Peri-Operative Outcomes after Open and Robot-Assisted Radical Cystectomy by Using an Advanced Bipolar Seal and Cut Technology (Caiman®): A Prospective, Comparative, and Multi-Institutional Study

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Objective: To report and compare the peri-operative outcomes of patients undergoing open (ORC) and robotic-assisted radical cystectomy (RARC) for bladder cancer performed with a radiofrequency seal and cut device (Caiman®).

Materials and Methods: Data of patients undergoing ORC or RARC between January 2015 and March 2016 at 6 Italian institutions were prospectively recorded and analyzed. Thirty-three (66%) and 17 (34%) patients were treated with ORC and RARC, respectively. The median age was 72 (64–78) years. Overall operative time was longer in RARC compared to ORC (389 ± 80.1 vs. 242 ± 62.2 min, p < 0.001), while the estimated blood loss during cystectomy was higher after ORC (370 ± 126.8 vs. 243.3 ± 201.6 ml, p = 0.03). The transfusion rate was significantly higher in the ORC compared to RARC (24.2 vs. 5.9%, p = 0.04). Eight (19%) and 7 (16.7%) patients experienced 30- and 90-day post-operative complications, with no significant difference between ORC and RARC. Length of stay was significantly shorter in RARC group (median 7 vs. 14 days, p < 0.001). Conclusion: Open and robot-assisted procedures were safely performed by using a new advanced bipolar seal and cut technology (Caiman®). RARC demonstrated to be superior to ORC in terms of bleeding, transfusion rates and length of hospital stay, despite longer operative time.

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Introduction

Radical cystectomy with pelvic lymph-node dissection (PLND) represents the standard of care for non-metastatic, muscle invasive bladder cancer or high-grade, refractory, multifocal, non-muscle invasive bladder cancer, and remains the most effective method for local control of the disease [1]. Currently, open radical cystectomy (ORC) is still the gold standard approach, but a significant morbidity, high complication rate and mortality is still related to this technique [2–4]. More recently, robot-assisted radical cystectomy (RARC) has emerged as an attractive alternative to ORC, aiming to reduce morbidity and complications, and to potentially improve peri-operative and functional outcomes [5–8].

Operative time, blood loss and the occurrence of intra- or post-operative complications are the main indicators of surgical quality. In recent years, several advanced sealing or stapling devices have been introduced in general and urological surgery with the aim to improve these peri-operative outcomes, especially blood loss and operative time. However, only few evidences in favor of these tools are available in literature to date, with no significant benefits actually offered in comparison to the standard hemostatic device [9, 10].

Aim of the present study was to report the intra-operative outcomes and complication rates in a prospective multi-institutional cohort of patients undergoing radical cystectomy for bladder cancer, performed with a radiofrequency seal and cut device (Caiman®). Furthermore, we sought to compare the peri-operative outcomes of individuals treated with either open or robot-assisted approaches.

Materials and Methods

We prospectively collected data of patients who underwent ORC or RARC for muscle invasive or high grade superficial bladder cancer in 6 high volume Italian Centers from January 2015 to March 2016. These patients were excluded: 1) with incomplete data; 2) undergone salvage radical cystectomies with palliative intent; 3) previously submitted to radical prostatectomy; 4) with coagulation disorders, severe liver or kidney impairment. According to these criteria, 50 consecutive patients were enrolled. ORC and RARC were performed by using a new sealing device (Caiman®, Aesculap AG, Tuttlingen, Germany).

PLND templates were defined as following: limited (external, internal iliac and obturator lymph nodes), standard (common iliac, external, internal iliac, obturator, presacral and peri-vesical lymph nodes) or super-extended (similarly to the standard PLND, plus pre-aortic and pre-caval lymph nodes) [11]. Whether to perform an extended or limited PLND was based on the preference of surgeons, according to the patient’s age, pathological stage, comorbidity and life expectancy.

Open and robot-assisted procedures were performed according to institutional preferences. In case of RARC, intracorporeal urinary diversion was performed in any case.

Table 1. Clinical data of the 50 patients enrolled in the study

| Variable                                      | Overall (n = 50) |
|-----------------------------------------------|-----------------|
| Age, years (mean ± SD)                       | 70 ± 11.2       |
| Median (IQR)                                 | 72 (64–78)      |
| BMI, kg/m2 (mean ± SD)                       | 26.5 ± 4.1      |
| Charlson Comorbidity Index, median (IQR)     | 2 (2–5)         |
| ASA score, median (IQR)                      | 2 (2–3)         |

ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range.
Table 2. Pathological and peri-operative data

| Variable                                      | Overall (n = 50) | ORC group (n = 33) | RARC group (n = 17) | p     |
|-----------------------------------------------|-----------------|-------------------|---------------------|-------|
| PLND template                                 |                 |                   |                     | 0.22  |
| Not performed                                | 9 (18%)         | 6 (18.1%)         | 3 (17.6%)           |       |
| Standard                                      | 25 (50%)        | 19 (57.6%)        | 6 (35.3%)           |       |
| Extended                                      | 12 (24%)        | 5 (15.2%)         | 7 (41.2%)           |       |
| Super-extended                                | 4 (8%)          | 3 (9.1%)          | 1 (5.9%)            |       |
| Nerve-sparing                                 |                 |                   |                     | 0.07  |
| Performed                                     | 4 (8%)          | 1 (3%)            | 3 (17.6%)           |       |
| Not performed                                 | 46 (92%)        | 32 (97%)          | 14 (82.4%)          |       |
| Global operative time, min (mean ± SD)       | 292 ± 97.5      | 242 ± 62.2        | 389 ± 80.1          | <0.001|
| Time for cystectomy, min (mean ± SD)         | 109 ± 57.2      | 96.1 ± 67.2       | 124 ± 40.5          | 0.15  |
| EBL during cystectomy, ml (mean ± SD)        | 303 ± 180       | 370 ± 126.8       | 243.3 ± 201.6       | 0.03  |
| Time for PLND, ml (mean ± SD)                | 57 ± 36.6       | 47.6 ± 22.1       | 69 ± 46.1           | 0.07  |
| EBL during PLND, ml (mean ± SD)              | 95 ± 82.6       | 102.5 ± 89.4      | 88.2 ± 78.1         | 0.62  |
| EBL overall, ml (mean ± SD)                  | 692 ± 450.5     | 777 ± 747.4       | 534 ± 153.2         | 0.21  |
| Intra-operative transfusions                  | 9 patients (18%)| 8 patients (24.2%)| 1 patient (5.9%)    | 0.04  |
| Mean number of blood units for each patient   | 1 unit          | 2 units           | 1 unit              |       |
| Length of stay, days (median, IQR)           | 12 (7–15)       | 14 (12–16)        | 7 (7–8)             | <0.001|

EBL = Estimated blood loss; IQR = interquartile range.

The following demographic and pathological data were prospectively recorded: age, gender, body mass index, American Society of Anesthesiologists score, Charlson Comorbidity index, ECOG performance status, clinical stage, and grade. Intra-operative data were: duration of detumoric steps of the procedure (cystectomy and lymphadenectomy), blood loss, intraoperative complications. Lastly, the following post-operative data were scheduled: pathological stage and grade, post-operative complications stratified according to the Martin’s criteria [12] and graded basing on the Clavien-Dindo classification [13], number of blood units administered after the procedure, length of hospital stay, rate and reasons for re-admission.

Follow-up data were obtained at the time of outpatients visit or by telephone calls. Institutional Review Board approval was obtained for this observational study. A flowchart of the study protocol is shown in figure 1.

Statistical Analysis

The means, standard deviations, medians, ranges and frequencies were used as descriptive statistics. Fisher’s exact test, the linear by linear association, Pearson’s chi squared and the Mann–Whitney U test were used to compare the 2 groups of patients. Statistical analyses were conducted using SPSS version 22.0 (Chicago, Illinois). Two-tailed p values less than 0.05 were considered statistically significant.

Results

Globally, 50 consecutive patients were evaluated. The median age was 72 (64–78) years. Thirty-three (66%) subjects underwent ORC (Group 1), while 17 (34%) were treated with RARC (Group 2). Thirty-seven (77.1%) patients were clinically diagnosed with muscle-invasive bladder cancer, mostly (94%) with high-grade. The 2 groups were comparable in terms of demographic, clinical and pathological characteristics, as reported in table 1.

A comparison of intra-operative outcomes between ORC and RARC is shown in table 2. Overall operative time was significantly longer in RARC group compared to ORC group (389 ± 80.1 vs. 242 ± 62.2 minutes, p < 0.001), while the estimated blood loss during cystectomy was lower (243.3 ± 201.6 vs. 370 ± 126.8 ml, p = 0.03). The 2 groups were comparable in terms of operative time for cystectomy, PLND and overall estimated blood loss (all p > 0.05).

Globally, 9 patients (18%) received intra-operative transfusions, with a median number of 1 red blood unit administered, with a transfusion rate significantly higher in ORC group (24.2 vs. 5.9%, p = 0.04). Only 1 event of intra-operative complication was described in 1 patient undergoing ORC (rectal injury repaired with 2-layers suturing, without colostomy). Technical problems or malfunctioning of the sealing device was observed only in 1 case, due to a defective closure of the jaws after repeated utilization during the procedure.

Eight patients (19%) experienced post-operative adverse events within 30 days, 5 (15%) and 3 (17.6%) undergoing ORC and RARC, respectively (p = 0.54). High-
grade Clavien complications were observed in 4 (50%) of these patients (2 in ORC and 1 in RARC group, respectively, \(p = 0.37\)). The reported complications were the following: urinary tract infection (n = 4), pneumonia (n = 4), wound infection (n = 2), urinary fistulas (n = 2), acute myocardial infarction (n = 1), occlusion (n = 1) and transient ischemic attack (n = 1).

The median length of hospital stay was considerably lower in the RARC group [7 (7–8) vs. 14 (12–16) days, \(p < 0.001\)].

During the follow-up, 7 (16.7%) complications were recorded between 30 and 90 days; high grade adverse events were found in 2 (28.6%) patients. Complications were the following: 1 wound dehiscence, 1 lumbar pain, 2 edemas of inferior limbs/genitalia, 1 lymphocele, 1 subocclusion and 1 intestinal occlusion, with no significant difference between ORC (n = 5) and RARC (n = 2). Two patients (4%) of the entire cohort – who had undergone ORC, died within 90 days from surgery for non-cancer related reasons (myocardial infarction in 1 case and pulmonary embolism in the other patient). No deaths were recorded in patients treated with RARC at the time of follow-up closure.

**Discussion**

The findings of our prospective, multi-institutional study suggest that robot-assisted approach, when compared to open surgery, allows reducing blood loss during cystectomy and the need for intra-operative transfusions, with a comparable incidence of post-operative complications and shorter length of hospital stay. To the best of our knowledge, this is the first prospective study evaluating and comparing the intra- and post-operative outcomes of patients undergoing ORC and RARC when performed by using an advanced sealing and cut device (Caiman®). To date, only few studies reported significant lower blood loss and transfusions rate when compared to other previously reported prospective, randomized and retrospective studies [5, 15, 16], with median blood loss ranging 208–1,118 ml, depending on the type (ileal conduit, neobladder) and surgical approach adopted (extracorporeal, intracorporeal) for urinary diversion [17]. It is important to underline the low need for intra-operative transfusions (5.9%) in our series, which is remarkably lower if compared to other RARC series, ranging 7–44% [17]. In our opinion these data are somewhat promising, even considering that all the robotic cystectomies were performed by a single surgeon during his learning curve. In the present study, RARC demonstrated to lower the blood loss compared to ORC during cystectomy (243 vs. 370 ml, \(p = 0.03\)) and during the entire procedure (534 vs. 777 ml), even if not statistically significant in the latter case. Furthermore, the rate of intraoperative transfusions was found to be lower in the RARC group (5.9 vs. 24.2%). These findings are not surprising, since many reports and systematic reviews of cumulative or randomized studies confirmed the advantage of robotic approach in decreasing the blood loss and transfusions rate when compared to open technique [5, 7, 15, 16, 18, 19].

In our series, global operative time was found to be significantly longer after RARC than ORC (389 ± 80.1 vs. 242 ± 62.2 minutes, \(p < 0.001\)). This result is comparable with most of the studies that have been published to date [8, 15, 16, 18]. The most complex surgical steps

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during RARC, especially considering the reconstructive phases (intracorporeal urinary diversion, ileal neobladder), actually represent the most important factors responsible for a longer operative time. Only few studies reported similar operative time between the 2 techniques [14, 19]. Notably, in the randomized trial by Parekh et al. [19], no surgical details were offered in terms of urinary diversion choice or approach (extracorporeal/intracorporeal); conversely, Gondo et al. [14] performed all the urinary diversion after RARC by an extracorporeal approach, thus offering a possible explanation for an overlapping operative time between the 2 techniques.

The overall 30- and 90-day complication rates were 19 and 35.7%, respectively; high-grade adverse events were recorded in 8 and 4% of our patients, respectively. The occurrence of 30-day complications was similar between patients undergoing ORC (15%) and RARC (17.6%). When compared to the previously published studies, however, our series shows a quite low occurrence of 30- and 90-day adverse events. Cusano et al. [8] reported a 30-day incidence of complication in 54.3 and 47.1% of patients treated with ORC and RARC, respectively (p = 0.33); similarly, Gondo et al. [14] showed adverse events after 30 days in 54.5% of ORC and 73.3% of RARC (p = 0.41). A quite higher occurrence of post-operative complications was reported in the 2 recent randomized trials as well. Bochner et al. [15] showed an overall complications rate of 66% after ORC and 62% after RARC (p = 0.66); Khan et al. [16] reported a 30-day complication rates of 70% in ORC and 55% in RARC patients (p > 0.05). In this randomized study, the 90-day complication rates did not differ significantly between ORC (70%) and RARC (55%, p = 0.068).

In the present study, the robotic approach halved the length of stay in comparison to open technique (7 vs. 14 days, p < 0.001), and equivalent data have been reported by other retrospective studies [7, 20]. Regardless of the surgeon’s experience, we believe that the unquestionable advantage offered by robot-assisted approach, with lower surgical trauma, less post-operative pain and faster recovery, are the main explanations for such finding. However, it must be noted is often difficult to compare length of stay among studies, as it could largely vary between different hospitals and countries, basing on internal policies or insurance duties. Indeed, 3 randomized trials failed to demonstrate a significant advantage offered by robotic approach, with comparable length of stay between ORC and RARC [15, 16, 18, 19]. Despite the prospective design and the multi-institutional patients’ recruitment, our study is not devoid of limitations. First, this is a quite small cohort, comparing 2 unbalanced and unmatched groups of patients, giving a potential exposure to several biases. Second, we did not perform a randomization between subjects treated with Caiman® and those without, constraining to compare any potential benefit with the results already reported in literature.

Conclusion

Data obtained from our multi-institutional, prospective study of robot-assisted and open radical cystectomy with PLND showed the safety and efficacy of a new advanced bipolar seal and cut technology (Caiman®) in the demolitive steps of the procedure, contributing to potentially limit the blood loss in our series. Robot-assisted approach demonstrated to be superior to open technique in terms of bleeding, transfusion rates and length of hospital stay, despite a longer operative time. Other prospective studies with a larger cohort of patients are needed in order to confirm and validate these promising data.

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