

Review

Systematic review and meta-analysis of non RCT's on health related quality of life after radical cystectomy using validated questionnaires: Better results with orthotopic neobladder versus ileal conduit



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Abstract

Purpose: The current literature on the impact of different urinary diversions on patients' health related quality of life (HR-QoL) showed a marginally better quality of life scores of orthotopic neobladder (ONB) compared to ileal conduit (IC). The aim of this study was to update the review of all relevant published studies on the comparison between ONB and IC.

Materials and methods: Studies were identified by searching multiple literature databases, including MEDLINE, CINAHL, the Cochrane Library, PubMed Data were synthesized using meta-analytic methods conformed to the PRISMA statement.

Results: The current meta-analysis was based on 18 papers that reported a HR-QoL comparison between IC and ONB using at least a validate questionnaire. Pooled effect sizes of combined QoL outcomes for IC versus ONB showed a slight, but not significant, better QoL in patients with ONB (Hedges' $g = 0.150$; $p = 0.066$). Patients with ileal ONB showed a significant better QoL than those with IC (Hedges' $g = 0.278$; $p = 0.000$); in case series with more than 65% males, ONB group showed a slight significant better QoL than IC (Hedges' $g = 0.190$; $p = 0.024$). Pooled effects sizes of all EORTC-QLQ-C30 aspects showed a significant better QoL in patients with ONB (Hedges' $g = 0.400$; $p = 0.0000$).

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Conclusions: This meta-analysis of not-randomized comparative studies on the impact of different types of urinary diversions on HR-QoL showed demonstrated a significant advantage of ileal ONB compared to IC in terms of HR-QoL.
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Keywords: Radical cystectomy; Urinary diversion; Ileal conduit; Orthotopic neobladder; Health related quality of life; Meta-analysis

Introduction

In the literature several surgical options of urinary diversion (UD) after RC have been described, from simply ureterostomy to orthotopic neobladder reconstruction. The ideal UD after RC should be easy to prepare and easy to handle, presenting few complications, low mortality and morbidity, protecting the upper urinary tract function as much as possible. Moreover it should be well accepted by the patient, thereby ensuring the best Health related quality of life (HR-QoL) as possible.

In the past years, there has been an increasing interest on quality of life outcomes in urological malignancies, developing new specific instruments with the aim to evaluate the HR-QoL of the urological patients and the impact of a health condition on their lives.

From the available published evidence^{1–3} is unclear if one form of transposed intestinal segment surgery is superior to another in terms of HR-QoL. Recently Ali et al. published a systematic review comparing orthotopic neobladder (ONB) to ileal conduit (IC) urinary diversion³; these authors concluded that ONB showed a marginally better quality of life scores compared to IC diversion especially when considering younger and fitter patients.³ The reason underlying the lack of significant differences between the different urinary diversions is multifaceted. One cause is the shortage of using validated tools to measure HR-QoL.

The aim of this study was to update the review of all relevant published studies on the comparison between ONB and IC using validated HR-QoL questionnaires.

Materials and methods

Literature search strategy

Studies were identified by searching multiple literature databases, including MEDLINE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), the Cochrane Library, PubMed. References from articles retrieved were searched manually. The “related articles” function in PubMed was also used. These databases were analyzed from the earliest report of quality of life in patients with urinary diversion in 1980 to February 2015.

The following keywords were used in all searches: “quality of life”, “urinary diversion”, “ileal conduit”, “neobladder”, “orthotopic neobladder”, “orthotopic diversion”. In the absence of randomized clinical trials, queries were limited

to both retrospective and prospective comparative full text peer-review papers published in the English language, involving human subjects who underwent IC versus ONB.

The literature search was conducted independently by 2 investigators of the research team (MAC, CD). Data extraction was recorded on customized tables; in case of disagreements between the two independent authors, a third independent authors resolved the disagreement (WA). The data items extracted were: first author, country, journal, year of publication, study design (retrospective versus prospective), setting (single center versus multi-center) number of patients, percentage of female patients, age (years), follow-up (months), percentage of patients in \leq pT2 BC, percentage of ileal ONB (IONB) within the ONB group, type of validated HR-QoL questionnaire used. Within each domain, data were further categorized into specific outcomes according to the different HR-QoL instrument used.

Statistical analyses

Data were synthesized using meta-analytic methods.⁴ The standard mean difference, or the effect size between the ONB and the IC urinary diversion, was calculated using Hedges’ *g* unbiased approach. Calculation of the effect sizes was based on means, differences in mean scores, *p* value, and simple sizes of the groups. Data were statistically pooled by the standard meta-analysis approach, meaning that studies were weighted by the inverse of the sampling variance. A test of heterogeneity was applied and the I^2 statistic computed. The I^2 statistic indicates the proportion of total variation among the effect estimates attributed to heterogeneity rather than sampling error, and has the advantage to being intrinsically independent of the number of the studies. When the test of heterogeneity was not significant ($p > 0.05$) and I^2 was less than 30 per cent,^{5,6} a fixed-effects model was adopted for evaluation of the results; otherwise, a random-effects model was used. Several characteristics within the two analyzed patients’ groups (ONB and IC) were identified and their effects on outcomes were examined. Categorical characteristics were treated as moderators and effectiveness was compared across subgroups formed by these moderators. Continuous characteristics were examined as covariates using random-effects (method of moments) meta-regression. We also assessed publication bias using the Egger’s *t* test and funnel plots with significance values based on 1-tailed *p* values.^{5,6} Comprehensive Meta-Analysis V.2[®] software (BIOSTAT,

Inc. Comprehensive Meta-Analysis V.2 Software [computer program]. Version V.2. Englewood, NJ: BIostat, Inc; 2009) was used for statistical analyses. Statistics reported in this meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁷ Based on conventional standards, effect sizes of *g* equal to 0.20, 0.50, and 0.80 were considered small, medium, and large, respectively.⁸

Results

Systematic review

Initial queries identified a total of 236 articles from all databases and search methods. Comparison of the retrieved titles identified 48 studies that were duplicates, thus leaving 188 abstracts for further evaluation (Fig. 1).

The literature search identified 22 papers^{1,9–29} that reported a HR-QoL comparison between IC and ONB using at least a validate questionnaire that were included in the final systematic review; the current meta-analysis was based on data extracted from 18 of them. Table 1 shows all details from the studies included in the systematic review and in the meta-analysis.

Table 2 shows all different validated HR-QoL tools used in the retrieved articles for systematic review and meta-analysis.

Meta-analysis

From all comparative papers included in the meta-analysis, 4 were from United States (US),^{11,16,20,25} 4 from Japan,^{12,15,19,21} 3 from Italy,^{22,23,27} 1 from Austria,¹³ 1 from Canada,²⁸ 1 from Germany,²⁶ 1 from Greece,¹⁷ 1

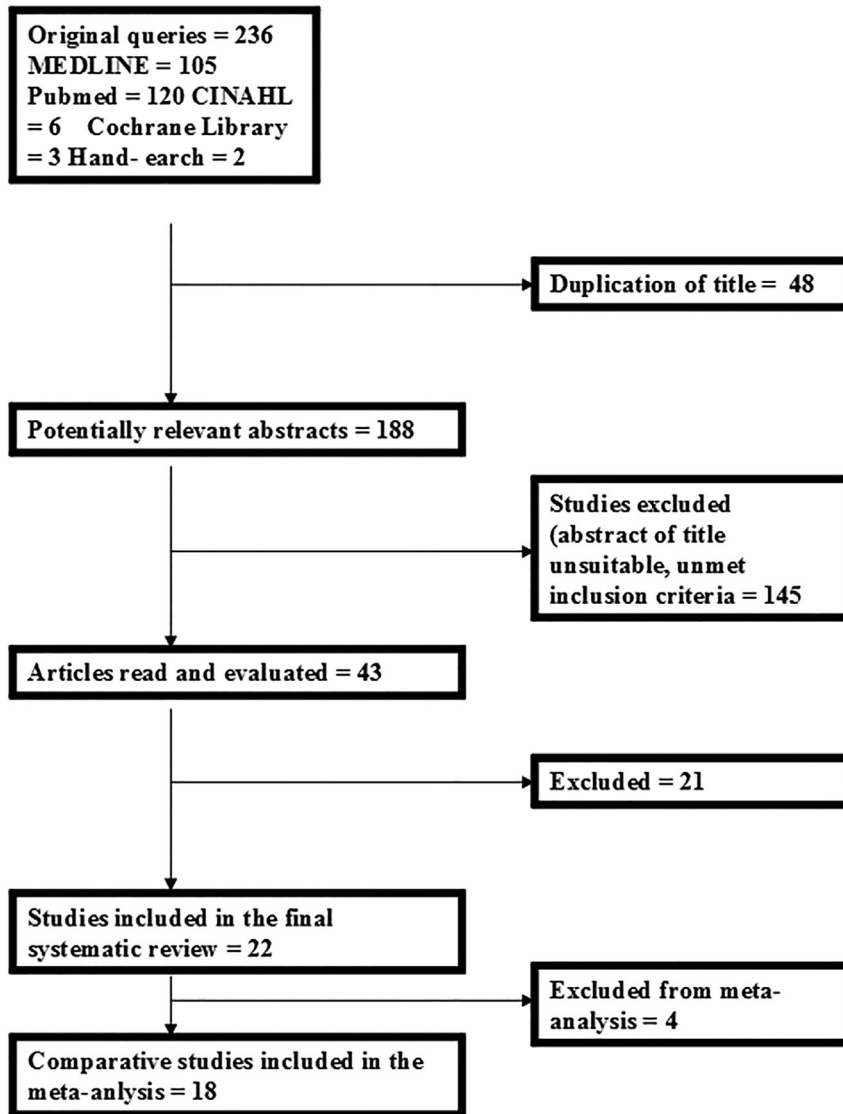


Figure 1. Articles identified and evaluated during the review process.

Table 1
Details of the papers included in the systematic review and meta-analysis.

1st author	Year	Country	Journal	Type of study	Setting	HR-QoL questionnaires used	Total no of patients (IC/ONB)	% Of ileal NB within ONB	% Of female pts	% pT2	Age (years)	Follow-up (months)	Conclusions	Included in meta-analysis
Mansson ⁹	1997	Sweden	BJU	Prospective	Single center	SIP; MCT	33 (17/16)	NA	NA	NA	IC = 71 (mean at surgery); ONB = 65 (mean at surgery)	4–9 weeks after surgery	Not significant lower SIP scores for patients with IC for both total (p = 0.08) and psychosocial dimension (p = 0.06).	Yes
Kitamura ¹⁰	1999	Japan	Int J Urol	Retrospective	Single center	EORTC-QOL-C30	57 (36/21)	100	27.27	NA	IC = 66 (median at surgery) and 73 (median at survey); ONB = 58 (median at surgery) and 59 (median at survey)	IC = 63.7 (median); ONB = 43.3 (median)	In the IC group patients received an ileal or colon conduit. The IC patients had changes the way of bathing and used public baths less frequently (p < 0.0001). Score about loss of sexual desire was higher in IC patients (p < 0.05). ONB patients felt a stronger desire to void like before the operation (p < 0.005). Items about satisfaction with the treatment were not significantly different. In each group almost every patient accepted and adapted the present status of general QoL.	No: see conclusions; data reported unsuitable for meta-analysis
McGuire ¹¹	2000	US	Ann Surg Oncol	Retrospective	Single center	SF-36	76 (38/38)	100	0	NA	IC = 70 (median at survey; range 48–83); ONB = 64 (median at survey; range 37–78)	IC = 42 (median; range 4–90); ONB = 48 (median; range 9–103)	Patients with IC had significantly decreased mental quality of life (p = 0.01) than population-based norm.	Yes

Fujisawa ¹²	2000	Japan	Urology	Retrospective	Single center	SF-36	56 (20/36)	2.78	32.14	NA	IC = 70.6 (mean at surgery \pm 7.5 SD) and 73.5 (mean at survey \pm 8.9 SD); ONB = 61.4 (mean at surgery \pm 8.2 SD) and 63.5 (mean at survey \pm 7.9 SD)	IC = 44.3 (mean \pm 32.8 SD); ONB = 31.3 (mean \pm 33.1 SD)	No significant difference between the two groups.	Yes
Hobish ¹³	2000	Austria	World J Urol	Retrospective	Single center	EORTC-QOL-C30	102 (33/69)	100	26.47	NA	IC = 65.1 (mean at surgery); ONB = 60.7 (mean at surgery)	IC = 55.5 (mean); ONB = 28.3 (mean)	QoL is preserved to a higher degree after ONB than after IC diversion.	Yes
Kulaksizogly ¹⁴	2002	Turkey	Eur Urol	Retrospective	Single center	EORTC-QOL-C30; BDI	64 (49/15)	100	5.88	NA	Population = 5.4 (mean age at surgery \pm 8 SD; range 38–70)	Population = 27.7 (mean \pm 7.3 SD; range 12–46)	Not comparative evaluation between IC and ONB (comparison between patients with or without preop. depression).	No: data unsuitable for meta-analysis
Hara ¹⁵	2002	Japan	BJU Int	Retrospective	Single center	SF-36	85 (37/48)	54.17	0	NA	IC = 58.5 (mean at surgery \pm 12.5 SD); ONB = 60.85 (mean age at surgery \pm 8.5 SD)	IC = 130.9 (mean \pm 101.6 SD); ONB = 43.8 (\pm 34.1)	No significant difference in any score between IC and ONB	Yes
Dutta ¹⁶	2002	US	J Urol	Retrospective	Single center	SF-36; FACT-G	72 (23/49)	100	19	74	Population = 67.1 (mean age at survey \pm 9.7 SD)	Population = 32.28 (mean \pm 17.76 SD)	Patients with ONB had marginal QoL advantage (p = 0.06)	Yes
Protogerou ¹⁷	2004	Greece	BJU Int	Retrospective	Single center	EORTC-QOL-C30	108 (58/50)	100	16.67	NA	IC = 65 (mean at surgery; range 54–72); ONB = 61 (mean at surgery; range 48–67)	IC = 28 (mean; range 14–72); ONB = 26 (mean; range 16–70)	No significant differences in the QoL	Yes
Allareddy ¹⁸	2006	US	Cancer	Retrospective	Multi-center	FACT-BL	82 (56/26)	NA	25.6	82.93	Population = 64.4 (mean at surgery) and 65 (median at surgery)	Population = 100.6 (mean) and 95 (median)	Within the 26 patients having continent diversion, the authors considered both continent cutaneous diversion and neobladder. There were no significant differences in QoL scores between continent and IC diversion groups.	No: impossible to distinguish between continent diversion and ONB

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Table 1 (continued)

1st author	Year	Country	Journal	Type of study	Setting	HR-QoL questionnaires used	Total no of patients (IC/ONB)	% Of ileal NB within ONB	% Of female pts	% pT2	Age (years)	Follow-up (months)	Conclusions	Included in meta-analysis
Kikuchi ¹⁹	2006	Japan	Jpn J Clin Oncol	Retrospective	Single center	FACT-BL	35 (20/15)	100	20.4	73.5	Population = 69.6 (mean at survey \pm 9.3 SD)	Population = 83 (mean \pm 50.2 SD; range 20–202)	No significant differences in FACT-G mean scores. Significant less trouble controlling urine in IC patients ($p = 0.018$). Significant worse QoL score regarding body image in IC group ($p = 0.036$). Significantly lower urinary function scores in ONB ($p < 0.001$).	Yes
Gilbert ²⁰	2007	US	Cancer	Retrospective	Single center	BCI	188 (66/122)	NA	18.62	87.76	IC = 73.6 (median at survey); ONB = 64.9 (median at survey); population = 69 (median at survey, range 41–89)	Population = 34.8 (median; range 2.4–117.6)	In elderly patients (aged 75 or older) no significant differences among urinary diversion subgroups in any QoL area.	Yes
Saika ²¹	2007	Japan	Acta Medica Okayama	Retrospective	Multi-center	EORTC-QOL-C30	78 (56/22)	NA	20.51	NA	IC = 80.1 (median at surgery; range 75–92); ONB = 78.5 (median at surgery; range 75–90.5)	IC = 48 (median; range 3.6–134.4); ONB = 39.6 (median; range 3.6–80.4)	No significant difference between IC and ONB groups. Patients with ONB aged 65 or older had significantly lower scores for role-physical functioning and role emotional functioning than those younger ($p < 0.05$).	Yes
Autorino ²²	2008	Italy	EJSO	Retrospective	Single center	SF-36	79 (44/35)	100	0	74.68	IC = 65.9 (mean at surgery \pm 5.9 SD); ONB = 63.5 (mean at surgery \pm 7.2 SD)	IC = 35.5 (mean \pm 14.4 SD); ONB = 28.3 (mean \pm 18.8 SD)	In elderly patients (aged 75 or older) GHS scores in ONB group were higher than in IC but the difference was not statistically significant ($p = 0.16$). All the other scores were comparable.	Yes
Sogni ²³	2008	Italy	Urology	Retrospective	Multi-center	EORTC-QOL-C30; EORTC-QOL – BLM30	34 (18/16)	NA	NA	NA	IC = 78.9 (median at surgery); ONB = 77.5 (median at surgery); population range = 75–86	Population = 42 (mean; range 12–68)	No significant difference between IC and ONB groups. Patients with ONB aged 65 or older had significantly lower scores for role-physical functioning and role emotional functioning than those younger ($p < 0.05$).	Yes

Philip ²⁴	2009	UK	Ann R Coll Surg Eng	Retrospective	Single center	SF-36	52 (24/28)	100	23.08	NA	IC = 73.5 (median at surgery; range 32–85); ONB = 65.5 (median at surgery; range 50–79)	IC = 12 (median; range 3–75); ONB = 15 (median; range 3–39)	ONB patients had not significant higher mean scores when compared to IC in all HR-QoL scales, except marginally lower scores in vitality, social functioning and bodily pain. ONB patients had significantly better physical functioning (p = 0.037) than IC patients.	Yes
Somani ¹	2009	UK	Urology	Prospective	Multi-center	EORTC-QOL-C30; SEIQoL	32 (29/3)	NA	28.12	NA	Population = 69 (mean at surgery; range 41–80)	9–12 months after surgery	No significant difference in scores between IC vs ONB. Body image did not appear to be an important consideration when patients (already counseled and consented for) are faced with making a decision to have an IC.	No: data unsuitable for meta-analysis
Hedgepeth ²⁵	2010	US	Oncology	Prospective	Single center	BCI	224 (85/139)	NA	18.88	75.11	IC = 71.09 (mean at surgery ± 8.23 SD); ONB 60.76 (mean at surgery ± 9.30 SD)	Baseline and at 1, 6, 12, 24, 48, 72, 96 months after surgery	No difference in body image scores between IC and ONB patients, with older patients having slightly better scores. Urinary function was better in IC patients (p < 0.0001), but the bother was the same (p = 0.32). Time appeared to improve function and bother scores for both (p = 0.004 and p = 0.017, respectively).	Yes
Erber ²⁶	2012	Germany	ISRN Urology	Retrospective	Single center	EORTC-QOL-C30; EORTC-QOL – BLM30	58 (24/34)	100	20.3	42.53	IC = 70 (mean at surgery; range 64–75); ONB = 62 (mean at surgery; range 56–66)	IC = 33.2 (mean ± 32.77 SD); ONB = 50.6 (mean ± 44.98 SD)	Patients with ileal ONB had significantly better GHS and QoL (p = 0.02), better physical functioning (p = 0.02), but also a higher rate of diarrhea (p = 0.004).	Yes

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Table 1 (continued)

Ist author	Year	Country	Journal	Type of study	Setting	HR-QoL questionnaires used	Total no of patients (IC/ONB)	% Of ileal NB within ONB	% Of female pts	% Of pT2	Age (years)	Follow-up (months)	Conclusions	Included in meta-analysis
Gacci ²⁷	2013	Italy	Health and Quality of Life Outcomes	Retrospective	Multi-center	EORTC-QOL-C30; EORTC-QOL – BLM30; FACT-BL	25 (16/9)	100	100	68	Population = 67.3 (mean at surgery ± 8.7 SD) and 73.1 (mean at survey ± 8.7); IC = 74.4 (mean at survey ± 8.8 SD); ONB = 71.8 (mean at survey ± 7 SD)	Population = 60.1 (mean; range 36–122)	Only female patients evaluated. No significant difference between IC and ONB subgroups.	Yes
Metcalfe ²⁸	2013	Canada	Canad J Urol	Retrospective	Multi-center	FACT-VCI	84 (53/31)	100	14.28	75	IC = 68 (mean at survey); ONB = 62 (mean at survey)	Population = 67.20 (median; range 25.2–111.6)	Type of UD was not associated with QoL after RC.	Yes
Singh ²⁹	2014	India	BJU Int	Prospective	Single center	EORTC-QOL-C30	164 (80/84)	54.76	12.8	82.93	IC = 58.7 (mean at surgery ± 8.96 SD); ONB = 56.1 (mean at surgery ± 7.26)	6, 12 and 18 months after surgery	At 6,12 and 18 months post-op., physical functioning (p < 0.001, p < 0.001, and p = 0.001, respectively), role functioning (p = 0.001, p = 0.01, and p = 0.003, respectively), social functioning (p = 0.01 for each follow-up step), and GQoL (p < 0.001, p < 0.001 and p = 0.002, respectively) were better in ONB patients. The financial burden related to BC treatment was significantly lower in ONB patients at 6, 12 and 18 months of follow-up (p = 0.05, p = 0.05 and p = 0.005, respectively).	Yes

SD = standard deviation; IC = ileal conduit diversion; ONB = orthotopic neobladder diversion.

Table 2
Different validate HR-QoL instruments used in the retrieved articles for systematic review and meta-analysis.

Instrument	Generic	Cancer-specific	Bladder cancer – specific	Brief description
BCI (Bladder Cancer Index)			X	36 item questionnaire for patients with bladder cancer and/or urinary diversion evaluating 3 domains (urinary function, bowel habits and sexual function)
BDI (Beck Depression Inventory)	X			21 question multiple choice inventory for individual aged 13 and over, with the aim to measuring the severity of depression, with items relating hopelessness, irritability, fatigue, weight loss.
EORTC-QLQ-C30		X		30 items questionnaire with 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptoms scale (fatigue, pain, and nausea/vomiting) and a global health and quality of life scale
EORTC-QLQ-BLM30			X	30 items questionnaire for patients with muscle invasive bladder cancer with additional items concerning urostomy problems, body image, use of catheters
FACT-G (Functional Assessment of Cancer Therapy – General)	X	X		27 item questionnaire evaluating 4 domains (physical social/family, emotional and functional well being)
FACT-BL (Bladder)			X	27 + 12 item questionnaire specific for patients with bladder cancer
FACT-VCI (Vanderbilt Cystectomy Index)			X	27 + 12 item questionnaire specific for patients with bladder cancer who underwent cystectomy and various urinary diversions
HADS (Hospital Anxiety and Depression Scale)	X			14 items scale with ordinal data to determine anxiety (7 items) and depression (7 items) experiencing by patients
MTC (Meta Contrast Technique)	X			Projective test measuring personality factors, especially defensive strategies
POMS (Profile of Mood Status)	X			65 items psychological rating scale using to evaluate mood states
QWB (Quality of Life Well Being Scale)	X			71 items questionnaire (20 min to complete) evaluating overall status and well being with 4 domains (physical activities, mobility, symptom/problem complexes)
SEIQoL DW (Schedule for Evaluation of Individual Quality of Life Direct Weighting)	X			Semi structured interview based instrument with 5 domains (cues) elicited by the interviewer; the patient evaluate the relative importance of each QoL with a disk
SF-36	X			36 item survey evaluating 2 major domains: physical health (physical functioning, role-physical, bodily pain and general health) and mental health (vitality, social functioning, role emotional and mental health)
SIP (Sickness Impact Profile)	X			68 item questionnaire measuring physical mental and social aspects of health status in 6 subscales: somatic autonomy, mobility control, mobility range, social behavior, emotional stability score, psychological autonomy/communication

from India,²⁹ 1 from the United Kingdom (UK),²⁴ and 1 from Sweden.⁹ Three were prospective cross-sectional studies,^{9,25,29} the remaining showed a retrospective design. Four were multi-center studies,^{21,23,27,28} all others single center settings. According to the different validated HR-QoL tool used, two utilized the BCI,^{20,25} 6 the SF-36,^{11,12,15,16,22,24} 6 the EORTC-QoL-C30,^{13,17,21,23,26,27} 3 the FACT-BL-VCI,^{19,27,28} 3 the EORTC-QoL-BLM30.^{23,26,27} Overall 1553 patients were analyzed (712 IC versus 841 ONB, with more than 85% of ileal neobladder); the majority of patients were males (more than 78%) with a population having a range age of 38 years up to 92 years and a range follow-up of 1 month up 202 months.

Pooled effect sizes of combined QoL outcomes for IC versus ONB showed a slight, but not significant, better QoL in patients with ONB [Hedges' $g = 0.150$ ($-0.010/$

0.310 95% CI); $p = 0.066$] (see Fig. 2). Fig. 3 showed the Funnel plot with Egger's t test for publication bias.

Table 3 shows the categorical moderators analyses (see Table 3). Patients with IONB showed a significant better QoL than those with IC [Hedges' $g = 0.278$ ($0.125/0.431$ 95% CI); $p = 0.000$] (see Fig. 4). Moreover in case series with more than 65% males, ONB group showed a slight significant better QoL than IC [Hedges' $g = 0.190$ ($0.025/0.356$ 95% CI); $p = 0.024$] (Table 4).

Sub-analyses by validated HR-QoL questionnaires

Sickness impact profile (SIP)

The standardized SIP questionnaire, a measure of health status initially developed in 1973 and validated with a three stage process in 1976, was revised in 1981, showing a

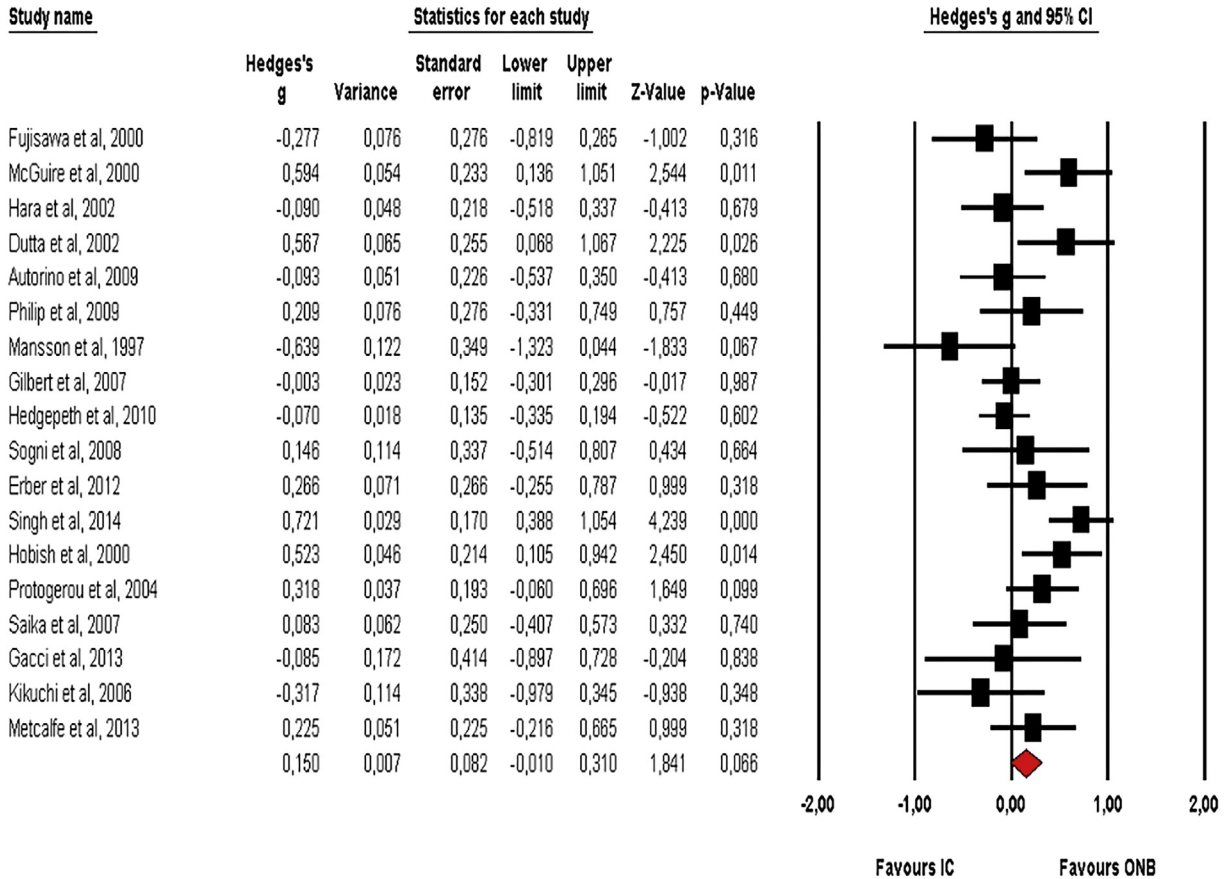


Figure 2. Forest plot of overall combined HR-QoL domains for IC versus ONB. A random-effects model was used for meta-analysis because $I^2 = 54.706\%$ and $p = 0.003$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

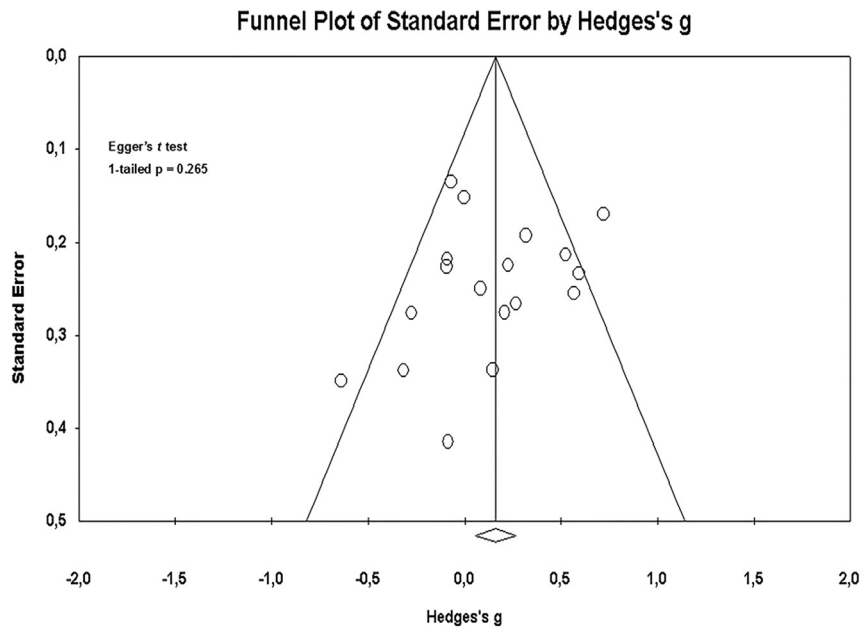


Figure 3. Funnel plot with Egger's t test for publication bias of overall combined selected papers for meta-analysis.

Table 3
Moderator analyses of combined QoL outcomes from all selected articles.

Moderator	No of papers	Effects model	Pooled effect size of Hedges' <i>g</i> (95% CI; <i>p</i> value)	<i>I</i> ² for heterogeneity (%)
Population age				
<75 years	16	Random	0.152 (−0.024/0.328; <i>p</i> = 0.090)	51.335
>75 years	2	Fixed	0.105 (−0.288/0.499); <i>p</i> = 0.600)	0
Population follow-up				
<36 months	7	Random	0.193 (−0.108/0.494; <i>p</i> = 0.208)	71.266
>36 months	11	Random	0.112 (−0.066/0.289; <i>p</i> = 0.217)	33.587
Type of study				
Prospective	3	Random	0.051 (−0.634/0.737; <i>p</i> = 0.884)	89.496
Retrospective	15	Fixed	0.160 (0.040/0.280; <i>p</i> = 0.009)	24.291
Setting				
Multi-center	4	Fixed	0.130 (−0.146/0.406; <i>p</i> = 0.355)	0
Single center	14	Random	0.154 (−0.041/0.348; <i>p</i> = 0.121)	64.861
Urologic journal				
No	8	Fixed	0.033 (−0.440/0.181; <i>p</i> = 0.660)	15.923
Yes	10	Random	0.225 (−0.017/0.466; <i>p</i> = 0.069)	61.367
Type of ONB				
Only IONB	10	Fixed	0.278 (0.125/0.431; <i>p</i> = 0.000)	19.382
NA	5	Fixed	−0.050 (−0.222/0.121; <i>p</i> = 0.564)	0
Other ONB ± IONB	3	Random	0.141 (−0.504/0.786; <i>p</i> = 0.668)	85.362
Gender				
10–35% females	12	Random	0.205 (0.019/0.391; <i>p</i> = 0.030)	56.895
All females	1	Fixed	−0.085 (−0.897/0.728; <i>p</i> = 0.838)	0
All males	3	Random	0.132 (−0.309/0.572; <i>p</i> = 0.558)	66.307
NA	2	Random	−0.241 (−1.011/0.528; <i>p</i> = 0.539)	61.862
Pathological stage				
<50%pT2	1	Fixed	0.266 (−0.255/0.787; <i>p</i> = 0.318)	0
>75%pT2	3	Random	0.208 (−0.262/0.677; <i>p</i> = 0.386)	86.606
65–75%pT2	5	Random	0.103 (−0.196/0.402; <i>p</i> = 0.499)	34.448
NA	9	Random	0.139 (−0.095/0.374; <i>p</i> = 0.245)	50.571
Publication year				
≤2005	7	Random	0.183 (−0.126/0.493; <i>p</i> = 0.246)	66.668
>2005	11	Random	0.123 (−0.061/0.308; <i>p</i> = 0.190)	46.171

The moderators highlighted in bold letters may affected significantly the results of the comparison between the groups (IN VS ONB).

test–retest reliability of 0.92 and internal consistency of 0.94.³⁰ This behaviorally based measure of health status contains 136 items, each describing a sickness-related behavioral change and grouped into 12 categories that can be scored individually or together for a total score.³⁰ The more dysfunction, the higher the SIP scores. Månsson et al.⁹ found not statistically significant lower SIP scores for patients with IC for both total (*p* = 0.08) and psychosocial dimension (*p* = 0.06).

Short form – 36 (SF-36)

SF-36 questionnaire, a tool able to measure the perception of the health status of the population, validated in several languages, is a generic HR-QoL instrument that contains 36 questions assessing eight aspects of HR-QoL, including physical functioning (PF), role-physical functioning (RP), role-emotional functioning (RE), vitality (VI), mental health (MT), social functioning (SF), bodily pain (BP) and general health (GH).³¹ These scales can also be also grouped into physical (PCS) and mental (MCS) components scores. The higher the score, the better the results.³² Overall no differences were found between IC

vs ONB groups comparing scores from all HR-QoL aspects of the SF-36 (see Figs. 5 and 6).

Bladder Cancer Index (BCI)

The BCI questionnaire is a reliable, disease-specific HR-QoL instrument developed using standard psychometric methodology at the University of Michigan; this questionnaire consists of 36 questions covering urinary, bowel, and sexual health with 2 subdomains that address function and bother separately.^{20,25} This questionnaire has been evaluated with test–retest validity, internal consistency and divergent/convergent validity, and showed a robust multidimensional HR-QoL measure. The index consists of 34 items within 3 primary domains and 2 subdomains. Higher scores correspond to better health states.

Pooled effects sizes of all BCI aspects (bowel bother and function, urinary bother and function, sexual bother and function) did not show significant difference between IC vs ONB patients [Hedges' *g* = −0.038 (−0.165/0.089 95% CI); *p* = 0.556] (see Fig. 7). However sexual function was significantly better in ONB patients [Hedges' *g* = 0.381 (0.115/0.647 95% CI); *p* = 0.005]; on the other

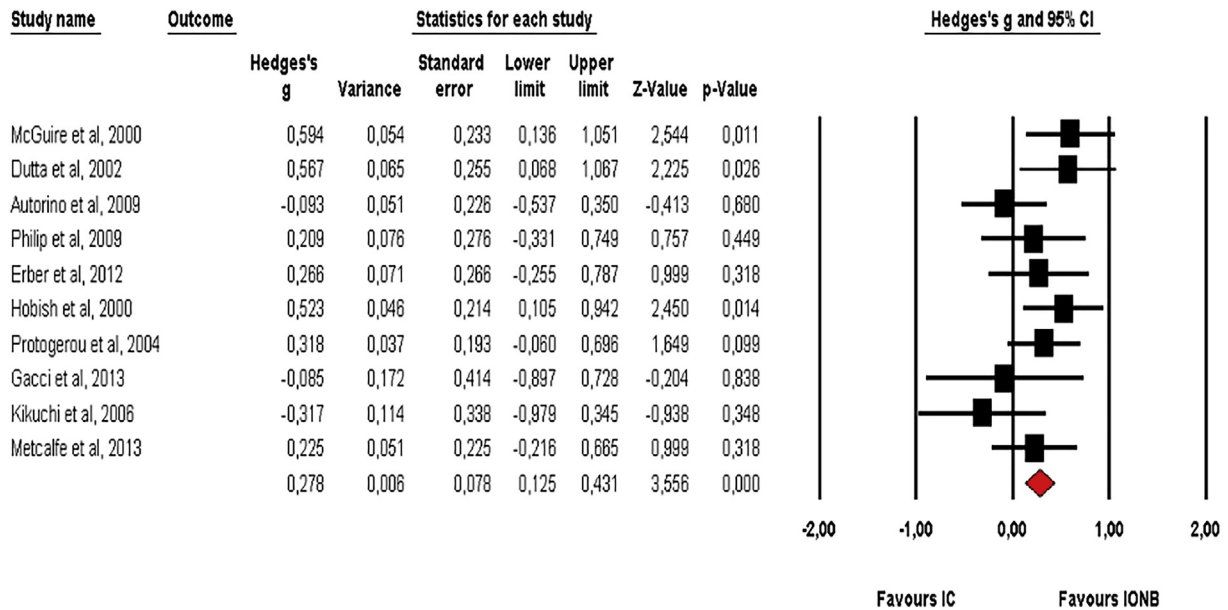


Figure 4. Forest plot of overall combined HR-QoL domains for IC versus IONB. A fixed-effects model was used for meta-analysis because $I^2 = 19.382\%$ and $p = 0.265$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

hand urinary function was significant better in IC group [Hedges' $g = -0.448$ ($-0.714/-0.181$ 95% CI); $p = 0.001$].

European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC-QLQ-C30) and EORTC-QLQ-BLM30 module

The EORTC-QLQ-C30 is a copyrighted instrument, which has been translated and validated into 81 languages. This is a 30-item questionnaire is composed of multi-item scales and single items reflecting the multidimensionality of the QoL construct.^{33,34} It comprises five functional scales covering physical (PhF), role (RF), emotional (EF), cognitive (CF) and social aspects (SF), and one scale

of global health status/QoL (GQoL). It also includes 3 multi-item symptom scales of fatigue (FA), nausea/vomiting (NV) and pain (PA), and six single items that deal with dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI) and financial difficulties (FI) caused by the disease or its treatment. For functional and overall scales higher scores represent a better outcome on QoL, whereas for symptom and single-item scales higher scores correspond to more problems and a reduced QoL.

The EORTC-QLQ-BLM30 is a module from the EORTC that specifically evaluates the impact of RC and reconstructive surgery in terms of HR-QoL in patients with muscle invasive bladder cancer. This questionnaire

Table 4
Analyses of each aspect of QoL assessed by the EORTC-QLQ-C30.

QoL-C30	No of papers	Effects model	Pooled effect size of Hedges' g (95% CI; p value)	I^2 for heterogeneity (%)
AP	7	Random	0.085 (-0.160/0.329; $p = 0.497$)	47.049
CF	6	Fixed	0.212 (0.039/0.384; $p = 0.016$)	0
CO	6	Fixed	0.257 (0.085/0.430; $p = 0.003$)	0
DI	7	Random	0.025 (-0.251/0.301; $p = 0.858$)	58.145
DY	6	Fixed	0.162 (-0.010/0.334; $p = 0.065$)	0
EF	6	Fixed	0.266 (0.094/0.439; $p = 0.002$)	29.960
FA	7	Random	0.173 (-0.095/0.442; $p = 0.206$)	55.530
FI	6	Random	0.505 (-0.121/1.132; $p = 0.114$)	91.355
GQoL	6	Random	0.712 (0.061/1.363; $p = 0.032$)	91.713
NV	6	Fixed	0.195 (0.023/0.367; $p = 0.026$)	0
PA	6	Fixed	0.147 (-0.025/0.319; $p = 0.093$)	0
PhF	7	Random	0.797 (0.066/1.529; $p = 0.033$)	93.416
RF	6	Random	0.660 (-0.037/1.357; $p = 0.064$)	92.800
SF	6	Random	0.562 (-0.055/1.179; $p = 0.074$)	91.012
SL	6	Fixed	0.286 (0.114/0.459; $p = 0.001$)	27.406

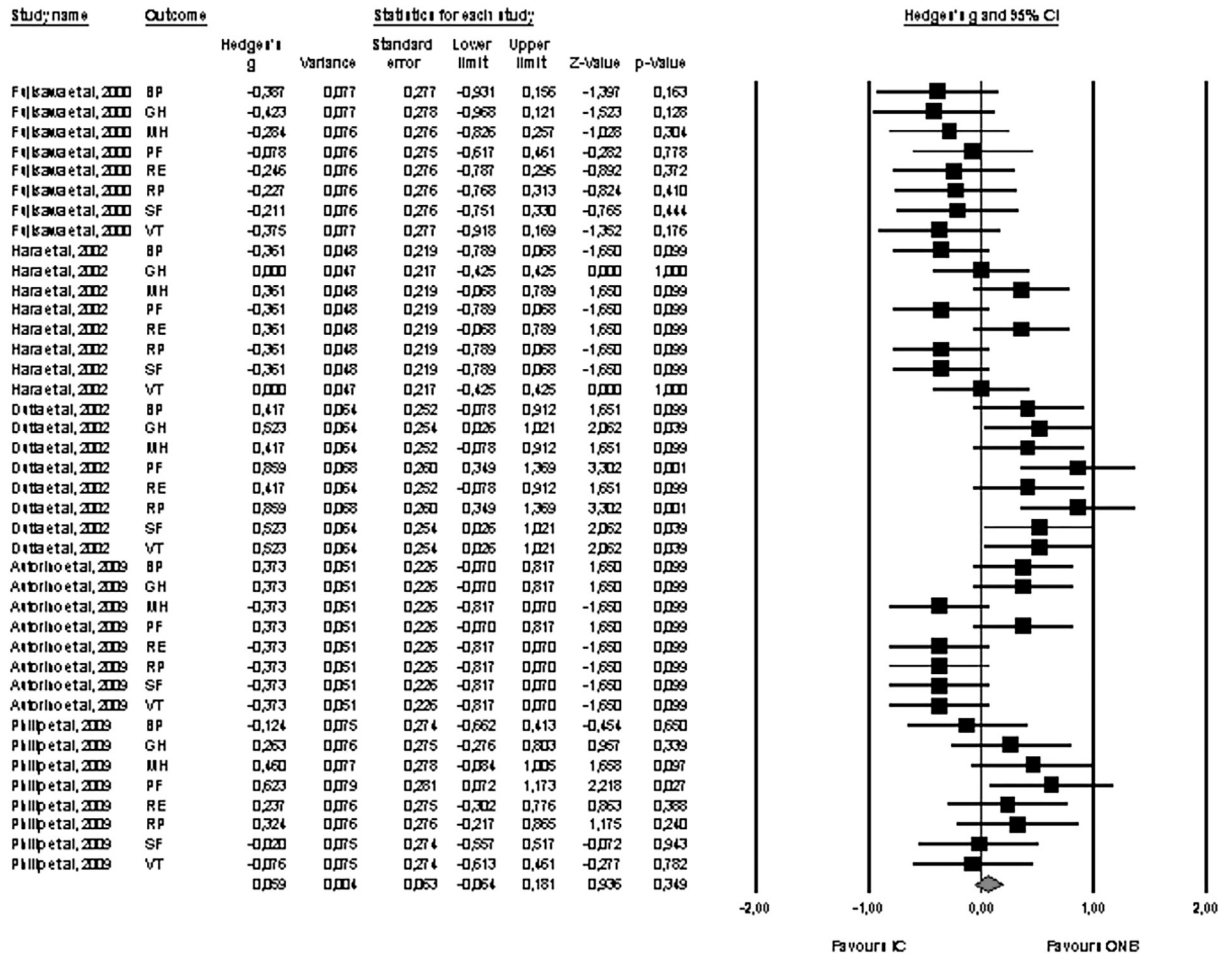


Figure 5. Forest plot of pooled effect sizes of the 8 aspects of the SF-36. A random-effects model was used for meta-analysis because $I^2 = 60.830\%$ and $p = 0.000$. Standard mean difference estimates for individual papers, calculated using Hedges' g, are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

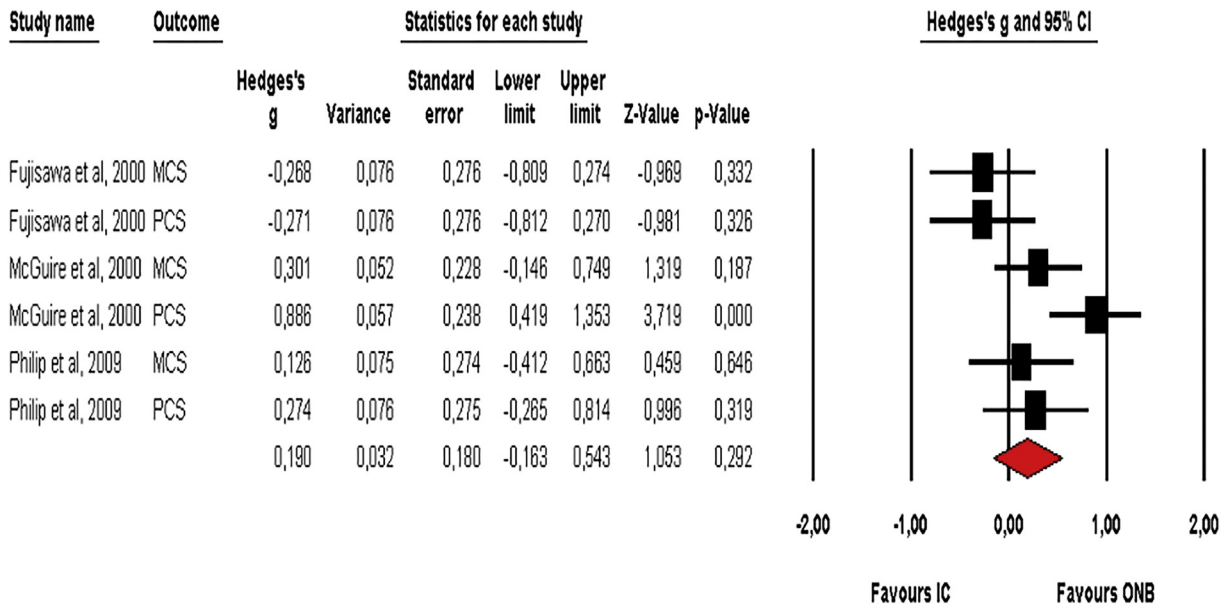


Figure 6. Forest plot of pooled effect sizes of outcomes from SF-36, analyzing physical (PCS) and mental (MCS) components scores. A random-effects model was used for meta-analysis because $I^2 = 65.220\%$ and $p = 0.013$. Standard mean difference estimates for individual papers, calculated using Hedges' g, are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

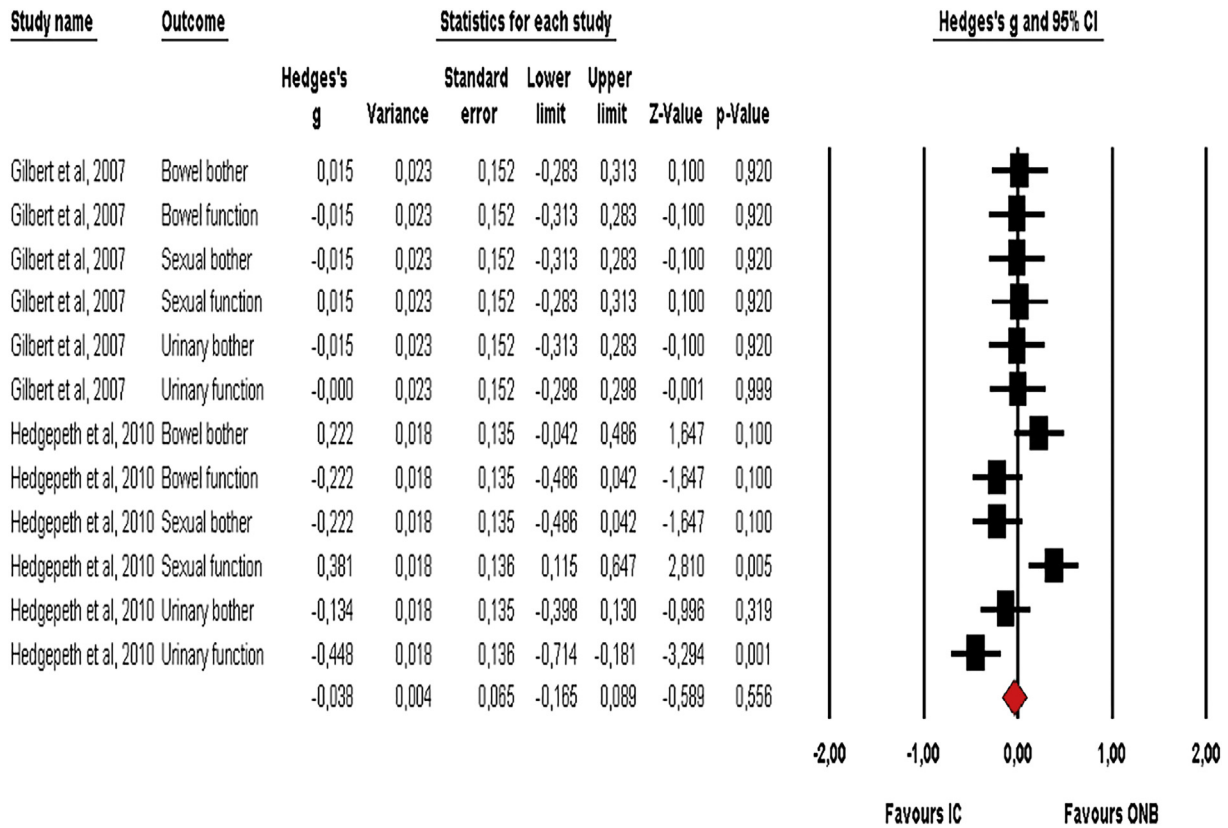


Figure 7. Forest plot of pooled effect sizes of all aspects from BCI. A random-effects model was used for meta-analysis because $I^2 = 59.203\%$ and $p = 0.005$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

has not been validated, but has completed the Phase 3 of the module development. For the symptoms/single items, a higher score means a higher level of symptoms/problems.

Pooled effects sizes of all EORTC-QLQ-C30 aspects showed a significant better QoL in patients with ONB [Hedges' $g = 0.400$ (0.227/0.573 95% CI); $p = 0.000$] (see Fig. 8). Analyzing each aspect of EORTC-QLQ-C30,

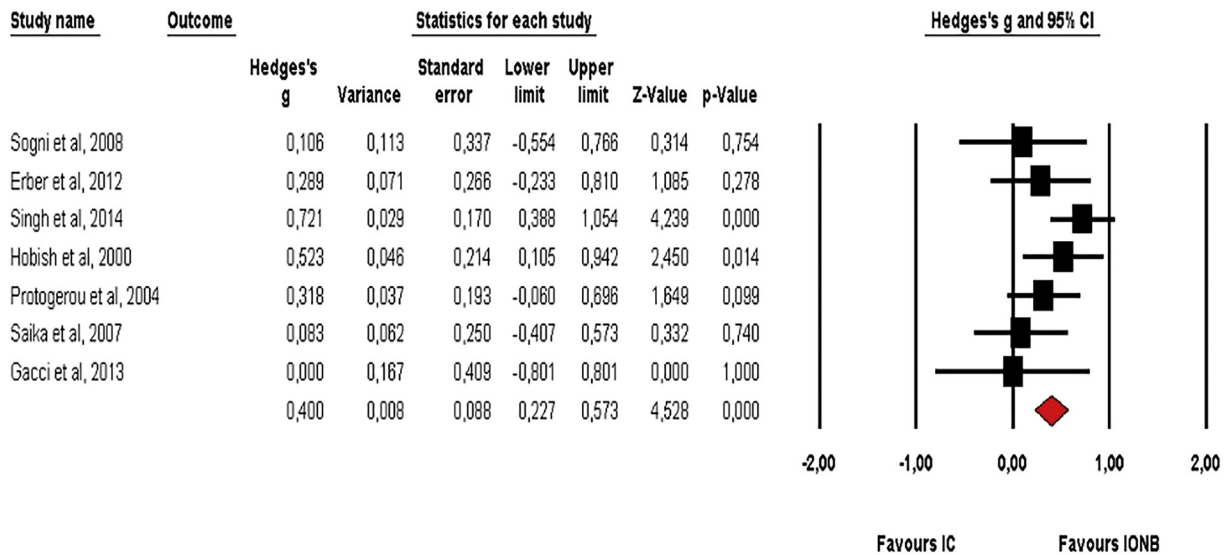


Figure 8. Forest plot of pooled effect sizes of all combined aspects from EORTC-QLQ-C30. A fixed-effects model was used for meta-analysis because $I^2 = 20.846\%$ and $p = 0.271$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

cognitive functioning (CF) [Hedges' $g = 0.212$ (0.039/0.384 95% CI); $p = 0.016$], emotional functioning (EF) [Hedges' $g = 0.266$ (0.094/0.439 95% CI); $p = 0.002$], physical functioning (PhF) [Hedges' $g = 0.797$ (0.066/1.529 95% CI); $p = 0.033$], and global health status/quality of life (GQoL) [Hedges' $g = 0.712$ (0.061/1.363 95% CI); $p = 0.032$], were significantly better in patients with ONB. Moreover in ONB group less constipation (CO) [Hedges' $g = 0.257$ (0.085/0.430 95% CI); $p = 0.003$], nausea and vomiting (NV) [Hedges' $g = 0.195$ (0.023/0.367 95% CI); $p = 0.026$], and sleep disturbance (SL) [Hedges' $g = 0.286$ (0.114/0.459 95% CI); $p = 0.001$], were observed.

Pooled effect sizes of QLQ-BLM30 aspects showed an overall significantly less level of symptoms/problems in patients with ONB [Hedges' $g = 0.259$ (0.033/0.86 95% CI); $p = 0.025$] (see Fig. 9), mainly due to better future perspectives [Hedges' $g = 0.448$ (0.037/0.859 95% CI); $p = 0.033$].

Functional Assessment of Cancer Therapy – General – Bladder – Vanderbilt Cystectomy Index (FACT-G, FACT-BL, FACT-VCI)

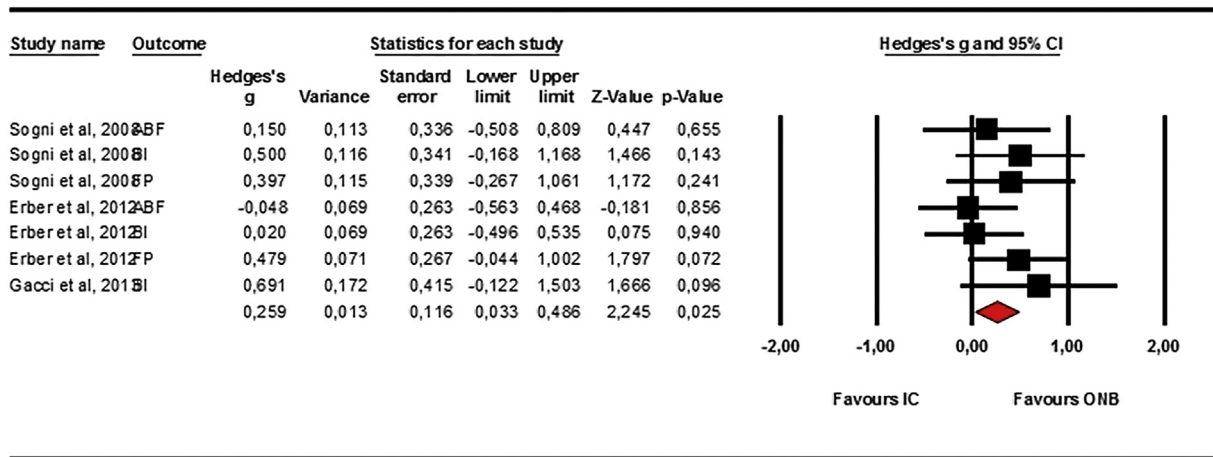
The FACT-BL is an assessment tool evaluating patients' bladder cancer specific HR-QoL.³⁵ It includes physical (PWB), social/family (SWB), emotional (EWB), and functional (FWB) well being (these domains together constitute the FACT-G) that are relevant to all cancer patients. It also includes a subscale labeled "additional concerns" that is comprised of items relevant to patients treated with RC and urinary diversion. The survey is composed of 39 questions. A total of 17 additional questions were added to the FACT-G to create the Vanderbilt Cystectomy Index (FACT-VCI).³⁵ EWB and PWB lower scores match to higher HR-QoL; high SWB and FWB scores indicate a high level of

HR-QoL. Pooled effect sizes of the FACT-G domains did not demonstrate any association between type of urinary diversion (IC vs ONB) and QoL [Hedges' $g = -0.131$ (-0.426/0.164 95% CI); $p = 0.385$] (see Fig. 10).

Discussion

The current meta-analysis examined 18 comparative studies [three prospective^{9,25,29} and fifteen retrospective^{11–13,15–17,19–24,26–28}] addressing the impact of different types of UD on HR-QoL with validated questionnaire, except for EORTC-QLQ-BLM30 questionnaire, that has not been validated but has completed the Phase 3 of the module development.

The types of UD evaluated were IC and ONB. The results of the present analysis confirm a marginally, but not significant, better QoL scores of ONB compared to IC.³ A possible reason of the worse results in the studies addressing on generic ONB could be the high heterogeneity of the studies' populations. Running the one study removed analysis, omitting 4 studies^{9,12,19,25} the pooled effect sizes became significant in advantage of the ONB subgroup. Moreover, excluding the two papers in whom a case series could be an updating of others previously published,^{12,15} the pooled analysis became in favor of ONB (Hedges' $g = 0.190$, $p = 0.028$). Also excluding other two papers with the same team groups,^{20,25} the significance in favor of ONB was confirmed (Hedges' $g = 0.242$, $p = 0.011$). Re-including in the analysis only two of the more above mentioned papers,^{15,25} with the most updating case series, the result in favor of ONB persisted (Hedges' $g = 0.187$, $p = 0.036$). Moreover, analyzing only the studies comparing exclusively IC vs ileal ONB,^{11,13,16,17,19,22,24,26–28} the advantage of the latter patients' subgroup was significant. Unfortunately, it was not



Meta Analysis

Figure 9. Forest plot of pooled effect sizes of EORTC-QLQ-BLM30. A fixed-effects model was used for meta-analysis because $I^2 = 0\%$ and $p = 0.580$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

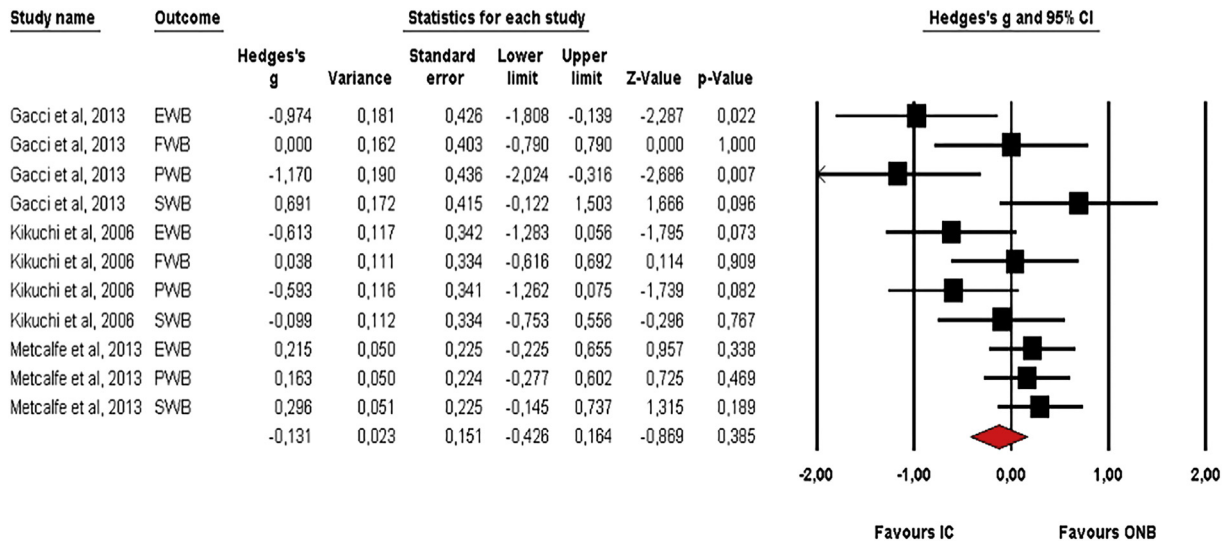


Figure 10. Forest plot of pooled effect sizes of the FACT-G domains. A random-effects model was used for meta-analysis because $I^2 = 59.211\%$ and $p = 0.006$. Standard mean difference estimates for individual papers, calculated using Hedges' g , are shown in boxes and the summary of effect as a diamond; 95% CI indicates 95% confidence interval.

possible to analyze the different orthotopic neobladder types, due to the very small number of studies discriminating between the different surgical techniques.

Another possible reason of the lack of overall significant differences between IC and ONB could be due to the generic tools of assessment often used to evaluate HR-QoL, not suitable and unreliable for this purpose and unable to specifically measure HR-QoL in this patients' population. Actually some attempts addressing to this query, in order to develop HR-QoL questionnaires specific for different UD are emerging in the most recent literature.³⁶

From the moderators analyses, gender, study design and the type of validated questionnaire used represented factors affecting the results of the pooled effect sizes analyses.

Regarding the impact of the gender on HR-QoL after RC, in our analysis, study populations with more than 65% men showed a better HR-QoL in the ONB subgroup. Actually, there are sparse information in the literature. Gacci et al.²⁷ in a series of only long-term disease-free female survivors after RC, did not find significant difference between IC and IONB subgroups; in contrast women with cutaneous ureterostomy endorsed a worse HR-QoL compared with those who underwent IC or IONB, mostly due to the worse physical and emotional perception of their body image.

In our analysis the retrospective cross-sectional design of the studies was associated with a significant better impact of ONB compared to IC. The prospective studies assessed in the present meta-analysis^{9,25,29} had a relatively short follow-up, ranging from 4 to 9 weeks after surgery⁹ up to 96 months.²⁵ Månsson et al.,⁹ having the shortest follow-up, found not significant lower SIP scores for patients with IC for both total ($p = 0.08$) and psychosocial dimension score ($p = 0.06$); Hedgepeth et al.,²⁵ at a maximum follow-up of 96 months, did not find differences

in body image scores between IC and ONB patients, with older patients having slightly better scores. However they stated that urinary function was better in IC patients ($p < 0.0001$), but the bother was the same ($p = 0.32$). An important finding was that time appeared to improve function and bother scores for both groups ($p = 0.004$ and $p = 0.017$, respectively). Actually time represents a key point in patients' satisfaction after RC, because a long coexistence with a UD may be able to change the attitude of patients towards it, becoming part of themselves, establishing a longer practice for the management of the UD, and affecting the degree of adaptation to their new life with the UD.³⁶

The pooled effects sizes from the articles using the BCI questionnaire^{20,25} in order to analyze bowel bother and function, urinary bother and function, sexual bother and function, did not show significant differences between IC vs ONB patients; however, although urinary function was significant better in IC group, sexual function was significantly better in ONB patients.

These findings are partially in contrast with the belief that continent neobladder offers better urinary function, preserving the body image of the patients. A possible explanation is that the complication related to the neobladder management, such as day/night-time incontinence, reduced bladder control and sensation, the need of continence aids and "bladder care regime", may affect quality of life in the first months after radical cystectomy, reducing urinary function of the ONB patients. Moreover, ONB patients are often younger and with a longer life expectation, and these factors become a major burden and impact of the disease on their quality of life. With regard to the sexual function, patients with ONB can maintain their original body image, ameliorating the psychological impact with their sexual lives.

The pooled effect sizes from the studies using of the EORTC-QLQ-C30, revealed a superior HR-QoL in BC patients who received an ONB compared to patients who received an IC. Reasons for these discrepant findings are unknown, but may be related to differences in patient characteristics, study design, and/or outcome assessment.²⁸

Singh et al.²⁹ documented that, using the EORTC-QLQ-C30 in a prospective cohort of patients, at 6, 12 and 18 months post operatively, physical functioning ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively), role functioning ($p = 0.001$, $p = 0.01$, and $p = 0.003$, respectively), social functioning ($p = 0.01$ for each follow-up step), and GQoL ($p < 0.001$, $p < 0.001$ and $p = 0.002$, respectively) were better in ONB patients. Moreover the financial burden related to BC treatment was significantly lower in ONB patients in all of analyzed follow-up steps ($p = 0.05$, $p = 0.05$ and $p = 0.005$, respectively). In our study cognitive functioning (CF), physical functioning (PhF), emotional functioning (EF) and global health status/QoL (GQoL) were significantly associated with a better HR-QoL in patients with ONB when compared to IC. Moreover in this latter group of patients we showed a significant worsening in constipation (CO), nausea and vomiting (NV) and sleep disturbance (SL). In contrast, analyzing papers using the FACT, we observed a slight, not significant advantage of the IC groups. However it was not possible to perform a comparison between IC and ONB using the FACT items more specific for cystectomy ad different UD, due to the lack of published data suitable for meta-analytical evaluation.

In our analysis age did not represent an independent moderator affecting patients' HR-QoL when comparing IC and ONB.

Fujisawa et al.¹² found that, when patients with a NB were divided into two groups according to age, patients 65 years old or older had significantly lower scores for RP and RE than those younger. Sogni et al.²³ found that, in elderly patients (aged 75 or older), GHS scores in ONB group were higher than in IC but the difference was not statistically significant ($p = 0.16$). All the other scores were comparable. Saika et al.²¹ did not document significant differences among urinary diversion subgroups in any QoL area in elderly patients (aged 75 or older). Hedgepeth et al.²⁵ did not find difference in body image scores between IC and ONB patients, with older patients having slightly better scores. Metcalfe et al.²⁸ documented that younger age was independently associated with increased RC-specific QoL. However, unfortunately, it is difficult to compare this finding with existing data since no study has examined age using validated HR-QoL tools.

Our study has the strength to be the first meta-analysis published on this topic. However it has also an important limitation due to the type of the analyzed studies, not-randomized, most of them retrospective. Moreover it presents other limitations. First, we did not include studies published in languages other than English, unpublished studies,

dissertations, or abstracts from conference proceedings. On the other hand, including only published materials ensures that higher quality, peer-reviewed studies were included in the meta-analysis; conversely, excluding unpublished studies is likely to introduce an upward bias into the size of the effects found, which means that calculated effect sizes are likely to be larger. Addressing this limitation, publication bias appeared in only 2 studies.^{9,29} Second, given the number of moderators and the multiple outcomes we tested, we had a high chance of incidental findings of statistically significant moderators. To account for this bias, we interpreted moderators that were significant at a 0.05 level for an overall outcome and not those that were significant for a subgroup within particular outcome. Third, each of the moderators was examined in separate analyses. We did not assess multiple moderators in one meta-regression model due to the small number of studies for each outcomes. All the above mentioned limitations have to be considered when interpreting the findings.

Conclusions

This first meta-analysis of not-randomized comparative studies on the impact of different types of urinary diversions on HR-QoL showed a significant advantage of IONB compared to IC in terms of HR-QoL. Because of the presence of heterogeneity in several aspects of the analyzed papers, in order to corroborate the arguments in favor of the IONB as the urinary diversion of choice, randomized controlled trials comparing different types of UD using validated, disease-specific HR-QoL tools are needed, whenever technically feasible and oncologically justified.

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