in that it limited itself to female patients, but also inasmuch as it was performed in Italy using the same two questionnaires that were employed in our study. No statistically significant differences between the groups were found regarding any of the items in either of the EORTC instruments, including financial burden.

The discrepancy between Gacci's findings and the current study may be attributed in part to sample sizes (9 vs. 24 and 16 vs. 49 patients for the ONB and IC groups, respectively). It may also be related to the fact that ONB patients in Gacci et al. were older than our ONB patients (71.8 vs. 67 years), since older patients may experience a lower impact of disease on financial difficulties, both directly and through more moderate effects on variables such as body image or working life.

A prospective comparison of HRQOL between patients undergoing RC and IC (n = 80) or sigmoid/ileal ONB (n = 84) was performed in India, by Singh et al. [19]. Patients were evaluated with QLQ-C30 at baseline, and at a 6, 12 and 18 months. Cognitive and emotional scores did not differ between the two groups. However, financial difficulties were significantly greater among patients with IC as early as 6 months after the procedure. What is more, the gap between the two groups widened over time, as financial distress worsened for IC patients even as it improved for ONB patients (54.3 vs. 33.3, 61.5 vs. 30.9 and 70 vs. 23.8 at 6, 12 and 18 months of follow-up, in the IC and ONB groups, respectively), possibly as the latter group gradually adapt to the new situation. Indeed, a number of long-term studies point to the existence of a phenomenon of

adaptation over time [17,20]. As far as the worsening observed in the IC group is concerned, the authors suggested it could be due to the fact that the study population belonged to a low income group for whom ostomy management, required after IC, is too great an expense, especially in the long run. The findings reported by Singh et al. are at odds with our results, which pointed to greater financial difficulties among IONB patients. Indeed in Italy, the situation described by the authors would not arise, since any medical expense necessary following the operation would be covered by the national health system. Our finding is not easily interpreted. It may in part have to do with the younger age of our IONB population as compared to our IC group since, as discussed above, the effect of disease on the older patients' financial situation is likely to be less pronounced. Another possible explanation may involve differences in our subjects' baseline financial situation which, unfortunately, we were unable to measure. It should also be noted that Singh's patients were for the most part males (88%) while our population was exclusively female.

Our study constitutes a contribution to a small body of research addressing an important clinical question; a body of research which, however, does not appear to have thus far shown a clear advantage for one or the other UD procedure in terms of QOL.

Ours is one of few studies specifically focusing on long-term female RC survivors, but it also presents a number of weaknesses: it is cross-sectional and non-randomised, it lacks pre-RC baseline HRQOL measurements and is based on a limited, albeit relatively large, sample. Moreover, while the two UD groups were similar in terms of clinical and pathological characteristics, age differences may have confounded associations with HRQOL.

It should also be borne in mind that all QOL results based on interview data may suffer from potential sources of bias that risk

inducing responders to report relatively “optimistic” QOLs. Patients may, for example, respond according to what they believe their interviewer - in our case, the doctor - wishes to hear (Obsequiousness bias) [21] or they may feel the need to convince themselves of the usefulness of a traumatic intervention, in line with Festinger's theory of cognitive dissonance [21,22].

In 1957 Festinger et al. postulates that our actions shape our preference [22] and that our preferences are modulated by the mere act of choosing, in contrast with the normative decision theory, that suggests that our actions reflect our preference.

The cognitive dissonance theory is suggesting that difficult situations could cause psychological distress; in some difficult situations, patients could put in place specific attitude or behaviours, with the aim to conflict reduction and balance restoring [23].

As suggested by Occhipinti et al. [23] with regard to patients with colorectal cancer, patients experiencing a traumatic event may have a tendency to accentuate positive aspects of the event in question, enhancing the sense of well being, according to a cognitive dissonance response. It is, nevertheless, not likely that such tendencies would differentially affect the responses of the two UD groups, thus influencing observed associations.

Further large, prospective, randomised, long-term studies will be needed to help clinicians and patients choose the most beneficial UD method following RC.

Conclusions

Our study, based on long-term follow-up of women undergoing RC with IONB or IC, showed that there were no significant differences in quality of life between the two groups of women, with the exception of financial difficulties which appeared to affect IONB patients more than IC patients. Further large, prospective, randomised, long-term studies will be needed to help clinicians and patients choose the most beneficial UD method following RC.

Conflict of interest

None for all authors.

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