

Research Report

Functional Outcomes After Robotic Radical Cystectomy with Intracorporeal Diversion: A Systematic Review

Jorge Daza, Tashzna Jones, Matthew Raven, Andrew Charap, John P. Sfakianos, Reza Mehrazin, Nihal Mohamed and Peter Wiklund*

Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA

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Abstract.

BACKGROUND: Robotic assisted radical cystectomy (RARC) is considered a safe and feasible technique in patients with bladder cancer who are candidates for curative treatment. Intracorporeal urinary diversions (ICUD) represents one step forward into moving to an utterly minimal invasive procedure with the thought that it may improve patients outcomes and time to recovery after the surgical procedure. Overall, RARC has shown to provide similar oncological outcomes as other procedures. The impact of such approach in continence and sexual function of the patients is an important part of an integral health care of this subset of patients.

OBJECTIVE: To describe the functional outcomes of RARC with ICUD across different manuscript evaluating this field.

METHODS: A systematic literature search related to functional outcomes and diversion technique in RARC with ICUD, was performed on June 2019 using PubMed

RESULTS: Out of 22 manuscripts evaluated we included 11 in our analysis. Although the functional outcomes in the studies we have included in this analysis seem to be adequate and consistent, the evidence is poor when comparing RARC with ICUD versus other approaches

CONCLUSION: We consider that studies with better designs aiming to elucidate the impact of RARC with ICUD in the quality of life of the patients may improve the quality of the outcomes and would help to draw stronger conclusions

Keywords: Urinary bladder neoplasm, urinary incontinence, cystectomy, sexual Dysfunction, robotic surgical procedure, urinary diversion

INTRODUCTION

Radical cystectomy (RC) is the standard treatment for patients with muscle invasive bladder cancer (MIBC) [1, 2]. Prior research on outcomes of open radical cystectomy (ORC) showed a significant decline in functional status and health related quality of life (HRQOL) in patients treated with ORC

(e.g., sexual barriers due to urinary odor and frequent stoma care in ileal conduit patients and to urinary leakage in neobladder patients). Recently, randomized trials comparing the performance of open radical cystectomy (ORC) and RARC have been done mostly including extracorporeal diversions (ECUD). Parekh et al. reported in a randomized trial comparing ORC and RARC with ECUD that the latter is not inferior to the open approach regarding 2 year -progression free survival (PFS) and adverse events [3]. Moreover, a randomized trial comparing oncological outcomes between open and robotic approaches with ECUD

*Correspondence to: Peter Wiklund, MD, PhD, Department of Urology, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, 6th Floor, New York, NY, 10029, USA. Fax: +1 212 9874675; E-mail: peter.wiklund@mountsinai.org.

showed that there is no significant difference in recurrence, cancer-specific survival (CSS) and overall survival (OS) [4].

The safety of these two interventions has also been evaluated. A randomized three-arm trial comparing 30 and 90-day complication rates among ORC, RARC and laparoscopic radical cystectomy with ECUD showed no significant differences in those outcomes in patients who underwent RARC compared to those who had laparoscopic or ORC [5]. Likewise, a randomized trial that compared outcomes of ORC and RARC with ECUD found no significant difference in 30 and 90-day complication rates, length of stay, pathologic outcomes and 3–6-month quality of life related outcomes [6]. The findings of that trial on QoL related outcomes were consistent with a study that compared postoperative outcomes including health-related quality of life in patients who underwent RARC versus ORC [7].

The literature is scarce when looking at RARC with intracorporeal urinary diversion (ICUD) and few prospective randomized trials are available. A randomized trial that compared perioperative and oncological outcomes between RARC with ICUD versus ORC in patients with up to 4 years of follow-up found comparable disease-free survival, CSS and OS rates between the two intervention groups, although, a significant increase in the number of perioperative complications were observed in the ORC group [8]. Ergonomic benefits for surgeons and reduced blood loss were also noted.

Data on functional outcomes of RARC with ICUD is also limited. A systematic review showed that RARC with ICUD is feasible and provides good early, intermediate and long-term oncological and functional outcomes, and acceptable complication rates. A benefit was also found in length of stay and blood loss [9]. However, the data in regards to functional outcomes came from only 4 studies that evaluated 97 patients in total. On the other hand, when evaluating the benefits of RARC with ICUD versus laparoscopic or ORC, RARC with ICUD has shown equivalent oncological outcomes along with lower complication rates, in some cases, and similar health-related quality of life [9]. Because patients' functional outcomes following RARC with ICUD can negatively affect their health-related quality of life (HRQOL), synthesizing the evidence may shed some light on short and long-term impact of RARC with ICUD. Thus, the aim of this systematic review of the literature is to evaluate the potential benefit of RARC with ICUD on functional outcomes, specifically urinary continence

and sexual function, and their association with the type of urinary diversion.

METHODS

A systematic literature search related to functional outcomes and diversion technique in RARC with ICUD, RARC with ECUD diversion and ORC was performed on June 2019 using PubMed. The keywords robotic assisted radical cystectomy, intracorporeal urinary diversion, extracorporeal urinary diversion and open radical cystectomy were used alone or in combination. The first stage of the selection process consisted of initial screening of titles and abstracts. The second phase consisted of manuscripts reading. Retrospective and prospective comparative observational studies and randomized trials were evaluated. Studies including RARC with ECUD diversion, ORC and laparoscopic radical cystectomies solely were excluded. Studies including patients treated previously with bladder sparing techniques, cystectomy due to benign conditions or case reports were also excluded. Only publications in English were accepted. Functional outcomes and urinary diversion technique were evaluated across the three surgical approaches. This systematic review followed PRISMA guidelines.

Data were extracted independently by two authors. The following variables were extracted. Erectile function, Continence, type of diversion, LUTS.

OUTCOMES MEASURES

Functional outcome for robotic radical cystectomy with intracorporeal urinary diversion technique was the main outcome.

RESULTS

Functional outcomes

Since its introduction by Beecken in 2003 [10], RARC with ICUD has gained traction throughout the world as increasing number of centers are adopting this surgical approach. While various benefits have been shown for this procedure, it has yet to be determined whether there are any functional benefits to this procedure. Functional outcomes for ileal neobladders include continence and for both ileal conduits and neobladders include sexual function. Sexual outcomes are influenced in part by the level of nerve

142 preservation during the surgery, which also depends
143 on the disease burden determined by preoperative and
144 intraoperative evaluation. While there have been con-
145 cerns of local recurrence with nerve sparing, several
146 studies have demonstrated the safety of performing a
147 nerve sparing procedure with low rates of recurrence
148 [9, 11]. A continued challenge of assessing func-
149 tional outcomes still exists due to the small number
150 of patients recruited in these studies and the largely
151 retrospective nature of the analyses, which makes it
152 difficult to ascertain differences between the varying
153 techniques.

154 *Continence*

155 A number of factors have been shown to be influen-
156 tial to successful continence after RARC with ICUD
157 including pre-treatment levels of urinary function,
158 age, level of motivation, intact innervation to urethral
159 sphincter, and urethral length [8]. There are factors
160 specific to the newly constructed urinary reservoir,
161 which affect continence such as internal pressure,
162 reservoir capacity and time since surgery, and also
163 patient voiding patterns and habits (e.g., ability to
164 master Valsalva maneuver, number of urine discharge
165 per day).

166 Continence is often assessed in the literature based
167 on the number of pads used throughout the day and
168 night or the level of wetness of each pad. Most authors
169 define full continence as either no pad use or use of
170 1 pad per day and then proceed to grade on a spec-
171 trum from mild to severe based on additional pads
172 needed. However, the definition of continence is not
173 consistent among the studies. For example, Kulkarni
174 et al. defined daytime continence as no inconti-
175 nence (0-1 pad/day), mild (1-2 pads/day), moderate
176 (3 pads/day), and severe (>3 pads/day). Nocturnal
177 continence specifically was defined as good (dry
178 with no protection), fair (dry with 1 awakening), or
179 poor (wet, leakage, and incontinence during sleep)
180 [11]. Some reports regarding functional outcomes
181 in patients after RARC with ICUD have been pub-
182 lished. Tyrantzis et al. found in one of the first RARC
183 with intracorporeal neobladder (ICBN) cohorts that
184 day and nighttime continence rates were between
185 70–90% at 12 months. [12].

186 One of the challenges of evaluating the impact of
187 RARC with ICUD has been the small number of
188 patients available for assessment. Prior to the release
189 of Tyrantzis et al. study, there were no major cen-
190 ters reporting a patient cohort population adequately
191 sized for review and statistical analysis. Since then,

192 a number of centers have reported over 50 patients
193 in their cohorts. Although the study by Gok et al.
194 was appropriately sized with 98 patients, the study
195 lacked a comparison group to explore differences in
196 functional outcomes following RARC with ICUD
197 outcomes. Follow-up assessment of functional out-
198 comes spanned a minimum of 24-months. However,
199 only 61 patients met the criteria for functional assess-
200 ment [13]. This subset of patients was sorted into male
201 (57) and female (4) and was further classified into
202 bilateral, unilateral, and none nerve sparing groups
203 [13]. Overall, 60.6% of the cohort was continent (0-1
204 pad) after 24 months, 22.9% had mild incontinence
205 (1-2 pads), 9.8% had moderate (3 pads), and 6.5%
206 had severe daytime incontinence (>3pads) [13]. In
207 regard to nighttime incontinence, 40.9% had good
208 (dry) nighttime continence, 42.6% had fair (dry +1
209 awakening) incontinence, and 16.3% had poor (wet,
210 leakage, urge incontinence) nighttime incontinence.
211 90.8% of the cohort had bilateral and 4% unilateral
212 nerve preservation [13]. The preferred neo-bladder
213 technique was the Studer pouch. Although, the work
214 by Tyrantzis et al. provided a first insight of the RARC
215 with ICUD approach, better studies are needed to
216 assess the potential benefit of such technique over
217 other approaches.

218 Several other studies also provided data on func-
219 tional outcomes. Sim et al. reported a cohort that
220 included 28 patients who had undergone RARC
221 with ileal conduit (IC) and 73 a RARC with ICUD
222 neobladder (ICNB). Continence in the ICNB group
223 was defined as no pads per day and was 89.2%
224 for daytime and 67.6% at nighttime. The surgeons
225 employed a nerve sparing technique in 52/57 of
226 the men and 15/16 in the women [14]. Likewise,
227 Schwentner et al. reported a retrospective study
228 encompassing 62 patients, 50 men and 12 women.
229 All women had bilateral nerve sparing while 46/50
230 men had the same [15]. Continence in this context
231 was defined as <1 pad per day [15]. Functional out-
232 comes were measured at 12 months and the results
233 showed day and night time continence of 88% and
234 55.1% respectively [15]. These results across stud-
235 ies seem to be consistent and reproducible across
236 high volume centers. However, some of them reported
237 wide range of continence, which might be explained
238 by several factors such as lack of standardization of
239 the evaluation of incontinence across the different
240 studies and also different time-points at the learning
241 curve of the surgeons participating in each one of the
242 cohorts. Moreover, until this point the studies were
243 more descriptive and lacked comparison groups. In

244 some, the follow up period was too brief to evalu- 296
245 ate functional outcomes after the expected recovery 297
246 post-procedure. 298

247 In order to evaluate the impact of the learning curve 299
248 on the functional outcomes after RARC with ICUD, 300
249 Porreca et al. aimed to determine whether the use of 301
250 modular training program instructed by an experi- 302
251 enced robotic surgeon could be sufficient to improve 303
252 outcomes. The first 100 patients were grouped into 304
253 roughly thirds and assessed for improved outcomes, 305
254 including continence and sexual function. Conti- 306
255 nence was defined as either use of 0 or 1 pad. About 307
256 50% of patients had either unilateral or bilateral nerve 308
257 sparing RARC. Overall daytime and nighttime conti- 309
258 nence was 90.2% and 70.6%, respectively [16]. 310
259 Though not statistically significant, there was a trend 311
260 for improvement in continence throughout the differ- 312
261 ent groups of patients. Admittedly while RARC was 313
262 new to the surgeon, robotic surgery in general was not, 314
263 which likely played a role in the outcomes. The out- 315
264 comes did conclude that modular training might be 316
265 an effective strategy to overcome the learning curve 317
266 associated with this surgery. 318

267 While some studies included did not involve a 319
268 significant number of patients, they did shed light 320
269 on a number of factors important in understanding 321
270 outcomes related to RARC with ICUD. The Studer 322
271 approach was the most popular neobladder technique 323
272 used across different cohorts, though in some cases 324
273 the description of the surgical technique used in 325
274 some studies were not explained in detail (Table 1). 326
275 Therefore, comparing novel techniques versus more 327
276 traditional approaches is challenging. This may also 328
277 account for the wide range in continence rates within 329
278 each study and hamper the reproducibility of the tech- 330
279 nique and results at different centers. Asimakopoulos 331
280 et al., employed a specific approach of RARC with 332
281 ICUD while sparing nerves as well as seminal vesicles 333
282 in men. Similar to the Gok et al. study, there was 334
283 no control group for comparison. Still, the functional 335
284 results for this specific subset of patients were excel- 336
285 lent with 100% daytime continence at 12-months, 337
286 with continence being defined as 0 pads used. The 338
287 nighttime continence rates were also good at 72.5% 339
288 at 12-months [17]. The authors advocate for the use 340
289 of nerve sparing even in the setting of older patients 341
290 with poor sexual function prior to surgery because 342
291 it would lead to better continence. They used a Y 343
292 neo-bladder and buttonhole anastomosis technique 344
293 to attempt to prevent kinking and functional obstruc- 345
294 tion, which might account for the absence of clean 346
295 intermittent catheterization in this cohort and the low

296 post void residual urine [17]. On the other hand, 297
298 Tan et al. reported excellent continence outcomes 299
299 with the use of the pyramid shaped neobladder. This 300
300 cohort included 20 patients from a single institu- 301
301 tion. Results at 3-months follow-up showed 95% of 302
302 patients achieved daytime continence, whereas only 303
303 65% had achieved nighttime continence. Continence 304
304 defined in this context as 0-1 pads per day [18]. 305
305 Aiming to introduce technical variations Simone et 306
306 al. looked at neo-bladder reconstruction by incor- 307
307 porating titanium staples. The concern with using 308
308 a non-absorbable material in the urinary apparatus 309
309 relates to the formation of stones. Within this par- 310
310 ticular cohort, 2/45 patients developed stones. The 311
311 functional outcomes reported by Simone et al. were 312
312 similar to that of those reported in literature. The 2- 313
313 year daytime continence was 73.3% and the nighttime 314
314 continence was 55.5%, continence defined as no use of pads [19]. 315

316 Although the functional outcomes in the studies 317
317 we have included in this analysis seem to be good 318
318 and consistent, the evidence is poor when comparing 319
319 RARC with ICUD versus other approaches because 320
320 the number and quality of the cohorts is poor, the 321
321 follow up period is short and most of them do not 322
322 compare in between approaches. Satkunasivam et al. 323
323 compared RARC with ICUD to an ORC cohort. In 324
324 terms of overall pad use within a 24 hr period, no 325
325 statistically significant difference was found between 326
326 the 2 groups. However, In the RARC with ICUD 327
327 cohort 78.3%, 21.7% and 0% used day/night, night 328
328 only and day only pads, respectively while in the 329
329 ORC group the rates for day/night, night only and 330
330 day only pads were 50%, 42.2% and 7.8% respec- 331
331 tively. The difference across group was statistically 332
332 significant. Nonetheless, use of a large pad size was 333
333 found to be significantly increased after RARC with 334
334 ICUD than ORC during daytime and night time. It 335
335 is worth noting that the rate of patients who did not 336
336 use pads in the RARC with ICUD group was 16.7% 337
337 and 19% in the ORC. The median follow up time for 338
338 the robotic cohort was 9.4 months, while the median 339
339 follow up time for ORC was 62.1 months, which 340
340 clearly prevents an appropriate analysis [20]. Sim- 341
341 ilarly, Atmaca et al., compared RARC with ICUD 342
342 versus ORC patients. The successful preservation of 343
343 neuro-vasculature was higher in the robotic group 344
344 than the open group (93.7% vs 64.3%, $p=0.004$) 345
345 based on the subjective appreciation of the surgeon. 346
346 The daytime continence with no pad use (84.6% vs 347
347 75%, $p>0.05$) was higher in the robotic group; How- 348
348 ever, the difference was not statistically significant [11]. 349

Table 1
 Manuscript reporting functional outcomes after Robotic radical cystectomy with intracorporeal urinary diversion

Source	Year	Patients	Number of institutions	Number of Surgeons	NVB sparing	Type of Urinary Diversion	Daytime Continence	Nighttime Continence	Sexual Function
Atmaca et al.	2015	42-OPEN 32-ICUD total: 74	Single	5	93.7%- RARC 64.3%- open		Open- 75% Robotic- 84.6%	Open- 58.3% Robot- 46.1%	Open-IIEF 19, 22 + 18.7 Robot 5, 13.6 + 13.6
Gok et al.	2019	98; 92 males, 6 females only 61 for follow-up; 57 males, 4 females			90.8% bilateral 4% unilateral 5.1% none	Studer pouch	60.6%- continent 22.9%- mild 9.8% moderate 6.5% severe	40.9% good 42.6% fair 16.3% poor	R-mild dys- function- 11.1 +/- 4.6 IIEF RNone- 20.6 +/- 7.4
Asimakopoulou et al.	2016- france	40 men RARC + ICUD		1	100%	Y shaped ONB	100%- 12 months (0 pads)	72.5%- 12 months- (0 pads)	IIEF-6 score mean: 21.9 vs 24.4, 3 months and pre-op, respectively. No significant difference
Simone et al.	2016 Italy	45	Single			Partly stapled neobladder	73.2% – 12 months 0 pads	55.5% 12 months 0 pads	
Porreca	2 019	100	Single	AP- main with modular training program with PW	Mono- 33% Bilateral 17%	52%- ONB 32% IC 17% uretero- cutaneostomy	90.2% overall 87.5% G1 88.2%G2 94.4% G3 no significant Difference 12 months no or 1 pad	70.6% overall 75%G1 64.7% G2 72.2%G3 12 months no SS Diff	31% overall 30.3%G1 36.4%G2 26.5%G3 no significant Difference Erection adequate for penetration w/o PDE5I for ONB 3 months
Tyritzis et al.	2013	70	Single	2	8.1% unilateral 58.1% bilateral	Modified Studor	pad 12 months 88.2%- nerve sparing 88.9% non-nerve sparing 2-4/ moderate 5.7%- nerve sparing 6.2% non-nerve sparing >4 total inconti- nence 0%	0-1 73.5% 12 months 2-4/ moderate 14.7% without sparing 11.8%non- nerve sparing >4 8.8%nerve sparing 11.8%non- nerve sparing	Erection adequate for penetration 81% potent with or without PDE5 w/o PDE5 31.2-nerve sparing 9.5-non- nerve sparing w/ PDE5 50.0 nerve sparing 4.8.%

(Continued)

Table 1
(Continued)

Source	Year	Patients	Number of institutions	Number of Surgeons	NVB sparing	Type of Urinary Diversion	Daytime Continence	Nighttime Continence	Sexual Function
							0%		w/ injections 3.1-nerve sparing 9.5-non-nerve sparing
Satkunasivam et al.	2015	28- ONB 79 -open		3		All neo-bladders	Robotic: 0:16.7% 1-2:62.5% (79.2) 3-4:4.1% >5:16/7% open: 0:19% 1-2:64.6% 3-4:13.9% >5:2.5% **No significant difference		
Tan et al.	2015	20				Pyramid, refluxing ureters	95% 3 months	65%	
Collins et al.	2014	147 total 118 male 29 female				J shape-reflexing ureters, afferent limb			IIEF-5 \geq 17 is potency Or 50% success when performing intercourse w/wo PDEI
Sim et al.	2015	82- men 19 women 101 total	Multi-center (2)		IC: 0% NB: 52/57-M 15/16- F	IC- 28 ICNB: 73	89.2% 12 months <1 pad/day	67.6% 12 months	Erectile dysfunction Non-nerve sparing: 100% Nerve preservation: 48%
Schwentner et al.	2015	62 total 50 men 12 women	Multi-center (2)	2	Male 46/50 bilateral Female 12/12 bilateral	Studer pouch	88%	55.1%	Spontaneous erections 54%

Erectile dysfunction

Sexual function remains an important functional outcome after a radical cystectomy. Robotic surgery allows for better preservation of the neurovasculature of the pelvis, which may impact sexual function after surgery. Erectile dysfunction is regularly measured by the IIEF score [21]. IIEF scores range from <7 (severe sexual dysfunction) to >24 (no

dysfunction). An additional criterion added to the gradation of sexual function is the need to use PDE5 inhibitors. Others use a more basic definition including spontaneous erections or the ability to achieve successful penetration at least 50% of the time.

Porreca et al. reported data on sexual health and defined sexual potency as erection adequate for sexual penetration without need for PDE5 inhibitors. Sexual potency was reported as 31% overall within

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Table 2
Newcastle Ottawa score

Study	Representativeness of exposed cohort	Selection of the Non-Exposed Cohort from Same Source as Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of Outcome	Follow-Up Long Enough for Outcome to Occur (Median Duration of Follow-Up ≥ 6 Months)	Adequacy of Follow-Up	Quality Score
Atmaca et al.	Participants were 74 patients at the Ankar Ataturk Training and Research Hospital in Ankara, Turkey, previously diagnosed with invasive Bladder Cancer. They were not representative of the population and were not randomly selected.	Yes *	RARC vs open RC surgical procedures*	Yes *	Patient age, sex, preoperative BMI, International Index of Erectile function, ASA score, and Previous abdominal surgeries were controlled for. Physician expertise and previous experiences were not accounted for. *	Incontinence: Pad use per day (self assessment) Erectile function: International Index of Erectile Function (IIEF)	Yes (9 months)*	Only patients with 9 months follow up were selected.	5*
Gok et al. Asimakopoulos et al.									
Simone et al.	Participants were 45 consecutive patients with high grade urothelial carcinoma treated at the same tertiary hospital center in Rome, Italy from 2012 until 2014. They were not randomly selected	N/A. Study compares surgical parameters, functional and oncologic outcomes with those from a “cumulative analysis of 105 papers on oncologic and functional outcomes after RARC”	RARC, extended pelvic lymph node dissection, and intracorporeal partly stapled neobladder.*	Outcome of interest not stated at beginning of study	Cohorts not comparable (45 patients compared to the literature)	N/A	Yes (2 years) *	Minimum follow up for inclusion in study was 2 years.	2 *

(Continued)

Table 2
(Continued)

Study	Representativeness of exposed cohort	Selection of the Non-Exposed Cohort from Same Source as Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of Outcome	Follow-Up Long Enough for Outcome to Occur (Median Duration of Follow-Up \geq 6 Months)	Adequacy of Follow-Up	Quality Score
Porrec a et al. Tyrirtzis et al.	Participants were 70 patients who had undergone a RARC with modified Studer ileal neobladder. at the Karolinska Institute in Sweden between December 2003 and November 2012. Their data was selected retrospectively and they were not randomly selected.	N/A. No comparison group reported. Study looks at oncologic, functional, and complication outcomes.	RARC with totally intracorporeal modified Studer ileal neobladder formation. 69 of 70 cases completed by 2 surgeons with significant prior experience in open and robot assisted radical prostatectomies.*	Outcome of interest not stated at beginning of study	N/A	Oncologic outcomes: surgical margins assessed, as well as cancer specific mortality and recurrence at 24 months. Complication outcomes: Reported using clavien scores at 30 and 90 days. Functional outcomes: Patients interviewed by nurse regarding functional outcomes using a customized nonexternally validated questionnaire.	Yes *	All patients with up to 9 year follow ups were included.	2 *

Satkunasivam et al.	Participants were 28 men who underwent Intracorporeal orthotopic neobladder creation following RARC between 2012 and 2013 compared to previously characterized cohort of 79 men who underwent ORC. These patients were not randomly assigned to individual groups.	Yes *	RARC with iONB creation vs open RC with ONB creation *	Yes *	Covariables: time since surgery (in months), age at time of surgery (in years), ASA score, BMI, presence of diabetes mellitus, previous radiation therapy, and neoadjuvant or adjuvant chemotherapy were accounted for. Cohorts differed in their times of enrollement. *	Study measures mailed in HRQOL questionnaires from patients at least 12 months after surgery.	Yes *	32 iONB men were contacted, 28 were included. Response for ORB cohort was 179/295, of which 79 males with ONB creation were included. *	6*
Tan et al.	Participants were 20 patients who underwent a RARC with an intracorporeal neobladder formation using a pyramid detubularised folding pouch configuration between July 2011 and March 2014. These patients were retroactively selected and not randomly assigned.	NA. Study describes surgical technique, and measures functional and oncologic outcomes including renal function. No comparison group is reported.	RARC with iNB and bilateral pelvic lymphadenopathy. *	Yes *	N/A	Postoperative upper tract cystogram between 3–6 weeks postop, CT scan of chest, abdomen, and pelvis performed at 6 and 12 months. Continence measured at 6 and 12 months by number of pads required over 24 hr period. *	Yes * Median follow up 21.5 months	Not specified	4*

(Continued)

Table 2
(Continued)

Study	Representativeness of exposed cohort	Selection of the Non-Exposed Cohort from Same Source as Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of Outcome	Follow-Up Long Enough for Outcome to Occur (Median Duration of Follow-Up \geq 6 Months)	Adequacy of Follow-Up	Quality Score
Collins et al.	Participants were 80 patients who underwent urinary diversion with an intracorporeal modified Studer neobladder. using Standard Da Vinci (for first 20 patients) and Da Vinci Si (for remaining 60 patients). Patients were retroactively selected and not randomly assigned.	No: Findings compared to similar studies performed elsewhere.	Urinary diversion with an intracorporeal modified Studer neobladder	Yes *	N/A: no <i>p</i> values reported in comparison of groups.	Outcomes assessed at 3, 6, 12, 18, and 24 months; and thereafter once a year. Functional outcomes: Potency and measured using IIEF score and continence assessed via nurse interview. Oncologic outcomes: overall and cancer specific survival at 36 and 60 months	Yes: mean follow up 31 months	Not specified: retrospective study	

Sim et al.	Participants were 101 patients who underwent RARC and intracorporeal urinary diversion at two tertiary academic centers between October 2009 and October 2014. The patients were retrospectively selected and weren't randomly assigned	Yes*	RARC followed by either intracorporeal ileal conduit or neobladder formation *	Yes*	N/A: no <i>p</i> values reported in comparison of groups.	Complications: Early (<30 days) and late (>30 days) complication severity measured by Clavien score. Oncologic outcomes: 3 year cancer specific and overall survivals. Functional outcomes: Questionnaire and IIEF score. *	Yes: "Average" follow up 27.5 months *	Not specified: retrospective study	5*
Schwentner et al.	Participants were 62 patients who underwent RARC and orthotopic neobladder formation at two academic centers between October 2009 and October 2014. The patients were retrospectively selected and weren't randomly assigned.	Yes*	RARCs with intracorporeal neobladder formation *	Yes *	N/A: no values reported.	Perioperative variables: operating time, blood loss, hospital stay Complications: Perioperative and postoperative complications measured via Clavien-Dindo system. Functional outcomes: Continence: pad use Sexual function: NA Oncologic outcomes: cancer specific and overall survival rate (time not recorded), as well as mortality	Yes: "average" follow up 37.3 months *	Not specified: retrospective study	4*

365 90 days after surgery [16]. No assessment 12 months
366 after surgery was done, therefore, this functional out-
367 come seems more anecdotal than clinically relevant
368 as it is expected that potency improves gradually dur-
369 ing the first postoperative year.

370 Similarly to reported data for continence, Tyrirtzis
371 et al. remains an important point of comparison for
372 sexual function. Tyrirtzis et al. defined potency as
373 the erection adequate for penetration with or with-
374 out the use of phosphodiesterase type 5 inhibitors at
375 12 months [12]. All women in their cohort received
376 nerve-sparing surgery, which involves preservation
377 of the autonomic nerves at the anterior vaginal wall
378 at the 10 and 2 o'clock position [12]. 4/6 women
379 remained sexually active postoperatively [12]. Over-
380 all, 81.2% of the nerve-spared male patients were
381 potent with or without PDE5 medication at 12 months
382 [12].

383 Other studies reviewed previously for continence
384 also addressed sexual function. Atmaca et al. pro-
385 vided an additional point of comparison by assessing
386 sexual function pre and postoperatively. Patients were
387 initially grouped into 2 categories based on the type
388 of surgical procedure and preoperative sexual func-
389 tion according to IIEF score. Postoperatively they
390 were further grouped into subcategories of bilat-
391 eral, unilateral or no neurovascular bundle sparing.
392 Results showed that those with no sexual dysfunction
393 prior to the surgery reported better sexual func-
394 tion or higher IIEF score postoperatively than those
395 that had mild sexual dysfunction [11]. Additionally,
396 those patients with mild sexual dysfunction required
397 more frequent use of PDE5 inhibitors than those
398 that had no dysfunction [11]. Surprisingly, although
399 more of the RARC with ICUD had neuro vascular
400 sparing surgery, this cohort reported a lower mean
401 IIEF 9 months postoperatively than the open group.
402 However, none of these results were statistically sig-
403 nificant.

404 Consistent with those findings, Sim et al. also
405 reported on sexual function using the IIEF5 12
406 months after surgery [14]. Nerve sparing was
407 attempted for both men and women. Nerve sparing
408 in women involved preservation of the tissues on the
409 lateral aspect of the vagina, which are autonomic
410 nerves. 63.4 % of males and 78.9% of females had a
411 nerve sparing surgery. All the patients who had nerve-
412 sparing technique had ICNB while none of the patient
413 who underwent a ileal conduit had nerve preserva-
414 tion. Surprisingly and consistent with Atmaca et al.,
415 the reported erectile function was better in the patient
416 with no nerve preservation (100% vs 48%). However,

417 only descriptive statistics were provided, therefore,
418 no statistical significance was obtained [14].

419 Gok et al. subdivided a cohort preoperatively into
420 mild sexual dysfunction and no sexual dysfunction
421 using IIEF scores. Among those with mild dysfunc-
422 tion prior to surgery ($n=8$), 4 needed postoperative
423 use of PDE-5I and had a mean IIEF score of $11.1 \pm$
424 4.6 (5–20 range) at follow-up [13]. Among those
425 without preoperative sexual dysfunction, 6 required
426 use of PDE5 I, and the mean was 20.6 ± 7.4 (8–25
427 range). It is important to note that 91.3% of the
428 patients with no ED had bilateral nerve-sparing tech-
429 nique compared to 75% of the patients with mild
430 dysfunction [13].

431 Some modifications to the technique has been
432 attempted in order to improve sexual function in
433 patients after RARC with ICUD. Asimakopoulos et
434 al. employed a specific technique involving preser-
435 vation of the seminal vesicles under the assumption
436 that it would preserve the lateral cholinergic fibers
437 that are important for continence and assessed sexual
438 function using IIEF-6 scores pre and postopera-
439 tively. Preoperatively the mean IIEF-6 score was 24.4
440 [21–29], and postoperatively at 3 months it was 21.9.
441 The difference was not found to be statistically sig-
442 nificant. Patients were instructed to take Tadalafil for
443 2 months after surgery and as needed thereafter. Only
444 9 of the patients did not achieve normal EF [17].

445 Manuscripts discussing specifically sexual func-
446 tion in women after RARC with intracorporeal
447 diversion could not be find. We found some papers
448 that evaluate this matter marginally. Collins et al.
449 reported a satisfactory sexual function at 12 months
450 ranging from 70 – 90% in both men and women,
451 which is also consistent with Tyrirtzis et al., which also
452 reported a satisfactory sexual function at 12 months in
453 70 to 90% in both genders [12, 22]. Therefore, more
454 and better designed studies are warranted in order to
455 address comprehensively the impact of the surgery in
456 the quality of life of women specifically discussing
457 the sexual domain.

458 DISCUSSION

459 The topic of ICUD has gained significant trac-
460 tion since it was first discussed in 2003 [10]. While
461 there have been studies assessing its validity and
462 equality regarding operation time, blood loss and
463 other metrics, few have adequately assessed overall
464 functional outcomes as compared to ECUD or open
465 surgery. Continence and sexual function remain the

two most important functional outcomes when studying patients who underwent RARC with ICUD. The first hurdle we found when evaluating continence and sexual function is the lack of consistency of methods to report such outcomes. Different scores and methods were used across studies. Therefore, drawing conclusions from the studies was very challenging. We consider that prospective studies using already validated methods such as IIEF, might improve the quality of the outcomes.

The overall determinants of functional outcomes are based on factors such as the degree of nerve preservation, type of urinary diversion, age, manual dexterity of patients, pre-operative comorbidities, and patient motivation. The vast majority of urinary diversions performed consist of ileal conduits and neobladders. Because of the lack of contraindications to ileal conduits in patients cleared for RARC, Ileal conduits account for the majority of urinary diversions performed. There are, in contrast, several absolute contraindications to neobladder creation and many more relative ones. However, neobladders remain an attractive option to younger patients and those with a strong desire to preserve their continence.

Regardless of the specific neobladder or urinary diversion technique performed, functional outcomes seem to be significantly better in patients when there is special attention to the preservation of the pelvic neuro-vasculature. In women specifically, Tyrirtzis et al. have demonstrated that preservation of the pelvic organs can lead to better functional outcomes [12]. Other mechanisms are certainly involved as we showed previously in some cohorts, how patients with reported bilateral nerve preservations did worse compare to patients without nerve preservation technique, which we considered explain the influence of other variables besides nerve sparing [12]

While many of the studies reviewed here did not explicitly state the reason for the adoption of an ICUD versus ECUD, the functional outcomes reported here provide evidence that this technique is a viable option that can provide patients with good functional outcomes with respect to continence and preservation of erectile function. As demonstrated by Porreca et al., training programs can provide surgeons with the tools to be successful in overcoming the learning curve associated with this technique.

In spite of the limitations of this literature review driven by the quality of the studies we found. We consider that RARC with ICUD is a feasible and safe option for patients as it has been previously reported [13]. Moreover, and as part of the main focus of

this systematic review we consider that functional outcomes including continence and sexual are equivalent between RARC with ICUD and what has been reported for ORC and RARC with ECUD. Moreover, although the evidence limited to compare the impact of ICNB and ileal conduits in the sexual function of the patients, we did not find any study suggesting a significant difference in the impact of either of the two techniques and the decision of which approach is better in each case should be based on a comprehensive analysis of the multiples factors that may affect the oncological outcomes, presence of contraindications for ICNB and patient motivation. We consider that studies with better designs aiming to elucidate the impact of RARC with ICUD in the quality of life of the patients may improve the quality of the outcomes and would help to draw stronger conclusions

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AUTHOR CONTRIBUTIONS

JD: data collection, interpretation of data, manuscript writing; TJ: data collection, interpretation of data, manuscript writing; MR: manuscript writing, interpretation of data; AC: manuscript writing, interpretation of data; JPS: manuscript editing; RM: manuscript editing; NM: manuscript editing; PW: project development, manuscript editing.

ETHICAL CONSIDERATIONS

This paper was IRB exempt. No human or animal research was involved in the elaboration of this manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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