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## Disclosure of Interests

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Abbreviations: Gem/Doce, gemcitabine and docetaxel; NMIBC, non-muscle-invasive bladder cancer.

# How can we reduce morbidity after robot-assisted radical cystectomy with intracorporeal neobladder? A report on postoperative complications by the European Association of Urology Robotic Urology Section Scientific Working Group

Robot-assisted radical cystectomy (RARC) is a technically challenging procedure associated with high overall postoperative morbidity [1,2]. Relative to other forms of urinary diversion, neobladder reconstruction is associated with a higher complication rate [3]. As low morbidity represents one of the pivotal surgical outcomes, efforts must be focused on minimizing the morbidity rate. To achieve this goal, it is crucial to understand the most common complications associated with RARC to allow surgeons to take action to prevent their occurrence. To the best of our knowledge, only a few studies have evaluated the type of

complications that may occur after RARC with intracorporeal neobladder, and the generalizability of their results is limited [1–5]. Previous studies have reported complications from small single-institution or single-surgeon series of patients who underwent RARC with either extracorporeal or intracorporeal neobladder, or did not use standardized criteria to report complications [6]. The present study aimed to characterize the type of complications occurring after RARC with intracorporeal neobladder in order to improve peri-operative management, highlight areas of need for future studies and, ultimately, reduce RARC morbidity.

On behalf of the European Association of Urology (EAU) Robotic Urology Section Scientific Working Group, we created a multi-institutional database of 980 patients who underwent RARC and intracorporeal neobladder at 16 high-volume European centres between 2003 and 2022. All patients with incomplete information on postoperative outcomes were excluded. Our final population included 858 individuals. The surgical technique was previously described [7]. Postoperative outcomes were collected according to the EAU recommendations (11/14 criteria; Table S1) [6]. Complications were scored using the Clavien–Dindo classification system, grouped by type and severity (severe: Clavien–Dindo score  $\geq 3$ ), and divided into early (<30 days) and late (31–90 days). We compared the type of complication between patients who received and those who did not receive neoadjuvant therapy (nadJT) using Fisher's exact test. Finally, by using a multivariable logistic regression model, we evaluated if the rate of complications was associated with amount of surgical experience of each centre (coded as the total number of RARCs with intracorporeal neobladder performed in that centre before the patient operation) or operating time after accounting for potential confounders (age, body mass index [BMI], American Society of Anesthesiologists [ASA] score, sex, preoperative T stage, and nadJT).

The majority of patients were male (87%), healthy (76% had an ASA score  $\leq 2$ ), and had muscle-invasive tumours (55%; Table S2). The median (interquartile range [IQR]) age at surgery and median (IQR) BMI were 64 years (58, 69) years and 26 (23.8, 28.4) kg/m<sup>2</sup>, respectively. Almost all patients underwent pelvic lymphadenectomy (98%). The neobladder reconstruction technique was the Studer/Wiklund in 557 patients (65%), S pouch in 16 (1.9%), Gaston in 163 (19%), vesica ileale Padovana in 102 (12%) and Hautmann in 20 (2.3%). The median (IQR) operating time was 366 (300, 440) min and the urinary diversion time was 166 min. The median (IQR) length of stay was 10 (7, 15) days (Table S3). Overall, 514 (60%) and 223 patients (26%) experienced at least one complication and at least one severe complication within 3 months, respectively. One patient died within 1 month due to a complication (sepsis), and six patients died between 2 and 3 months after surgery (two from thromboembolic events, one from sepsis and three from cancer progression). Overall, 13 (1.5%) and 28 patients (3%) required intra-operative and postoperative blood transfusion, respectively. The rate of complications was highest in the first month post-surgery (early 52% vs late 20%). UTI was the most common complication at both time points (early: 20%, late: 10%; Fig. 1, Table S4). The most common early complications after UTI were paralytic ileus (10%) and urinary leakage/fistula (9%). The most frequent late complications after UTI were ureteric stricture (3%) and

urinary leakage/fistula (2%). Although UTI was the most common occurrence, this was not severe in the majority of cases (Fig. 1, Table S4). Urinary leakage/fistula and urinary device complication (defined as mispositioning or obstruction of the bladder catheter and/or ureteric stents) were the most common severe early complications, whereas ureteric stricture and lymphocele/lymphorrea were the most common severe late complications.

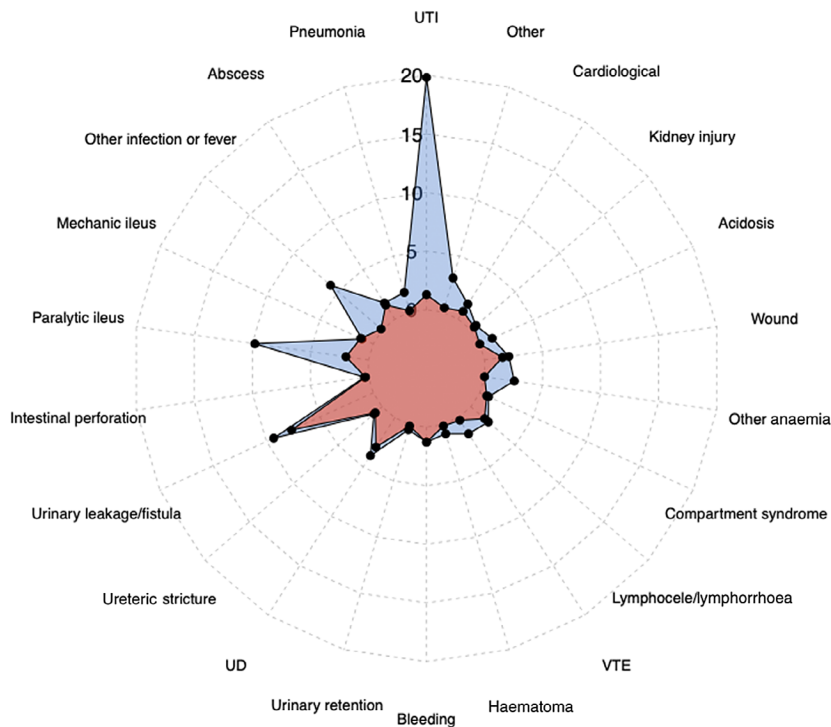
Among female patients, the most common early complications were UTI (20%), urinary leakage/fistula (7%) and paralytic ileus (6.5%), whereas the most common late complications were UTI (9%), ureteric stricture (3%) and urinary leakage/fistula (3%).

Approximately half of the population received nadJT (48%; Table S5). There were no significant differences in the rate of overall (59% vs 60%;  $P = 0.8$ ) and severe (26% vs 26%;  $P > 0.9$ ) complications between patients who received and those who did not receive nadJT. However, the rates of fever of unknown origin and paralytic ileus were significantly higher in the nadJT group (fever of unknown origin: 9% vs 4%,  $P = 0.012$ ; paralytic ileus: 13% vs 7%,  $P = 0.008$ ). On multivariable analysis, the centre's surgical experience was inversely associated with both overall (odds ratio [OR] 0.97, 95% CI 0.94, 0.99) and severe complications (OR 0.97, 95% CI 0.93, 1.00) after accounting for potential confounders (Table S6). By contrast, operating time was associated only with overall complications (OR 1.03, 95% CI 1.02, 1.05; Table S7).

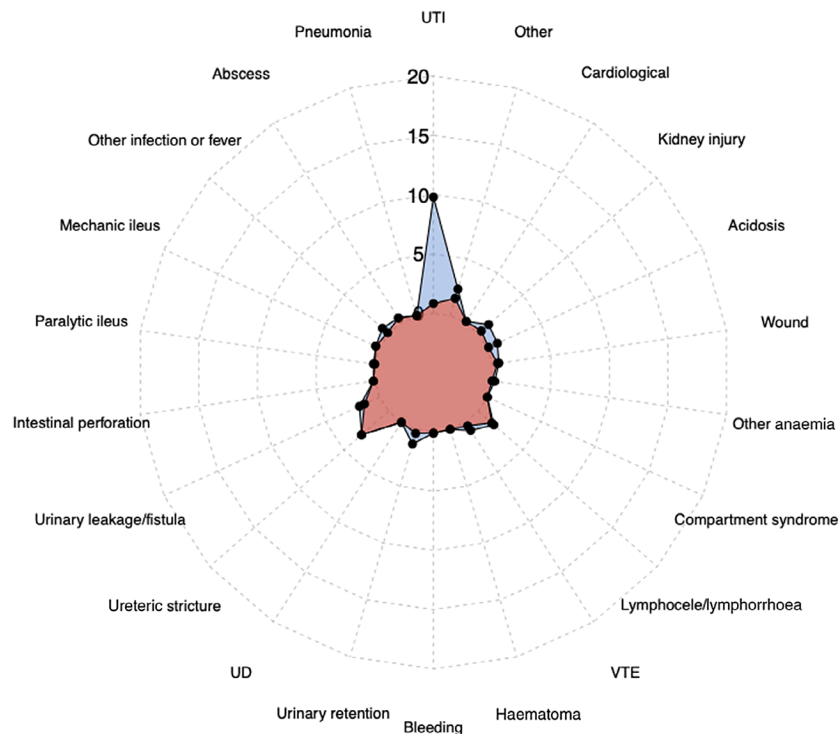
In the present study, we evaluated complications after RARC with intracorporeal neobladder. Our findings have several clinical implications. First, despite the rate of complications decreasing with increasing centre experience (multivariable analysis results), probably as a reflection of surgical learning and improvement in surgical technique, our results highlight a high overall rate of complications after RARC. This study therefore supports the need for future efforts aimed at improving surgical technique and peri-operative management. In particular, investigations are needed to improve bowel function recovery and ureteric-neobladder anastomosis, which, as emerged in our results, is frequently affected by leakage or stenosis. In the meantime, our findings could be used for modifying the peri-operative management of these patients. The enhanced recovery after surgery (ERAS) protocol was implemented in an effort to reduce some of these complications (e.g., paralytic ileus) [8] and should therefore be applied in clinical practice. Regarding the high incidence of urinary leakage/fistula, clinicians should consider performing a leakage test before removing stents and bladder catheters. Overall, UTI was the most common complication, although often not severe. Thus, performing a urine test and/or urine culture before surgery could be useful to prevent the incidence of this occurrence. Our results also underline the importance of

**Fig. 1** Distribution of early (a) and late (b) complications of patients who underwent robot-assisted radical cystectomy and intracorporeal neobladder reconstruction. Overall and severe (Clavien–Dindo grade  $\geq 3$ ) complications are reported in blue and red, respectively. UD, urinary device; VTE, venous thromboembolism.

**(a) Early complications**



**(b) Late complications**



careful management of the urinary device. Indeed, mispositioning or obstruction of the urinary device was one of the most common early severe complications. Finally, clinicians should be aware that the incidence of fever of unknown origin and paralytic ileus is higher in patients who received nadJT.

Despite several strengths, this study has some limitations. First, all patients underwent surgery at a tertiary referral centre with significant experience in robotic surgery. Second, the complication rate may be underestimated as it was based on the presence of condition codes, with the absence of such a record taken to indicate the absence of complications. However, it is important to note that our focus was on the most common type of complication following RARC and intracorporeal neobladder, and this aspect may be less affected by the aforementioned limitation compared to the overall rate of complications. Indeed, we can speculate that all types of complications were underestimated equally. Finally, because the follow-up was relatively short, the incidence of some late complications (e.g., ureteric stricture) may be underestimated.

To conclude, our results provide useful information for improving the management of patients who underwent RARC with intracorporeal neobladder. Moreover, our findings point to the need for future studies aimed at optimizing RARC and intracorporeal neobladder and reducing the incidence of complications following surgery.

## Disclosure of Interests

Alberto Martini and Guillaume Ploussard own equity in Oltre Medical Consulting, LLC, Toulouse, France.

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Abbreviations: ASA, American Society of Anesthesiologists; EAU, European Association of Urology; IQR, interquartile range; nadJT, neoadjuvant therapy; RARC, robot-assisted radical cystectomy.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** The quality criteria for accurate and comprehensive reporting of surgical outcomes recommended by the EAU Guidelines on reporting and grading of complications.

**Table S2.** Descriptive characteristics of 858 patients who underwent RARC and intracorporeal neobladder.

**Table S3.** Surgical outcomes of 858 patients who underwent RARC and intracorporeal neobladder.

**Table S4.** Overall complications grouped by type and divided into early (within 1 month) and late (between 2 and 3 months).

**Table S5.** Rate of complication for patients how received vs how did not receive neoadjuvant therapy (nadJT).

**Table S6.** Multivariable model to assess the association between center experience and risk of overall and severe complications (Clavien-Dindo score  $\geq 3$ ) within 3 months.

**Table S7.** Multivariable model to assess the association between operative time and risk of overall and severe complications (Clavien-Dindo score  $\geq 3$ ) within 3 months.

# Improving fluorescence confocal microscopy for margin assessment during robot-assisted radical prostatectomy: The LaserSAFE technique

Several studies have demonstrated that the NeuroSAFE technique is safe and accurate in guiding nerve-sparing decisions during robot-assisted radical prostatectomy (RARP) [1,2]. However, it remains uncertain whether this translates to better functional outcomes. The NeuroSAFE PROOF trial (<https://www.neurosafeproof.com/>) will generate Level 1 evidence to answer this question [3]. Recruitment is complete, and the study is in the follow-up phase with results expected in mid-2024. In identifying centres for this study, logistic concerns owing to the time- and resource-intensive nature of NeuroSAFE were found to be prohibitive for many NHS centres where RARP is performed in volume [4]. Therefore, we were interested in exploring potential alternatives to replace frozen section, such as ex vivo fluorescence confocal microscopy (FCM), as it can quickly generate digital scans of unfixed specimens, requiring minimal tissue preparation and consumables [5].

The first report to evaluate FCM as a tool for analysing positive surgical margins (PSMs) in RARP specimens described a Mohs-like technique to sample the posterolateral surface of the prostate [6]. Concordance with final pathology

was almost perfect; however, the procedure required up to 25 min to perform [7]. Recently in this journal, Baas et al. [8] described the results of analysing en face shavings of the posterolateral surface of the prostate using the Histolog® Scanner (SamanTree Medical SA, Lausanne, Switzerland), a commercially available, portable, laser confocal microscope with a large objective lens that is capable of scanning an area of 48 × 36 mm in 50 s. They found a sensitivity of 86% and specificity of 96% compared to the final pathology analysis (FPA), and a substantial agreement with NeuroSAFE ( $K = 0.80$ ). Nevertheless, both techniques still require the surgeon or pathologist to cut the area of interest to be analysed. This has limitations such as possible capsule retraction at the borders of the specimen leading to false positive margins, and the need for expertise in sample processing to avoid affecting final pathology results.

To address these limitations, we have developed the LaserSAFE technique to process intact RARP specimens using the Histolog Scanner to scan the entire posterolateral surface en face. This paper describes the LaserSAFE technique and reports its preliminary accuracy performance metrics.