A systematic review and meta-analysis of the long-term outcomes of ileal conduit and orthotopic neobladder urinary diversion

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Abstract

Introduction: We aimed to perform a systematic review and meta-analysis on the long-term durability, incidence of complications, and patient satisfaction outcomes in ileal conduit (IC) and orthotopic neobladder (ONB).

Methods: A systematic electronic literature search was performed in Medline, Embase, Cochrane Library, and Scopus using MeSH and free-text search terms “Urinary diversion” AND “Ileal conduit” AND “Neobladder.” The search concluded June 19, 2018. Inclusion criteria were those patients who had a cystectomy and required urinary diversion by either IC or neobladder.

Results: In total, 32 publications met the inclusion criteria. Data were available on 46,787 patients (n=36,719 for IC and n=10,068 for ONB). Meta-analyses showed that IC urinary diversions performed less favorably than ONB in terms of re-operation rates, Clavien-Dindo complications, and mortality rates; odds ratios (ORs) and 95% confidence intervals (CIs) were 1.76 (1.24, 2.50) p<0.01, 1.16 (1.09, 1.22) p<0.01, and 6.29 (5.30, 7.48) p<0.01, respectively. IC urinary diversion performed better than ONB in relation to urinary tract infection rates and ureteric stricture rates, OR and 95% CI 0.67 (0.58, 0.77) p<0.01 and 0.70 (0.55, 0.89) p<0.01, respectively.

Conclusions: Our results show that there is no significantly increased morbidity with ONB compared to IC. Selection of either urinary diversion technique should be based on factors such as tumor stage, comorbidities, surgical experience, and patient acceptance of postoperative sequelae.
Introduction
There are many conditions which necessitate removal of the urinary bladder using cystectomy.\textsuperscript{1} The most common indication is cancer of the urinary bladder but in some cases cystectomy is indicated to treat benign disease such as interstitial cystitis.\textsuperscript{1} Cystectomy therefore requires replacement of the urinary bladder with a procedure known as urinary diversion.\textsuperscript{1} Urinary diversion is a form of urinary reconstruction and most commonly involves the use of a gastrointestinal (GI) segment to replace part or all of the function of the urinary bladder.\textsuperscript{1} An optimal bladder replacement should be able to hold large intravesical volumes whilst maintaining low pressure values in order to restore normal function and preserve the upper urinary tracts.\textsuperscript{1}

Lifelong postoperative complications are common with any type of urinary diversion.\textsuperscript{1} These can be divided into three broad groups, (i) Metabolic complications which are due to the intestinal segment’s resorptive capacity, (ii) Neuromechanical aspects which affect storage volume and diversion compliance and (iii) Technical-surgical complications which result in post-operative morbidity.\textsuperscript{1}

Ileal conduit has long been considered the gold standard for replacement of the urinary bladder. However, orthotopic neobladder has a superior cosmetic appearance and better preservation of body image.\textsuperscript{2} The aim of this systematic review and meta-analysis is to perform a robust comparison of ileal conduit and orthotopic neobladder urinary diversion and to provide practitioners with a summary of the global trends for reconstructive preferences in urinary diversion.

Methods
Search strategy
This review was planned and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).\textsuperscript{3}

A systematic electronic literature search was carried out in Medline, Embase, Cochrane Library and Scopus. Using MeSH and free text terms, the search strategy was: “Urinary diversion” AND “Ileal conduit” AND “Neobladder”. Titles and abstracts retrieved by the June 2018 search were screened independently by two authors (EB and ND), following the removal of duplicates. Where there was any uncertainty regarding inclusion, full texts were retrieved and assessed for inclusion. Excluded studies were listed with reasons given for their exclusion.

Eligibility criteria
Inclusion criteria were those patients who have had a cystectomy for any reason and required urinary diversion by either ileal conduit or orthotopic neobladder. Exclusion criteria were review articles, case reports, commentaries, letters, conference abstracts without sufficient outcome data and failure to meet the inclusion criteria.
Data extraction and outcomes
The following data were extracted from each study: author’s name, journal of publication, year of publication, country of origin, study type, total number of patients and patient demographics (age, sex, body mass index [BMI]). Information regarding the following outcomes were recorded from each eligible study. The primary outcome measures were quality of life, measures of long-term durability (including re-operation, urinary tract infections (UTI) and ureteric stricture), post-operative morbidity, post-operative mortality and length of stay. Secondary outcome measures were physiological changes including active reflux, mucous, upper tract dilatation/hydronephrosis, renal scarring, metabolic changes, urinary stones, and health economics.

Statistical analysis
Data were presented as a mean±SD for continuous variables. Differences between outcomes measured were considered significant at p<0.05 (Stata). Meta-analysis was performed with Review Manager Version 5.3 software. The Mantel-Haenszel model was used for meta-analysis of dichotomous data and the inverse variance model for meta-analysis of continuous data.

Results
Eligible studies
In total, 2907 articles were identified. Following the removal of duplicates (n=1458), 1449 articles were screened, of which 1417 were excluded as they did not meet the inclusion criteria. In total, 32 articles were included in the qualitative and quantitative analysis; see the PRISMA diagram in Figure 1 for the flow of studies through the review and the reasons for which studies were excluded.

Data were available for 46,787 patients in the studies included in this review (n=36,719 for ileal conduit and n=10,068 for orthotopic neobladders). Study characteristics are summarised in Table 1. In total there were 16 prospective case-control studies, one of which was a prospective case-control study with matched-pair analysis and 16 retrospective case-control studies.

Patient demographics (including patient age, male to female ratio and patient BMI) were reported, if available; these are outlined in Table 2 and Table 3. The mean patient age between the ileal conduit and orthotopic neobladder groups was significantly different, 69.65 ±5.84 in the ileal conduit group versus 61.07 ±4.47 in the orthotopic neobladder group, 95% Confidence Interval (CI) 8.44, 8.71, p <0.01, with patients undergoing ileal conduit urinary diversion being older overall. The mean BMI of the ileal conduit and orthotopic neobladder groups were significantly different; 25.7 ±4.6 in the ileal conduit group versus 23.7 ±3.3 in the orthotopic neobladder group 95% CI 175, 2.25, p<0.01. The sex ratio in both groups was significantly different (11:2 male:female in the ileal conduit group versus 11:1 male:female in the orthotopic neobladder group, p <0.01).
Primary outcomes

Quality of life
Patient satisfaction, general measures of health status and disease specific measures of quality of life were not reported in a standardised manner across the studies. This precludes meaningful statistical analysis. Of the 32 included publications, 5 compared quality of life in patients with either diversion type.\textsuperscript{13, 18-24, 34, 35} Using The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire,\textsuperscript{37} Navarro \textit{et al} found a better acceptance in orthotopic neobladders versus ileal conduits.\textsuperscript{13} The scale used by the authors rates overall quality of life on a 7 point scale, where 1=Very Poor and 7=Excellent.\textsuperscript{37} Sogni \textit{et al}. also used the QLQ-C30 questionnaire as well as the bladder cancer-specific module EORTC QLQ-muscle-invasive bladder cancer module 30 (BLM 30)\textsuperscript{38} and found that the quality of life reported in both groups was comparable but with a non-significant higher quality of life rating seen in the orthotopic neobladder group.\textsuperscript{34} Erber \textit{et al} also used the QLQ-C30 questionnaire and reported overall quality of life as 58±25.3 in the ileal conduit group and 72.3±19.5 in the neobladder group.\textsuperscript{24} Sherwani \textit{et al} used a simple satisfaction scale of “Very Good”, “Good”, “Poor” to compare quality of life between the two groups and reported higher ratings in the orthotopic neobladder group.\textsuperscript{18} Finally, Thulin \textit{et al} had patients rate quality of life as “high”, “moderate” or “low”.\textsuperscript{35} Of these, 68% of patients with an orthotopic neobladder reported their quality of life as “high” compared to 53% of ileal conduit recipients.\textsuperscript{35}

Measures of long-term durability
The measures of long-term durability included in this review were re-operation rates, UTI rates and ureteric stricture rates. The meta-analysis of these outcomes are detailed in Figure 2.

Of the 32 studies included in this review, 9 examined re-operation rates. The rate of re-operation was significantly greater in patients with an ileal conduit compared to patients undergoing orthotopic neobladder formation [Odds Ratio (OR) 1.76: 95% Confidence Interval (CI) 1.24, 2.50, p < 0.01]; see Figure 2A.

The incidence of UTI rates was reported in 11 studies. The incidence of UTI was significantly less in patients with an ileal conduit versus patients with an orthotopic neobladder [n = 1048/4013, 26.1% versus n = 433/1425, 30.4% respectively, OR 0.67: 95% CI 0.58, 0.77, p < 0.01]. This is reported in Figure 2B.

Ureteric stricture rates in both groups were reported in 9 publications. The incidence of the ureteric stricture was statistically less significant in patients undergoing ileal conduit urinary diversion versus patients with orthotopic neobladder, shown in Figure 2C [n = 249/3533, 7.0% versus n = 109/1241, 8.8% respectively, OR 0.70: 95% CI 0.55, 0.89, p < 0.01].

Complications
Post-operative morbidity, reported in 21 publications, was described using the Clavien-Dindo classification in 12 publications.\textsuperscript{6, 7, 10-14, 15, 19-22, 26, 28, 33, 39}
The incidence of post-operative morbidity was significantly higher in patients undergoing ileal conduit urinary diversion versus those undergoing orthotopic neobladder urinary diversion as shown in Figure 3A [n = 15659/25264, 61.9% versus n = 5102/8478, 60.1% respectively; OR 1.16 95% CI 1.09, 1.22, p < 0.01]. Subgroup analysis of patients who suffered Clavien-Dindo 1-2 (minor) complications showed that patients undergoing ileal conduits were less likely to suffer a minor complication than those undergoing orthotopic neobladder urinary diversion, as shown in Figure 3B, this was not statistically significant [n = 1016/1802 56.4% versus n = 573/1029, 55.7%; OR 0.89 95% CI 0.75, 1.06, p = 0.21]. Subgroup analysis of those who suffered Clavien-Dindo 3-5 (major) complications showed that patients with ileal conduits were significantly more likely to suffer a major complication than those with orthotopic neobladders, as shown in Figure 3C [n = 375/1802, 20.8% versus n = 184/1029, 17.9%; OR 1.25 95% CI 1.02, 1.53, p = 0.03].

Post-operative mortality was reported in 21 publications. The mortality rate in patients with ileal conduit urinary diversion is significantly higher than that of patients undergoing orthotopic neobladder [n = 3227/33656, 9.6% versus n = 142/8810, 1.6%; OR 6.29 95% CI 5.30, 7.48, p < 0.01] as demonstrated in Figure 4.

Length of stay
Seven publications reported length of stay for ileal conduit and orthotopic neobladder groups as a mean ±SD as outlined in Figure 5. Length of stay was shorter in the ileal conduit group compared to the orthotopic neobladder group 17.56±8.61 days versus 19.93±7.85 days with a mean difference of -0.74 [95% CI -1.30, -0.18, p < 0.01]. Eleven other publications reported length of stay as median and range and these are outlined in Table 4.

Secondary outcomes

Physiological changes
For the purpose of this review, physiological changes following urinary diversion were defined as: active reflux, upper tract dilation or hydronephrosis, mucous, metabolic changes urinary stones and renal scarring.

The incidence of active reflux was reported in 2 of the 32 included publications. The forest plot in Figure 6A shows that patients undergoing ileal conduit urinary diversion are at lower risk of active reflux than those undergoing orthotopic neobladder, this was not statistically significant [n = 0/147 versus n = 1/81 respectively; OR 0.17 95% CI 0.01, 4.31 p = 0.28]. The incidence of upper tract dilatation/hydronephrosis was reported in 3 of the 32 included publications. Analysis shows that patients with ileal conduit urinary diversion are more likely to have hydronephrosis than those with orthotopic neobladders, shown in Figure 6B [n = 23/568,
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4.0% versus n = 9/297, 3.0% respectively, OR 1.56 95% CI 0.67, 3.62, p = 0.30]; again, not statistically significant.

The incidence of mucous production was less in patients with ileal conduit than those with orthotopic neobladder [n = 1/135, 0.7% versus n = 3/99, 3% respectively; OR 0.58 95% CI 0.08, 3.98, p = 0.58]. This was not statistically significant. This is demonstrated in Figure 6C.

The incidence of metabolic change is less in patients with an ileal conduit versus orthotopic neobladder, shown in Figure 6D. [n = 26/280 4.5% versus n = 37/330, 11.2% respectively: OR 0.57 95% CI 0.32, 1.03, p = 0.06]. This finding was not statistically significant.

The incidence of urinary stones was lower in patients with ileal conduit urinary diversion compared to orthotopic neobladder [n= 167/4719, 3.5% versus n = 85/1319, 6.4% respectively; OR 0.49 95% CI 0.37, 0.64, p < 0.01]. This is shown in Figure 6E. This was statistically significant.

There were no data reported in any of the included studies regarding the incidence of renal scarring in patients with either urinary diversion.

Health economics

None of the studies included in this review examined or made any comment on the economic impact of either ileal conduit or orthotopic neobladder urinary diversion precluding a comparison of cost of intervention or assessment of cost-benefit relationship.

Discussion

This study is a comprehensive review comparing ileal conduit and orthotopic neobladder urinary diversions. The choice of urinary diversion has significant implications for both the patient in terms of their future health and quality of life and for the surgeon and their methods. The choice of which urinary diversion to use also depends on many factors such as surgical skill, urethral disease or patient acceptance. It is therefore imperative that a thorough comparison is made of the outcomes of IC and ONB to provide practitioners with a comprehensive summary of the data to aid surgical and patient decision making.

It demonstrates that there is an overall preference towards ileal conduit urinary diversion and a tendency for this type of diversion to be performed in older patients. It also showed a higher re-operation rate and rate of post-operative morbidity and mortality in those patients who underwent an ileal conduit urinary diversion. Orthotopic neobladder urinary diversions, however, performed worse in terms of UTI, ureteric stricture, urinary stone rates.

In this study, comparison of patient age in the two groups showed that patients IC urinary diversion were significantly older than those patients undergoing ONB diversion. It can be reliably assumed that older patients have greater comorbidities so interpretation of results may be affected by this finding. Younger patients, likely with fewer comorbidities, tend to have a ONB diversion, possibly due to the widely accepted belief that ONB has a greater risk of perioperative complications due to its technical complexity. This is therefore likely to confound data relating to post-operative complication rates in each group. The larger numbers of ileal conduits performed in these studies compared to orthotopic neobladders demonstrates the preference for
ileal conduit as the choice of urinary diversion. This is likely to be multifactorial as addressed previously, including patient preference, surgical skill and other patient factors such as age or comorbidity.

From the included publications there was a better acceptance and quality of life in patients with orthotopic neobladder diversions than those with ileal conduit. However it is worth bearing in mind that each type of urinary diversion has inherently different challenges associated with it. According to meta-analysis there is a higher rate of UTI in the orthotopic neobladder group, potentially as orthotopic neobladders often require self-catheterisation which comes with the associated risk of bacterial inoculation. Meta-analysis also demonstrated a significantly higher risk of ureteroileal stricture in patients with an orthotopic neobladder than those with an ileal conduit urinary diversion, possibly due to the use of an anti-reflux mechanism in ureterointestinal anastomosis, however an antireflux mechanism was only used for ONB in two of the publications included in this review. This highlights the importance of forming a low pressure reservoir.

The studies included for analysis in this review focused predominantly on reporting perioperative data regarding ileal conduit urinary diversion and orthotopic neobladders, revealing a dearth of information on long-term outcomes of these two types of urinary diversion. This may explain the paucity of evidence relating to the long-term complications of urinary diversion.

Meta-analysis of those publications which reported post-operative morbidity using Clavien-Dindo shows a significantly higher morbidity in ileal conduit compared to orthotopic neobladder. This is potentially explained by noting that within this systematic review, patients undergoing ileal conduit tended to be older and have higher grade tumours, which may increase the risk of death independent of diversion type. It must also be considered that minor (CD 1-2) complications may be under reported given that many of the publications included in this review were retrospective case controls.

Meta-analysis of mortality rates between ileal conduit and orthotopic neobladder urinary diversion showed a significantly increased risk of death in those patients undergoing ileal conduit diversion compared to patients with orthotopic neobladders. However, patients undergoing ileal conduit tend to be older and have higher grade tumours, which may increase the risk of death independent of diversion type.

Meta-analysis of mean ±SD of length of stay demonstrated a significantly longer length of stay in patients undergoing orthotopic neobladder. Length of stay is sometimes dependent on the practice of individual institutions and thus it cannot be assumed that orthotopic neobladder urinary diversion always results in an increased length of stay but it is still an important consideration when deciding which type of urinary diversion to use.

With the exception of stones (which were significantly more likely in orthotopic neobladder), meta-analysis of the physiological changes considered in this review showed no statistically significant results. Nonetheless, consideration of physiological changes such as hydronephrosis, vesicoureteric reflux, mucous production, metabolic changes and urinary stones
is important when deciding between ileal conduit and orthotopic neobladder, particularly in patients with pre-existing conditions.

A cost-benefit comparison is a crucial aspect of assessing any intervention and there seems to be a complete lack of any such analysis in contemporary literature. This is certainly an aspect of urinary diversion which requires further study. In countries where universal or socialised healthcare does not exist, the type of urinary diversion a patient receives may depend on their ability to pay for this type.  

The main limitation of this meta-analysis is that the studies included for analysis consist of retrospective or prospective case-control studies. Other limitations include the small sample sizes contained within most publications, limiting the generalisability of the findings of this review and the non-standard reporting of outcomes. Thirdly, some data points were presented as median and range which precluded any analysis regarding these figures. Lastly, there is the potential for significant selection bias in all publications in that those undergoing orthotopic neobladder have lower stage tumours and would therefore have better postoperative outcomes in terms of recovery and mortality rates.  

However, this is a very robust analysis involving large numbers of patients with extensive follow up, using standardised questionnaires, and involves data from multiple institutions. This analysis also includes international publications and so is representative of global trends for reconstructive preferences in urinary diversion.

Conclusions
This systematic review and meta-analysis does not support the widely held perception that orthotopic neobladder is associated with increased risk of post-operative morbidity, however the reason for this may be multifactorial. Our findings demonstrated that orthotopic neobladder was associated with a lower rate of major (Clavien-Dindo 3-5) complications than the ileal conduit. However, larger cohort studies are required to reach a definitive conclusion as to which type of diversion is superior. Our results also reinforce that the selection of which type of urinary diversion to perform should be based on careful pre-operative counselling taking into account patient factors such as tumour stage and comorbidities, surgical skill and patient acceptance of the sequelae of either type of urinary diversion.
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Comparison of ileal conduit and orthotopic neobladders

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Figures and Tables

**Fig 1.**
Comparison of ileal conduit and orthotopic neobladders

Fig 2.

A

| Study or Subgroup | Ileal Conduit Events | Total Events | Orthotopic Neobladder Events | Total Events | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|--------------|----------------------------|--------------|----------------------------|
| Abe T et al. 2014 | 71                   | 493          | 16                          | 175          | 0.67 [0.94, 2.96]           |
| Erber et al 2012  | 25                   | 146          | 12                          | 115          | 1.77 [0.85, 3.70]           |
| Gubeke BM et al. 1998 | 9                | 66           | 10                          | 66           | 0.88 [0.33, 2.34]           |
| Gore JL et al. 2010 | 21                | 1252         | 2                           | 109          | 0.91 [0.21, 3.94]           |
| Hoffer M et al. 2012 | 21                | 245          | 2                           | 63           | 2.86 [0.65, 12.53]          |
| Mom MF et al. 2014 | 3                   | 13           | 2                           | 55           | 7.95 [1.17, 53.82]          |
| Parekh DJ et al. 2000 | 7                | 81           | 4                           | 117          | 2.67 [0.76, 9.45]           |
| Popov Z et al. 2007 | 2                  | 32           | 0                           | 52           | 0.61 [0.40, 0.85]           |
| Shervani A et al. 2009 | 2               | 13           | 0                           | 4            | 1.96 [0.68, 49.26]          |

Total (95% CI) 2341
Total events 161
Heterogeneity: Ch² = 6.98, df = 6 (P = 0.34); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)

B

| Study or Subgroup | Ileal Conduit Events | Total Events | Orthotopic Neobladder Events | Total Events | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|--------------|----------------------------|--------------|----------------------------|
| Collins et al 2013 | 0                    | 43           | 4                           | 70           | 0.17 [0.01, 2.33]           |
| Gubeke BM et al. 1998 | 1                 | 86           | 2                           | 66           | 0.49 [0.04, 5.56]           |
| Hoffer M et al. 2012 | 29                | 245          | 10                          | 63           | 0.71 [0.33, 1.55]           |
| Jung et al. 2006 | 3                    | 29           | 4                           | 19           | 0.09 [0.03, 2.20]           |
| Kim SH et al. 2014 | 15                   | 161          | 12                          | 147          | 1.16 [0.52, 2.56]           |
| Maro R et al. 2018 | 10                   | 130          | 14                          | 49           | 0.21 [0.09, 0.45]           |
| Nieuwenhuijzen JA et al. 2006 | 26         | 118          | 24                          | 65           | 0.45 [0.28, 0.72]           |
| Shervani et al. 2009 | 0                  | 13           | 4                           | 4            | 0.04 [0.00, 0.24]           |
| Tan et al. 2017 | 13                   | 100          | 9                           | 94           | 0.42 [0.16, 1.16]           |
| Thuin H et al. 2010 | 73                  | 190          | 59                          | 180          | 1.26 [0.63, 2.50]           |
| van Hemelrijck et al 2013 | 376     | 2918         | 291                         | 731          | 0.50 [0.35, 0.77]           |

Total (95% CI) 4013
Total events 1548
Heterogeneity: Ch² = 26.88, df = 10 (P = 0.003); I² = 63%
Test for overall effect: Z = 3.65 (P = 0.0001)

C

| Study or Subgroup | Ileal Conduit Events | Total Events | Orthotopic Neobladder Events | Total Events | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|--------------|----------------------------|--------------|----------------------------|
| Collins et al 2013 | 1                    | 43           | 3                           | 70           | 0.53 [0.05, 5.28]           |
| Gubeke BM et al. 1998 | 3                 | 86           | 1                           | 66           | 3.13 [0.31, 30.55]          |
| Jung et al. 2006 | 1                    | 29           | 4                           | 19           | 0.15 [0.01, 1.31]           |
| Kim SH et al. 2014 | 7                    | 161          | 4                           | 147          | 1.63 [0.47, 5.67]           |
| Nieuwenhuijzen JA et al. 2006 | 13         | 118          | 5                           | 62           | 1.41 [0.48, 4.16]           |
| Popov Z et al. 2007 | 2                   | 32           | 0                           | 52           | 8.61 [0.40, 185.21]         |
| Thulin H et al. 2010 | 10                 | 98           | 4                           | 60           | 2.30 [0.74, 8.44]           |
| van Hemelrijck et al 2013 | 306     | 2918         | 87                          | 731          | 0.57 [0.44, 0.74]           |

Total (95% CI) 3533
Total events 249
Heterogeneity: Ch² = 16.22, df = 8 (P = 0.04); I² = 51%
Test for overall effect: Z = 2.93 (P = 0.003)
Comparison of ileal conduit and orthotopic neobladders

Fig 3.

### A

| Study or Subgroup | Ileal Conduit | Orthotopic Neobladder | Odds Ratio M-H Fixed 95% CI | Odds Ratio M-H Fixed 95% CI |
|-------------------|---------------|-----------------------|--------------------------|--------------------------|
| Abe et al. 2014   | 193 (932)     | 423 (1,294)           | 1.87 [0.56, 4.49]        | Not estimable             |
| Abuzarqash OM et al. 2014 | 14 (30) | 12 (24)                | 0.88 [0.39, 2.02]        | Not estimable             |
| Angulo et al. 2014 | 2 (8)        | 4 (12)                | 1.22 [0.17, 3.42]        | Not estimable             |
| Antochi et al. 2015 | 59 (57)   | 57 (85)               | 1.85 [0.79, 3.22]        | Not estimable             |
| Cubillos et al. 2015 | 46 (45)   | 53 (70)               | 1.33 [0.56, 3.01]        | Not estimable             |
| De Ruvo et al. 2013 | 281 (217) | 210 (112)             | 1.23 [0.54, 2.81]        | Not estimable             |
| De Ruvo et al. 2015 | 33 (32)     | 33 (32)               | 1.00 [0.55, 1.86]        | Not estimable             |
| Erber et al. 2012  | 191 (140)     | 80 (155)              | 0.98 [0.56, 1.77]        | Not estimable             |
| Furse et al. 2010  | 157 (156)     | 91 (109)              | Not estimable            | Not estimable             |
| Hohenfellner et al. 2014 | 49 (31)   | 23 (35)               | 1.30 [0.66, 2.56]        | Not estimable             |
| Kim et al. 2014    | 78 (151)      | 7 (147)               | 0.32 [0.08, 1.26]        | Not estimable             |
| Massel M et al. 2011 | 33 (55)  | 55 (117)              | 0.86 [0.32, 2.32]        | Not estimable             |
| Nakao et al. 2013  | 15 (17)       | 33 (37)               | 0.91 [0.19, 4.37]        | Not estimable             |
| Naavi et al. 2013  | 48 (67)       | 60 (61)               | 0.61 [0.30, 1.21]        | Not estimable             |
| Nuevenhuizen et al. 2009 | 97 (118) | 100 (100)             | 0.92 [0.53, 1.58]        | Not estimable             |
| Popko et al. 2013  | 39 (32)       | 26 (62)               | 1.76 [0.54, 1.93]        | Not estimable             |
| Ropponen et al. 2013 | 31 (171) | 171 (196)             | 1.37 [0.66, 2.83]        | Not estimable             |
| Ropponen et al. 2014 | 130 (102) | 102 (129)             | 1.23 [0.54, 2.81]        | Not estimable             |
| Shaenwasser et al. 2000 | 52 (5)     | 2 (4)                 | 0.18 [0.04, 0.87]        | Not estimable             |
| Tan et al. 2015    | 133 (130)     | 43 (34)               | Not estimable            | Not estimable             |
| van Haren et al. 2013 | 262 (298) | 72 (73)               | 1.23 [0.56, 2.66]        | Not estimable             |

Total (95% CI): 283 (264)

Total events: 156 (102)

Heterogeneity: Chisq = 54.85 df = 14 (P = 0.0000) F = 14%

Test for overall effect: Z = 3.21 (P = 0.001)

### B

| Study or Subgroup | Ileal Conduit | Orthotopic Neobladder | Odds Ratio M-H Fixed 95% CI | Odds Ratio M-H Fixed 95% CI |
|-------------------|---------------|-----------------------|--------------------------|--------------------------|
| Abe et al. 2014   | 269 (493)     | 106 (175)             | 0.66 [0.47, 0.94]        | Not estimable             |
| Abuzarqash OM et al. 2014 | 12 (24)   | 12 (24)                | 0.89 [0.60, 1.37]        | Not estimable             |
| Angulo et al. 2014 | 1 (8)        | 1 (17)                | 0.43 [0.04, 4.60]        | Not estimable             |
| Antochi et al. 2015 | 58 (45)    | 35 (55)               | 1.00 [0.49, 2.09]        | Not estimable             |
| De Ruvo et al. 2013 | 102 (217) | 102 (112)             | 1.14 [0.67, 1.95]        | Not estimable             |
| De Ruvo et al. 2015 | 21 (20)     | 26 (32)               | 0.23 [0.08, 0.73]        | Not estimable             |
| Kim et al. 2014    | 115 (139)     | 25 (55)               | 2.23 [0.89, 5.51]        | Not estimable             |
| Massel M et al. 2011 | 32 (57)  | 33 (55)               | 1.41 [0.68, 2.87]        | Not estimable             |
| Nuevenhuizen et al. 2009 | 25 (118) | 32 (62)               | 1.40 [0.62, 3.16]        | Not estimable             |
| Ropponen et al. 2013 | 244 (146) | 186 (211)             | 0.64 [0.42, 0.97]        | Not estimable             |
| Tan et al. 2017    | 47 (171)      | 21 (34)               | 0.66 [0.36, 1.22]        | Not estimable             |

Total (95% CI): 1892

Total events: 110 (12)

Heterogeneity: Chisq = 44.64 df = 11 (P = 0.0000); F = 75%

Test for overall effect: Z = 6.21 (P = 0.001)

### C

| Study or Subgroup | Ileal Conduit | Orthotopic Neobladder | Odds Ratio M-H Fixed 95% CI | Odds Ratio M-H Fixed 95% CI |
|-------------------|---------------|-----------------------|--------------------------|--------------------------|
| Abe et al. 2014   | 111 (469)     | 33 (175)              | 1.73 [0.93, 3.21]        | Not estimable             |
| Abuzarqash OM et al. 2014 | 2 (79)    | 1 (24)                | 1.34 [1.11, 1.60]        | Not estimable             |
| Angulo et al. 2014 | 1 (8)        | 1 (12)                | 1.57 [0.69, 3.59]        | Not estimable             |
| Antochi et al. 2015 | 11 (55)    | 9 (55)                | 1.28 [0.60, 2.30]        | Not estimable             |
| De Ruvo et al. 2013 | 30 (217)   | 19 (112)              | 0.94 [0.51, 1.79]        | Not estimable             |
| De Ruvo et al. 2015 | 7 (40)      | 5 (32)                | 1.11 [0.31, 4.03]        | Not estimable             |
| Kim et al. 2014    | 34 (147)      | 28 (161)              | 1.15 [0.65, 2.02]        | Not estimable             |
| Massel M et al. 2011 | 31 (129)  | 15 (55)               | 0.77 [0.33, 1.87]        | Not estimable             |
| Nuevenhuizen et al. 2009 | 19 (57)   | 10 (91)               | 0.48 [0.24, 0.97]        | Not estimable             |
| Ropponen et al. 2013 | 32 (116) | 16 (62)               | 0.47 [0.22, 0.80]        | Not estimable             |
| Tan et al. 2017    | 21 (100)      | 7 (34)                | 1.03 [0.38, 3.01]        | Not estimable             |

Total (95% CI): 1892

Total events: 151

Heterogeneity: Chisq = 15.68 df = 11 (P = 0.05); F = 30%

Test for overall effect: Z = 2.14 (P = 0.03)
Fig 4.

| Study or Subgroup | Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|--------|-------|--------|-------------------------------|
| Abe T et al. 2014. | 4      | 493   | 1      | 1.42 [0.66, 12.82]            |
| Aboumarzouk OM et al. 2014. | 2      | 39    | 1      | 1.24 [0.11, 14.50]            |
| Antonelli A et al. 2016. | 1      | 85    | 1      | 1.00 [0.76, 1.32]             |
| Collins et al 2013 | 1      | 43    | 1      | 1.54 [0.10, 26.97]            |
| Guerek BM et al. 1998 | 0      | 66    | 0      | Not estimable                 |
| Kim SH et al. 2014 | 3      | 161   | 3      | 0.91 [0.18, 4.50]             |
| Memon MF et al. 2014 | 3      | 139   | 2      | 0.56 [0.09, 3.60]             |
| Nahar J et al. 2018 | 993    | 10197 | 20     | 1.63 [2.31, 5.68]             |
| Nieuwhuizen JA et al. 2008 | 3      | 118   | 2      | 0.78 [0.13, 4.81]             |
| Pereira DJ et al. 2000 | 0      | 81    | 0      | Not estimable                 |
| Popov Z et al. 2007 | 1      | 32    | 0      | 5.00 [1.26, 12.52]            |
| Poggianni et al. 2014 | 17     | 349   | 4      | 2.23 [0.77, 7.03]             |
| Roghmann P et al. 2013 | 224    | 1586  | 50     | 1.50 [1.11, 2.05]             |
| Sogn F et al. 2008 | 3      | 53    | 2      | 1.90 [0.14, 5.70]             |
| Tan WS et al. 2017 | 3      | 100   | 1      | 1.92 [0.10, 10.15]            |
| van Herelrijk et al. 2013 | 1969 | 2316  | 54     | 2.01 [0.91, 4.52]             |
| Total (95% CI)       | 13886  | 8610  | 160.6% | 6.29 [5.30, 7.48]             |

Fig 5.

| Study or Subgroup | Mean | SD | Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|-------------------|------|----|------|----|-------|--------|----------------------------------|
| Aboumarzouk OM et al. 2014. | 9.3  | 9.4 | 2.3  | 1.3 | 39    | 24     | -0.10 [-0.99, 0.79]              |
| Guerek BM et al. 1998 | 13    | 13 | 7     | 8.75 | 66    | 66     | 4.3% [0.000, 2.70]               |
| Kim SH et al. 2014. | 19.3  | 19.8 | 16.8 | 6.25 | 101   | 101    | 2.74% [-3.190, 0.900]            |
| Nahar J et al. 2018 | 10.3  | 10.4 | 10.4 | 10.9 | 662   | 662    | 4.65% [-0.050, 1.344]            |
| Popov Z et al. 2007 | 41    | 41 | 13.5 | 1.25 | 46    | 46     | 5.0% [10.75, 7.04]               |
| Shenvani A et al. 2009 | 15    | 15 | 2.25 | 4.75 | 25    | 25     | 4.9% [4.07, 6.82]               |
| Sogn F et al. 2009 | 15    | 15 | 6.5  | 19   | 7     | 7      | 3.2% [0.900, 6.91]              |
| Total (95% CI)       | 10547 | 1031 | 106.6% | -0.34 | -0.18 | -0.34 [-0.10, 0.18]             |

Heterogeneity: Chi² = 19.71, df = 6 (P = 0.003), I² = 78%
Test for overall effect: Z = 2.60 (P = 0.009)
Comparison of ileal conduit and orthotopic neobladders

**Fig. 6**

| Study or Subgroup | Ileal Conduit Events | Ileal Conduit Total | Orthotopic Neobladder Events | Orthotopic Neobladder Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Jung J et al. 2006| 6                    | 20                  | 0                             | 19                            | Not estimable                 | 0.17 [0.01, 3.11]             |
| Nieuwenhuzen JA et al. 2008 | 6        | 118                | 1                             | 62                            | 100%                          | 0.17 [0.01, 3.11]             |
| Total (95% CI)   | 147                  | 81                  | 100%                          | 0.17 [0.01, 3.11]             |

**Note:** Heterogeneity: Not applicable
Test for overall effect: $Z = 1.07 (P = 0.28)$

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**Fig. 6**

| Study or Subgroup | Ileal Conduit Events | Ileal Conduit Total | Orthotopic Neobladder Events | Orthotopic Neobladder Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Abe T et al. 2014 | 19                   | 493                 | 4                             | 175                           | 61.1%                         | 1.71 [0.57, 5.11]             |
| Collins et al. 2013 | 1           | 43                  | 3                             | 70                            | 24.0%                         | 0.53 [0.35, 0.78]             |
| Popov et al. 2007 | 3                    | 32                  | 2                             | 32                            | 14.9%                         | 2.90 [0.41, 16.99]            |
| Total (95% CI)   | 66                   | 76                  | 100%                          | 0.17 [0.01, 3.11]             |

**Note:** Heterogeneity: Chi² = 1.16, df = 2 ($P = 0.56$); $I^2 = 0$
Test for overall effect: $Z = 1.06 (P = 0.30)$

---

**Fig. 6**

| Study or Subgroup | Ileal Conduit Events | Ileal Conduit Total | Orthotopic Neobladder Events | Orthotopic Neobladder Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Navarro et al. 2013 | 0                   | 1                   | 3                             | 31                            | 77.7%                         | 0.39 [0.01, 8.19]             |
| Nieuwenhuzen JA et al. 2008 | 1           | 112                 | 0                             | 62                            | 22.3%                         | 1.60 [0.10, 26.75]            |
| Total (95% CI)   | 135                  | 99                  | 100%                          | 0.17 [0.01, 3.11]             |

**Note:** Heterogeneity: Chi² = 0.00, df = 1 ($P = 0.97$); $I^2 = 0$
Test for overall effect: $Z = 0.55 (P = 0.58)$

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**Fig. 6**

| Study or Subgroup | Ileal Conduit Events | Ileal Conduit Total | Orthotopic Neobladder Events | Orthotopic Neobladder Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Cho et al. 2017   | 2                    | 32                  | 11                            | 62                            | 23.5%                         | 0.21 [0.04, 1.24]             |
| Navarro et al. 2013 | 4               | 17                  | 9                             | 37                            | 14.5%                         | 0.66 [0.25, 1.83]             |
| Nieuwenhuzen JA et al. 2008 | 1       | 115                 | 16                            | 82                            | 14.8%                         | 0.80 [0.10, 7.33]             |
| Popov et al. 2007 | 0                    | 81                  | 0                             | 117                           | Not estimable                 | Not estimable                 |
| Total (95% CI)   | 289                  | 130                 | 100%                          | 0.17 [0.01, 3.11]             |

**Note:** Heterogeneity: Chi² = 1.15, df = 3 ($P = 0.78$); $I^2 = 0$
Test for overall effect: $Z = 1.86 (P = 0.06)$

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**Fig. 6**

| Study or Subgroup | Ileal Conduit Events | Ileal Conduit Total | Orthotopic Neobladder Events | Orthotopic Neobladder Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|----------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Guruski et al. 1998 | 2                   | 66                  | 1                             | 65                            | 0.8%                          | 2.93 [0.18, 22.96]            |
| Ooi et al. 2010 | 2                   | 235                 | 10                            | 109                           | 10.0%                         | 0.25 [0.00, 5.06]             |
| Kim et al. 2014 | 2                   | 161                 | 1                             | 161                           | 0.6%                          | 0.91 [0.13, 6.84]             |
| Popov et al. 2007 | 0                    | 32                  | 1                             | 32                            | 0.9%                          | 0.33 [0.03, 3.34]             |
| Tan et al. 2017 | 1                    | 100                 | 0                             | 100                           | 0.6%                          | 1.94 [0.04, 81.14]            |
| Thulin et al. 2010 | 4               | 150                 | 6                             | 156                           | 4.7%                          | 0.62 [0.17, 2.23]             |
| van Herk et al. 2013 | 137   | 2918                | 68                            | 3135                          | 81.5%                         | 0.48 [0.35, 1.36]             |
| Total (95% CI)   | 171                  | 1313                | 100%                          | 0.17 [0.01, 3.11]             |

**Note:** Heterogeneity: Chi² = 4.35, df = 6 ($P = 0.63$); $I^2 = 0$
Test for overall effect: $Z = 5.13 (P < 0.0001)$
Table 1. Summary of studies included in the meta-analysis for ileal conduit and orthotopic neobladder

| Author (year)          | Origin   | Journal                          | Type of study | Level of evidence | IC (N) | ONB (N) |
|------------------------|----------|----------------------------------|---------------|-------------------|--------|---------|
| Abe et al, 2014        | Japan    | *Int J Urol*                      | RCC           | 3b                | 493    | 175     |
| Aboumarzouk et al, 2014| Poland   | *Cent European J Urol*           | PCC           | 3b                | 39     | 24      |
| Angulo et al, 2014     | Spain    | *Urology*                        | PCC           | 3b                | 8      | 12      |
| Antonelli et al, 2016  | Italy    | *Clin Genitourin Cancer*         | PCC           | 3b                | 85     | 85      |
| Belotti et al, 2012    | Italy    | *Anticancer Research*            | PCC           | 3b                | 223    | 111     |
| Cho et al, 2017        | Korea    | *Renal Failure*                  | RCC           | 3b                | 33     | 62      |
| Collins et al, 2013    | Sweden   | *Eur Urol*                       | PCC           | 3b                | 43     | 70      |
| De Nunzio et al, 2013  | Italy    | *Eur J Surg Oncol*               | PCC           | 3b                | 217    | 112     |
| Decaestecker et al, 2016| Belgium | *European Urology, Supplements*  | PCC           | 3b                | 40     | 32      |
| Erber et al, 2012      | Germany  | *IRSN Urol*                      | RCC           | 3b                | 23     | 34      |
| Gburek et al, 1998     | USA      | *Journal of Urology*             | RCC           | 3b                | 66     | 66      |
| Gore et al, 2010       | USA      | *Journal of Urology*             | RCC           | 3b                | 1252   | 109     |
| Hofer et al, 2012      | USA      | *Journal of Urology*             | PCC           | 3b                | 245    | 63      |
| Jung et al, 2006       | Korea    | *Korean Journal of Urology*      | PCC           | 3b                | 29     | 19      |
| Kim et al, 2014        | Korea    | *Jpn J Clin Oncol*               | RCC           | 3b                | 161    | 147     |
| Mano et al, 2018       | Israel   | *Urology*                        | RCC           | 3b                | 130    | 49      |
| Monn et al, 2014       | USA      | *Urologic Oncology: Seminars and Original Investigations* | RCC | 3b | 139 | 55 |
| Nahar et al, 2018      | USA      | *Journal of Urology*             | RCC           | 3b                | 10197  | 692     |
| Navarro et al, 2008    | Chile    | *Urology*                        | PCC           | 3b                | 17     | 37      |
| Nazmy et al, 2013      | USA      | *Journal of Urology*             | PCC           | 3b                | 67     | 91      |
| Nieuwenhuijzen et al, 2008| The Netherlands | *Eur Urol*                  | PCC           | 3b                | 118    | 62      |
Comparison of ileal conduit and orthotopic neobladders

| Authors              | Country                  | Journal                        | Study Type | Year | USA | PCC | IC | ONB |
|----------------------|--------------------------|--------------------------------|------------|------|-----|-----|----|-----|
| Parekh et al, 2000   | USA                      | Urology                        | RCC        | 3b   | 81  | 117 |
| Popov et al, 2007    | Republic of Macedonia    | Acta chirurgica jugoslavica    | RCC        | 3b   | 32  | 52  |
| Prcic et al, 2017    | Bosnia and Herzegovina   | Med Arch                       | PCC        | 3b   | 66  | 60  |
| Roghmann et al, 2013 | USA                      | Can Urol Assoc J               | RCC        | 3b   | 18782 | 6282 |
| Roghmann et al, 2014 | Germany                  | Int J Urol                     | RCC        | 3b   | 349 | 186 |
| Roghmann et al, 2017 | Germany                  | Journal of Urology             | PCC        | 3b   | 510 | 294 |
| Sherwani et al, 2009 | India                    | Int J Health Sci (Qassim)      | PCC        | 3b   | 13  | 4   |
| Sogni et al, 2008    | Italy                    | Urology                        | RCC        | 3b   | 53  | 32  |
| Tan et al, 2017      | United Kingdom           | Eur Urol Focus                 | PCC        | 3b   | 100 | 34  |
| Thulin et al, 2010   | Sweden                   | BJU Int                        | RCC        | 3b   | 190 | 180 |
| van Hemelrijk et al, 2013 | Sweden              | BJU Int                        | RCC        | 3b   | 2918 | 720  |

IC: ileal conduit; ONB: orthotopic neobladder; PCC: prospective case-control; RCC: retrospective case-control.
Comparison of ileal conduit and orthotopic neobladders

Table 2. Patient demographics from papers where age was reported as a mean ± standard deviation

| Author (year)          | Age (conduit) | Age (neobladder) | Male/female (conduit) | Male/female (neobladder) | BMI (conduit) | BMI (neobladder) |
|------------------------|---------------|------------------|-----------------------|--------------------------|---------------|------------------|
| Aboumarzouk et al, 2014 | 60±7.11       | 57±8.68          | 34/5                  | 24/0                     | 27.2±2.3      | 27.96±2          |
| Antonelli A et al 2016  | 63±8.8        | 63.5±6.7         | 69/16                 | 72/13                    | NR            | NR               |
| Belotti et al, 2012    | 70.4±8.1      | 60.6±0.9         | 183/34                | 90/21                    | 26.3±4.3      | 26.3±3.6         |
| Cho et al, 2017        | 69.5±8.1      | 64.5±8.6         | 23/10                 | 52/10                    | NR            | NR               |
| Collins et al, 2013    | 69.9±6.7      | 59.8±9.0         | 31/11                 | 62/8                     | 24.8±3.1      | 26.1±3.4         |
| De Nunzio et al, 2013  | 71±9.75*      | 63±0.25*         | NR                    | NR                       | 26.4±6*       | 25±3.25*         |
| Decaestecker et al, 2016| 71±1.5*       | 63±1.25*         | 29/11                 | 27/5                     | 26±4.25*      | 26±3.75*         |
| Gburek B et al, 1998   | 69±11.75*     | 62±12.75*        | 66/0                  | 62/4                     | NR            | NR               |
| Hofer et al, 2012      | 69.7±3.75*    | 59.7±15          | NR                    | NR                       | NR            | NR               |
| Jung et al, 2006       | 65.6±9.9      | 60.8±8.3         | NR                    | NR                       | NR            | NR               |
| Kim et al, 2014        | 67.1±8.9      | 59.4±9.4         | 115/32                | 156/5                    | 23.6±3.3      | 24±3.1           |
| Monn et al, 2014       | 72.6±10       | 59.6±9           | 107/32                | 49/6                     | NR            | NR               |
| Nahar et al, 2018      | 68.8±10.1     | 62.8±10          | 8835/1362             | 663/29                   | NR            | NR               |
| Parekh et al, 2000     | 68±12.75*     | 60±13.5*         | 48/33                 | 97/20                    | NR            | NR               |
| Roghmann et al, 2013   | 69.6          | 60.8             | 81/19                 | 91/9                     | NR            | NR               |
| Sherwani et al, 2009   | 59            | 53.3             | NR                    | NR                       | NR            | NR               |
| Thulin et al, 2010     | 70.1          | 64.3             | 134/56                | 165/15                   | NR            | NR               |

*Estimated standard deviation based on the Range Rule of Thumb. BMI: body mass index; NR: not reported.
Table 3. Patient demographics from papers where age was reported as a median and range

| Author (year)         | Age (conduit) | Age (neobladder) | Male/female (conduit) | Male/female (neobladder) | BMI (conduit) | BMI (neobladder) |
|-----------------------|---------------|------------------|-----------------------|--------------------------|--------------|-----------------|
| Abe et al, 2014       | 70 (37–89)    | 63 (25–86)       | 364/129               | 164/11                   | 23 (14.6–35.1)| 23.3 (16–31.5)  |
| Angulo et al, 2014    | 74.5 (70–82.2)| 66 (61.5–75)     | 5/3                   | 12/0                     | 27.7 (23.2–31.8) | 27.3 (25.5–28.5) |
| Erber et al, 2012     | 70 (64–75)    | 62 (56–66)       | 98/48                 | 110/5                    | NR           | NR              |
| Mano et al, 2018      | 72 (65–78)    | 60 (53–65)       | 112/18                | NR                       | NR           | NR              |
| Nieuwenhuijzen et al, 2008 | 70 (46–85) | 62 (32–73)       | 88/30                 | 59/3                     | NR           | NR              |
| Roghmann et al, 2014  | 72 (67–76)    | 61 (55–67)       | 256/93                | 158/28                   | 27.3 (24.6–29.8) | 26.1 (23.8–29.2) |
| Sogni et al, 2008     | 78.9 (75–88)  | 77.5 (75–82)     | NR                    | NR                       | NR           | NR              |
| Tan et al, 2017       | 67.4 (60.4–74.3) | 54.5 (48.6–61.6) | 75/25                 | 28/6                     | 27.2 (23.4–31) | 27.3 (23–28.5)  |

BMI: body mass index; NR: not reported.
Comparison of ileal conduit and orthotopic neobladders

Table 4. Studies where length of stay is reported as median and range

| Author (year)       | Ileal conduit       | Orthotopic neobladder |
|---------------------|---------------------|-----------------------|
|                     | n       | Median (range) | n       | Median (range) |
| Abe et al, 2014     | 493     | 39 (3–257)    | 175     | 42 (18–364)    |
| Angulo et al, 2014  | 8       | 9.5 (8–11)    | 12      | 8.5 (7.2–10.7) |
| Antonelli et al, 2016 | 85    | 17            | 85      | 21             |
| Belotti et al, 2012 | 223     | 20 (16–24)    | 111     | 24 (20–29)     |
| Collins et al, 2013 | 43      | 9 (6–142)     | 70      | 9 (4–78)       |
| Decaestecker et al, 2016 | 40    | 10 (5–36)    | 32      | 11 (6–39)      |
| Monn et al, 2014    | 139     | 8 (6–10)      | 55      | 7 (6–8)        |
| Nieuwenhuijzen et al, 2008 | 118 | 17 (6–53) | 62      | 15 (8–44)      |
| Parekh et al, 2000  | 81      | 8 (5–60)      | 117     | 7 (5–28)       |
| Roghmann et al, 2014 | 349   | 19 (16–24)    | 70      | 9 (17–23)      |
| Tan et al, 2017     | 100     | 10 (8–15.5)   | 34      | 11 (8.5–14)    |