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Robot assisted radical cystectomy with Florence robotic intracorporeal neobladder (FloRIN): Analysis of survival and functional outcomes after first 100 consecutive patients upon accomplishment of phase 3 IDEAL framework

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ABSTRACT

Introduction: Aim of the study was to evaluate the Florence intracorporeal neobladder (FloRIN) oncological and functional outcomes at the end of assessment phase (phase 3) IDEAL-Guidelines.
Materials and methods: This single-institution prospective series included consecutive patients treated with robot-assisted radical cystectomy (RARC) and FloRIN reconfiguration technique from February 2016 to June 2020. Functional features were evaluated six months after surgery. Patients were grouped into four quartiles according to time of radical cystectomy and impact of learning curve improvement was evaluated.
Results: One-hundred FloRIN were completed with a median console time of 373 (IQR: 312–415) minutes. Two cases were converted to open surgery. No intraoperative complications occurred. At pathological examination, 30% of patients were staged as pT $\leq$ 1 and 47% as pT $\geq$ 3. Transitional cell carcinoma was present in 87% of cases. Carcinoma in situ (CIS) and nodal involvement were observed in 38% and 29% of patients, respectively. At a median follow-up time of 17 (IQR: 7–28) months, 20 clinically relevant events (Clavien-Dindo$\geq$3) occurred. Operative time significantly decreased throughout the series (median minutes 435; 395; 365 and 330 in the four quartiles, respectively; $p < 0.001$). Similarly, early Clavien-Dindo$\geq$3 postoperative complications rate significantly decreased across the series (number of events: 1; 4; 0; 0; $p = 0.03$). Overall, 75% and 65% of patients achieved day-time and nigh-time continence, respectively. Twenty-seven patients experienced disease recurrence. Cancer-specific and overall survival were equal to 80%.
Conclusions: RARC with FloRIN reconfiguration showed worthy functional and survival outcomes, with learning curve improvement significantly influencing operative time and early complications rate across series.

Introduction

The progressively larger spread of robot-assisted radical cystectomy (RARC) led it to become, in barely one decade, the standard of care in many Institutions [1–3]. Three recent systematic reviews and metanalyses compared RARC with open radical cystectomy, basically reporting that RARC may provide some advantages in terms of blood loss, transfusion rates and, more limitedly,

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postoperative complication rates [4–6]. Nonetheless, the cost-effectiveness, the increased operative times, the lack of long-term oncological and functional analysis still burden on RARC use [7]. In 2016 our Institution introduced Florence robotic intracorporeal neobladder (FloRIN), a novel intracorporeal neobladder configuration (ICN). Ever since, we performed one hundred RARCs using the principles of FloRIN reconfiguration technique.

The first exploratory analysis was published in 2018, according to the Idea, Development, Exploration, Assessment, Long-term follow-up (IDEAL) Reporting Guidelines for the development of surgical projects [8]. Since we have now completed the fourth step of the IDEAL Framework (phase 3 - Assessment), in this paper we present the updated oncological and functional outcomes in a more representative cohort with an extended follow-up [9]. Further, we chose to focus on surgeon's expertise and learning curve improvements. Accordingly, we investigated two main endpoints 1) the feasibility and safety of the technique in a larger cohort, assessing the early and delayed complication rates, recurrence-free survival (RFS), cancer-specific survival (CSS), overall survival (OS) as well as functional outcomes; and 2) how surgeon's learning curve improvement impacted on peri- and postoperative outcomes.

Materials and methods

We analyzed the prospectively collected clinical and surgical data of all consecutive patients treated at our Institution from February 2016 to June 2020 with RARC, lymph node dissection (LND) and FloRIN reconfiguration. In the current study, we included all patients with clinical stage T1-T4N0–N1M0 amenable to radical cystectomy with curative intent and neobladder reconfiguration. Main exclusion criteria were: 1) presence of one or multiple tumor metastases at preoperative staging; 2) histopathological confirmation of bladder tumor at the level of prostatic urethra; 3) treatment without curative intent (cT4b, salvage or palliative cystectomies); 4) presence of urethral stricture.

Patient demographics, peri- and postoperative outcomes including operative time, conversion rate, complication rate, blood loss, length of hospital stay (LOS) and pathological data were thoroughly gathered. Preoperative work-up included chest and abdomen contrast enhanced CT scan. Tumor stage was classified according to the 2017 TNM criteria (8th_edition) [10]. Histopathology was reviewed according to the revised WHO 2016 classification [11]. The presence of ink at the resected margins on gross assessment, confirmed by microscopic extension of malignant cells at the stained margins, was reported as a positive surgical margin (PSM). Follow-up schedule included blood analysis and CT scan performed three months after surgery, then every 6 months from the first to the third postoperative year, followed by annual imaging assessment according to individual risk profile, as postulated by the EAU guidelines [12].

A description of the surgical technique was previously published [9,13] (Fig. 1). All surgical procedures were performed by a single highly experienced robotic surgeon (AM), alternated with the other fellow-members.

All eligible patients were offered the possibility to undergo neoadjuvant cisplatin-based chemotherapy before RARC. Patients with non-muscle invasive bladder cancer, cN+ disease and those presenting with severe cardiovascular morbidity or high preoperative creatinine levels, strongly contraindicating cisplatin administration, underwent immediate radical cystectomy. The enhanced recovery after surgery protocol (ERAS) was regularly applied [14]. Suitable patients underwent a nutritional assessment with a specific immune-nutrition, 7 days preoperatively.

Functional evaluation

The continence status was evaluated six months after FloRIN reconfiguration. All patients were thoroughly instructed to train the pelvic floor after the removal of the transurethral catheter and void the neobladder every 2–3 h on both day- and night-time. Six months after surgery, we offered to all the patients a functional evaluation of voiding outcomes and post-voiding residue. Day- and night-time continence was defined as need for up to one pad per day or night, respectively.

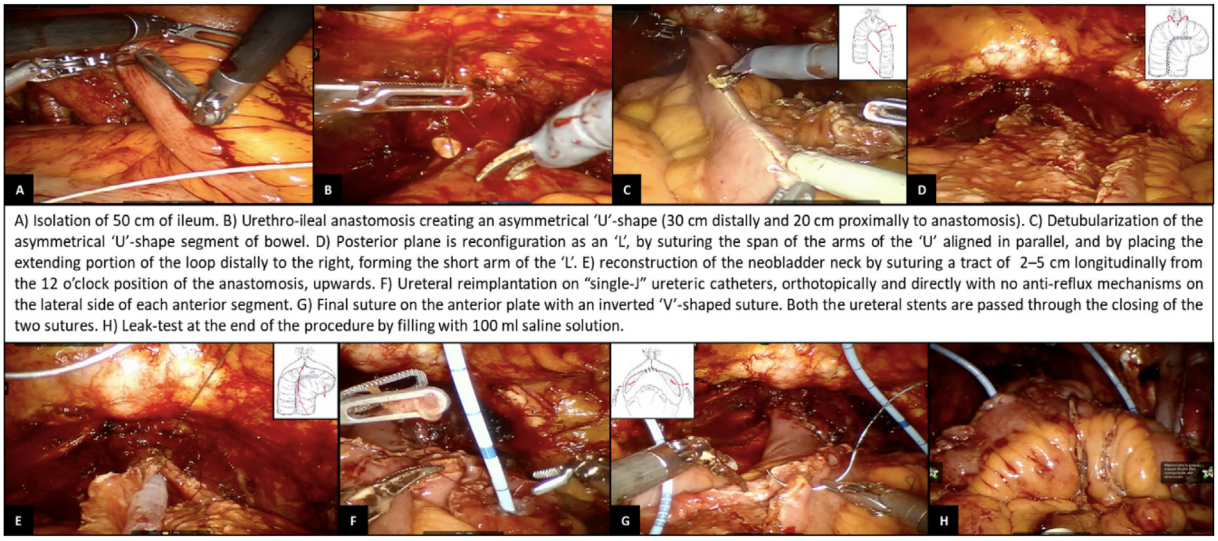
Statistical analysis

For statistical purposes, independent variables included all patient- and tumor-related data available in our Institutional database. First, descriptive statistics were obtained reporting medians (and interquartile ranges, IQR) for continuous variables, and frequencies and proportions for categorical variables, as appropriate. Continuous variables were compared by Student-t or Mann-Whitney *U* test based on their distribution (normality of variables' distribution was tested by the Kolmogorov-Smirnov test). Categorical variables were tested with the Chi-square test. The survival rate was assessed by Kaplan-Meier method, with the log-rank test (Mantel-Cox) estimating differences among variables levels. Patients were grouped into four quartiles according to time of radical cystectomy. Outcomes were compared between the quartiles using ANOVA and Fisher's exact test. Statistical analyses were performed using SPSS v. 24 (IBM SPSS Statistics for Mac, Armonk, NY, IBM Corp). All tests were two-sided with a significance set at $p < 0.05$.

Results

Baseline and perioperative outcomes

Overall, 100 patients were enrolled. Baseline intraoperative and postoperative features are reported in Table 1. Median age was 66.5 (IQR 59–71) and 81 (81%) were males. Median age adjusted CCI was 3 (IQR 2–4), median BMI was 25.9 (IQR 24–28.7) and 17 (17%) underwent neoadjuvant chemotherapy. Overall, 82 (82%) patients adhered to the ERAS pathway, 18 (18%) patients were finally excluded from the protocol for nausea not responding to medication. The median console time was 373 (IQR 312–415) minutes. Overall, 26 (26%) and 74 (74%) patients were treated with standard and extended LND respectively. Nerve- and sexual sparing radical cystectomy was performed in 12 men and 2 women, respectively. Median estimated blood-loss (EBL) was 400 ml (IQR: 230–550). No intraoperative complications were recorded. Two cases were converted to open surgery due to the impossibility to properly mobilize the ileum down to the urethra. The <30, 30–90 and > 90 days Clavien Dindo (CD) ≥3 complication rates were 5%, 8% and 7%, respectively (Table 2). Overall, at final histopathological examination, non-muscle invasive bladder cancer (pT0; carcinoma in situ [CIS]; pT1) was recorded in 30 patients, while pT2, pT3 and pT4 stage disease was observed in 23, 36 and 11 patients, respectively. Table 3 shows pathological results. Overall, 87% of patients had pure transitional cell carcinoma, while 12% showed histotypes variants (8 squamous, 2 micropapillary, 1 sarcomatous and 1 plasmocytoid), and one patient had no residual disease after neoadjuvant chemotherapy. CIS was reported in 38 patients, primary in 13 (13%) and concomitant in 25 (25%), respectively. The mean number of lymph nodes at pathological report was 25, ranging from 7 to 69. Among patients with pT2 disease or lower, nodal



A) Isolation of 50 cm of ileum. B) Urethro-ileal anastomosis creating an asymmetrical 'U'-shape (30 cm distally and 20 cm proximally to anastomosis). C) Detubularization of the asymmetrical 'U'-shape segment of bowel. D) Posterior plane is reconfiguration as an 'L', by suturing the span of the arms of the 'U' aligned in parallel, and by placing the extending portion of the loop distally to the right, forming the short arm of the 'L'. E) reconstruction of the neobladder neck by suturing a tract of 2–5 cm longitudinally from the 12 o'clock position of the anastomosis, upwards. F) Ureteral reimplantation on "single-J" ureteric catheters, orthotopically and directly with no anti-reflux mechanisms on the lateral side of each anterior segment. G) Final suture on the anterior plate with an inverted 'V'-shaped suture. Both the ureteral stents are passed through the closing of the two sutures. H) Leak-test at the end of the procedure by filling with 100 ml saline solution.

Fig. 1. Surgical steps of FloRIN reconfiguration.

Table 1
Preoperative, intraoperative and postoperative features.

Age, median (IQR)	66.5	(59.0–71.0)
Male patients, n (%)	81	81%
BMI, median (IQR)	25.9	(24.0–28.7)
Never-smokers, n (%)	19	19%
Former-smokers, n (%)	27	27%
Current smokers, n (%)	54	54%
Chemical exposure, n (%)	13	13%
Neo-adjuvant chemotherapy, n (%)	17	17%
CCI age adjusted, median (IQR)	3	(2–4)
Previous abdominal surgery, n (%)	25	25%
Hydronephrosis observed at CT scan, n (%)	38	38%
cT $\leq$ 2, n (%)	73	73%
cT $\geq$ 3, n (%)	27	27%
cN0, n (%)	79	79%
cN+, n (%)	21	21%
Intraoperative complications, n (%)	0	0%
Intraoperative blood transfusions, n (%)	0	0%
Conversion to open surgery, n (%)	2	2%
Console time (minutes), median (IQR)	373	312–415
Standard-LND, n (%)	26	26%
Extended-LND, n (%)	74	74%
Nerve/Sexual sparing, n (%)	14	14%
Time to canalization (days), median (IQR)	5	4–6
Time to drainage removal (days), median (IQR)	6	4–9
Time to hospital discharge (days), median (IQR)	14	9–16
Estimated Blood Loss (ml), median (IQR)	400	230–550
Haemoglobin level decrease (g/dl), median (IQR)	−2.9	−3.6; −1.9
Perioperative[a] rise of serum creatinine (>80% baseline), n (%)	10	10%

[a] Detected during hospitalization. CCI: Charlson Comorbidity Index. LND: Lymph node dissection.

involvement was observed in 7 (13%) patients, rising to 22 (47%) patients in those with pT3 disease or higher at final pathological examination. For pN+ patients, the median lymph node density (positive LNs/total LNs) was 13% (IQR 5–33). In three cases (3%) there was evidence of PSMs, two of them showing residual CIS on urethral margin.

Functional outcomes

To monitor the impact on renal function, we recorded the postoperative (6 months after surgery) serum creatinine level. Overall, the median creatinine value was 1.19 mg/dl (IQR: 0.94–1.44) and no patients experienced a significant rise (>50% from baseline). Concerning continence, 83% of patients reached the minimum 6 months follow-up time for a proper evaluation. Complete functional follow-up data are available for 69 (82%) of them. Overall, 52 (75.4%) patients reached the day-time continence ($\leq$1pad/day-time). Among the continent patients, 28 (40.6%) were dry (no pads during day-time), while 24 (34.8%) used one pad/12h. A complete nigh-time continence was achieved by 45 (65.2%) patients. Five cases (7.2%) had a post-void residue >100 ml detected by abdominal ultrasound or catheterization, 4 patients (5.8%) required a clean intermittent self-catheterization regimen. At uroflowmetry median Qmax value was 14 ml/s (IQR: 8.5–18.0), the median FloRIN voiding-volume was 285 ml (IQR: 234–335). The functional outcomes are reported in Table 4.

Table 2
Number of major adverse events (CD ≥ 3) after patient's discharge and sub analysis according to quartile subgrouping.

	<30 days	30–90 days	>90 days
Nephrostomy	1	4	1
Ureteral reimplantation	1	1	5
Ileal fistula/anastomosis revision	3	2	0
Sepsis	0	1	1
Total number of CD ≥ *3* events	5	8	7

Cohort subgrouping according to quartiles (n = 25 patients in each quartile)					
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P value**
Operative time (minutes), median (IQR)	435 (385–530)	395 (340–430)	365 (320–404)	330 (285–390)	<0.001
Rate of CD ≥ 3 events					
<30 days (n of events)	1	4	0	0	0.03
30–90 days (n of events)	2	1	2	3	0.78
>90 days (n of events)	2	2	3	0	0.22[a]

[a] not adequate follow-up length in the fourth quartile.

Table 3
Oncological outcomes and follow-up data.

pT0-CIS, n (%)	22	22%
pT1, n (%)	8	8%
pT2, n (%)	23	23%
pT3, n (%)	36	36%
pT4, n (%)	11	11%
pN0, n (%)	71	71%
pN+, n (%)	29	29%
pN1, n (%)	6	6%
pN2, n (%)	19	19%
pN3, n (%)	4	4%
Positive surgical margins, n (%)	3	3%
Number of lymph nodes removed; mean (SD; range)	25	(13; 7–69)
Follow-up months mean (SD; range)	19	(12.8; 3–55)
median (IQR)	17	(7–28)
Recurrence free survival, n (%)	73	73%
Time from RARC to recurrence (months), median (IQR)	5	(3–9)
Local recurrence, n (%)	5	5%
Systemic recurrence, n (%)	22	22%
Adjuvant chemotherapy, n (%)	17	17%
Adjuvant radiotherapy, n (%)	5	5%
Cancer specific survival, n (%)	80	80%
Overall survival, n (%)	80	80%
Patients lost at follow-up, *n (%)* [censored]	2	2%

Table 4
Functional outcomes. Complete functional outcomes were available for 69 patients.

Day-time continent patients (≤1 pad), n (%)	52	75.4%
Dry patients (0 pads), n (%)	28	40.6%
Nigh-time continent patients (≤1pad), n (%)	45	65.2%
Florin volume (ml); median (IQR)	285	(234–335)
Q max (ml/sec); median (IQR)	14	(8.5–18.0)
Significant post-void residue (>100 ml), n (%)	5	7.2%
Clean intermittent catheterization, *n* (%)	4	5.8%

Survival outcomes

Median follow-up time was 17 (IQR: 7–28; range 3–55) months. Overall, 27 patients experienced disease recurrence, being local in 5 and systemic in 22, respectively. The most frequent sites of distant metastasis were lung in 12 cases, bone in 5 cases, peritoneum in 3 cases and liver in 2 cases. Four patients with local recurrence required percutaneous nephrostomy placement. Median time from RARC to recurrence was 5 (IQR 3–9) months. Sixteen patients underwent a Cisplatin-Gemcitabine adjuvant chemotherapy, one received a Carboplatin-based adjuvant therapy. Radiotherapy was offered to 5 patients showing a single bone metastasis during follow-up. One patient developed urethral recurrence 16 months after RARC and was treated by endoscopic resection with subsequent negative follow-up. Overall, 80 patients are currently alive, 18 died due to disease progression, while 2 were lost at follow-up and, thus, were censored form survival analysis. Recurrence and survival outcomes for the entire population and Kaplan-Meier curves stratified for pT and pN stage are depicted in Table 3 and Fig. 2, respectively.

Quartile differences

No differences among the quartiles were found according to age, BMI and comorbidity burden. Operative time showed to significantly decrease throughout the series (median minutes 435; 395; 365 and 330 in the four quartiles, respectively; $p < 0.001$). Similarly, the early (<30 days) CD ≥ 3 postoperative complications rate significantly decreased across the series (number of events: 1; 4; 0; 0 $p = 0.03$) (Table 2). Conversely, blood transfusion rate ($n = 2$; $n = 5$; $n = 5$; $n = 2$ respectively; $p = 0.21$) and median time to canalization (5; 6; 4; 5 days; $p = 0.11$) were equally distributed among the four quartiles.

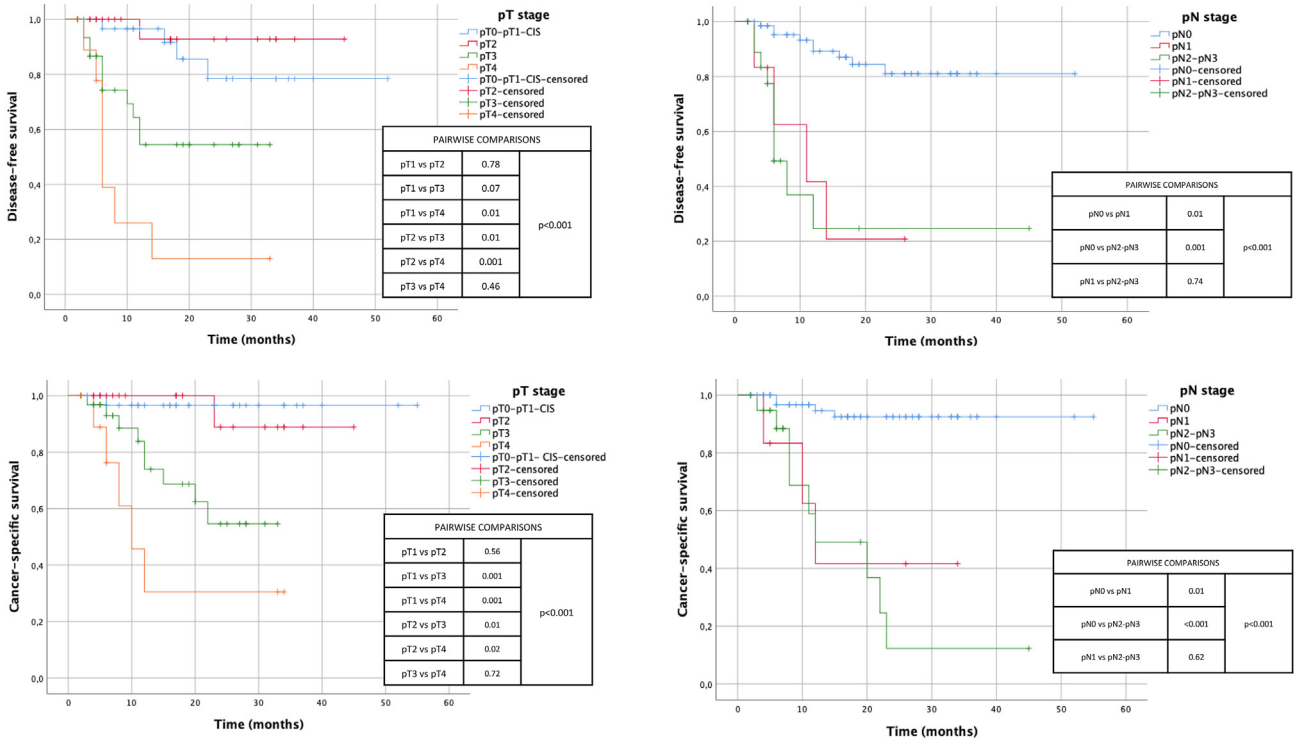


Fig. 2. Kaplan-Meier curves depicting disease recurrence and cancer-specific survival stratified according to pT-stage and pN-stage.

Discussion

Despite being at the far end of complexity in robotic surgery, only the ICN techniques enable the achievement of optimal benefits after RARC. Indeed, ICNs showed reduced evaporative fluid loss, intraoperative bleedings with faster recovery of bowel function and shorter LOS [15,16]. Several techniques for ICN reconfiguration have been described, some reproducing the steps of open surgery and some trying to simplify them. What is needed is a feasible and easily learnable technique, providing an ordinary-lifestyle functionality. According to the IDEAL-Collaboration guidelines [8], FloRIN technique conjugates the advantages of both ICN and robot-assisted approach, ultimately conceiving a reproducible robotic neobladder model [9]. Four years after its development, FloRIN reached a solid standardization. Herein we provide state of the art, oncologic and functional outcomes of FloRIN reconfiguration, focusing also on progressive improvements of the technique throughout the series. First key finding of our study is that FloRIN technique confirmed to represent an efficiently learnable neobladder configuration. The median console time of 373 min for the entire cohort meaningfully reduced to 330 median minutes for the last 25 cases, strongly highlighting a progressive, significant learning curve improvement over time. Hosseini et al. recently reported a median operative time of 359 min in 158 patients treated with RARC-ICN modified Studer ileal-neobladder, documenting a relevant decrease in surgical time with the improvement of the learning curve (from 479 to 328 min) [17]. Simone et al. reported a slightly faster procedure with a median operative time of 305 min after 45 robotic intracorporeal Padua Ileal Neobladder, by using a stapler-suture for the bladder neck reconfiguration [18]. Similarly, Porreca et al. showed a progressive decrease in overall surgical time (from 390 to 325 min) in a series of 52 totally intracorporeal RARCs [19]. As such, our median operative time was consistent as compared to contemporary series, confirming FLORIN excellent time efficiency.

When it comes to complications after ICN, larger studies with standardised reporting of complications described rates of major complications (CD $\geq$ 3) ranging from 15% to 30% and Authors often limited the observational period to the first 90–180 postoperative days [17,18,20–24]. Our outcomes are consistent with other RARC and ICN reports, with <30, 30–90 and > 90 days severe complication rates at a reasonable 5%, 8% and 7%, respectively, lower than the 30% threshold supported as a benchmark by the Pasadena consensus panel [15]. The rate of early clinically relevant complications significantly reduced throughout the series, emphasizing the importance of learning curve improvement. In addition, we also observed a decrease in >90 days severe postoperative complications, though not significant. However, the impact of learning curve on our delayed events was biased by a shorter follow-up time in the fourth quartile.

Concerning the functional outcomes and especially continence, many preoperative features such as gender, age and BMI, postoperative status, disease staging, nerve/sex sparing approach and timing of evaluation after RARC all play a key role. A reliable comparison of functional results should therefore compare similar cohorts. Our continence rate (six months $\leq$1pad/day-time: 74%; $\leq$1pad/night-time 65%) is consistent with reports at similar timing, showing a 53% day-time dry rate at six months [25].

In this regard, robotic assistance might play a key role in early continence recovery. In fact, the robotic surgeon is able to perform an accurate apical dissection preserving a longer functional length of membranous urethra and carry out a more precise urethro-ileal anastomosis using a running suture, thus reducing the risk of anastomotic dehiscence and early incontinence, as compared to standard open approach. Moreover, according to our previously published surgical technique, the addition of posterior reconstruction is pivotal to approximate the Denonvilliers' fascia to the posterior wall of the neobladder, thus obtaining a tension free-anastomosis and providing at the same time pelvic support. Overall, the median volume of the FloRIN neobladder (285 ml) resulted

appropriate for a physiological day-time and night-time dynamic of micturition. The low rate of post-void residual urine, together with the good Qmax value (14 ml/s) showed how patients can reach a good voiding regimen already six months after surgery. The observation of postoperative serum creatinine levels (median: 1.2 mg/dl) upholds the evidence that renal function remained stable after surgery.

The oncological outcomes in our series reflect the relatively high rate of non-organ-confined disease (47% pT3-T4), with extensive nodal involvement (23% pN2-N3). At a median follow-up of 17 months the overall recurrence rate was equal to 27%. Collins et al., analyzed a multicentric dataset of 717 RARCs reporting a recurrence rate of nearly 25% at 24 months on a cohort with slightly less aggressive staging features than ours (33% pT3-T4; 18% pN+) [26]. Several Authors reported a RFS ranging from 64% to 81% at a similar follow-up time [24,27,28]. In our series, most of the recurrence were systemic (22%), while local recurrences occurred in 5% of cases. In line with our findings, the RAZOR trial showed a systemic and local recurrence rate of 22% and 8% after RARC, respectively [27]. The International Robotic-Cystectomy Consortium recorded a distant and local recurrence rate of 18% and 9%, respectively. As shown in our Kaplan-Meier plots, patient selection is pivotal for survival outcomes. Indeed, higher pT-pN stage showed detrimental impact on both disease and cancer-specific survival. Finally, despite the high rate of locally-advanced disease, our PSM of 3% was at the lower limits of the range reported by largest cohorts of RARCs (3–17%) [26,27,29,30].

As a study limitation, concerns might be raised about our relatively short follow-up time, potentially affecting the reliability of survival analysis. A shorter observation period in the fourth quartile might have influenced also the number of major postoperative adverse events, ultimately biasing the assessment of learning curve influence on our delayed postoperative complications rate. On the other hand, a longer follow-up would have probably revealed higher continence rates. We are also aware that the other fellow-members who have alternated with the main surgeon may have represented a moderate bias when assessing perioperative outcomes. In this regard, it should be highlighted that an integrated team work policy was developed since the very early phase of the FloRIN development. As such, we might consider the reduction in operative time and early postoperative complications as the expression of team learning curve improvement.

Acknowledged these limitations, we present the largest series so far with integrated oncologic and functional outcomes after RARC and FloRIN configuration. Since new surgical procedures need robust evaluation for safety and effectiveness, the adoption of the IDEAL Guidelines Framework for FloRIN development and standardization bolsters the trustworthiness of our results. Moreover, the assessment of a real-life cohort, without strict exclusion criteria, confirms the feasibility of this technique. The detailed recording of intra- and post-operative data, with very few missing cases, allowed a precise assessment of the parameters observed, while the inclusion of functional features provided a comprehensive analysis of postoperative outcomes.

Conclusions

The features of FloRIN conform with those of the ideal neobladder. The safety and the feasibility of RARC with FloRIN configuration is endorsed by the survival outcomes observed in our cohort, aligned with literature reports. Moreover, the FloRIN functional features accomplish the needs of physiological voiding dynamic. Operative time and early clinically relevant complications rate meaningfully improved across the series, strongly supporting the reproducibility of this technique also in a real-life context within a non-preoperatively selected cohort of patients.

Statement of ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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None.

CRediT authorship contribution statement

Andrea Minervini: Conceptualization, Methodology, Writing – review & editing. **Fabrizio Di Maida:** Formal analysis, Data curation, Writing – original draft. **Giovanni Tasso:** Formal analysis, Data curation, Writing – original draft. **Andrea Mari:** Writing – original draft, Data curation. **Riccardo Bossa:** Investigation. **Simone Sforza:** Investigation. **Antonio Andrea Grosso:** Investigation. **Riccardo Tellini:** Data curation. **Gianni Vittori:** Formal analysis. **Giampaolo Siena:** Writing – review & editing. **Agostino Tuccio:** Writing – review & editing. **Lorenzo Masieri:** Conceptualization, Methodology, Writing – review & editing. **Marco Carini:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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