**Original article**:

**Robot-assisted versus open radical cystectomy in patients receiving perioperative chemotherapy for muscle-invasive bladder cancer: the oncologists’ perspective from a multicenter study**

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On behalf of the Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC)

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**Running title:** Robot-assisted versus open radical cystectomy as multimodal management of UBC.

**Keywords:** Urothelial carcinoma; Cystectomy; Robot-assisted surgery; Muscle-invasive disease; Perioperative chemotherapy

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**Abstract:**

**Background**:

Little is known about the outcomes of robot-assisted radical cystectomy (RARC) compared to open radical cystectomy (ORC), combined with perioperative chemotherapy, for muscle-invasive urothelial bladder carcinoma (UBC).

**Objective**: We aimed to evaluate if surgical and oncological outcomes with different surgical approaches in the context of multimodal treatment.

**Design, Setting, Participants:** Data from 28 centers was collected with cystectomy performed between 01/2000 and 07/2013.

**Intervention**: RARC or ORC combined with perioperative chemotherapy for muscle-invasive UBC.

**Outcome measures and statistical analysis:** Fisher’s exact tests, χ2 tests, and Wilcoxon rank sum tests were used to compare RARC or ORC groups. Logistic and Cox regression analyses were performed to evaluate potential prognostic factors.

**Results and limitations**:

688 patients (n=603 ORC and n=85 RARC) were eligible for the analyses. 60.6% received neoadjuvant and 45.1% adjuvant chemotherapy. No statistically significant difference was found in baseline characteristics between the ORC and RARC groups. Median (interquartile range, IQR) time from surgery to adjuvant chemotherapy was 1.9 months (1.4-2.4) for RARC and 1.9 months (1.4-2.5) for ORC (p=0.98). Median (IQR) number of removed lymph nodes was 21 (14-35) with RARC and 13 (8-21) with ORC (p<0.001); results were confirmed in subgroup analyses. No difference was found in multivariable analyses in either the rate of positive surgical margins (p=0.54 and p=0.78), rate of neobladder diversion (p=0.33 and p=0.51), relapse-free survival (p=0.31 and p=0.23), or overall survival (p=0.63 and p=0.69).

**Conclusions**:

In this study no substantial differences in efficacy outcomes or ability to deliver adjuvant chemotherapy were observed between RARC and ORC. The increasing use of RARC is justifiable from the oncological viewpoint.

**Patient summary:** In retrospective study of patients who received perioperative chemotherapy for muscle-invasive UBC, we found no difference in efficacy and surgical outcomes between RARC and ORC. Performing RARC seems to be justifiable in a multidisciplinary setting.

**Introduction**:

Urothelial bladder cancer (UBC) is a highly aggressive disease, being the 5th most common cancer in the Western world and the second most frequent malignancy of the urinary tract after prostate cancer.[1] For patients who present with a localized high-risk disease, i.e. patients either who have a non muscle-invasive tumor but have failed standard conservative treatments or those with upfront or who have developed muscle invasive disease, radical cystectomy is the mainstay of curative treatment. Key negative prognostic factors are the regional lymph node spread of the disease and the local extent. For this reason, the achievement of negative surgical margins and the extent of the lymph node dissection have a recognized paramount importance in UBC, being the number of lymph nodes removed at the time of radical cystectomy the objective of several manuscript on this topic.[2-6]

For patients with muscle-invasive tumors, the highest possibilities of cure can be obtained by associating a systemic therapy in most cases.

The administration of neoadjuvant chemotherapy improves overall survival (Level 1 evidence) and is included in the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines, whenever cisplatin-based regimens can be safely administered.[7,8] However, pre-operative therapy is underutilized worldwide for many reasons, and neoadjuvant chemotherapy is administered in about 20% of cases.[8,9] Conversely, the administration of adjuvant chemotherapy has yielded multiple controversial and negative studies, yet it is still frequently administered and recent data from a large clinical trial, a population-based study and a meta-analysis have supported its use in selected patients with high-risk features.[11,12]

Advances in technology have facilitated the spread of minimally-invasive techniques to perform radical cystectomies, and robot-assisted laparoscopic approaches have been developed and improved in many centers. Robust literature is already available about the safety outcomes of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC). Key parameters including the length of hospital stay, intraoperative blood loss, and early and delayed post-surgical complications have been already described.[13,14] Most of these data are relative to patients who were offered surgery with no additional therapy, and thus far limited information about the comparative results of RARC and ORC is available for patients who have been administered perioperative chemotherapy. For example, the time between chemotherapy administration and surgery, or *vice-versa*, yields paramout importance for patient’s cure, as well as to know whether there might be some differences in the above-mentioned surgical parameters in patients who have received multimodal treatment. With the aim to compare the most important surgical and oncological results between RARC and ORC in the context of multimodal disease management, an international, multicenter, retrospective study was carried out.

**Patients and Methods**:

*Patient selection*:

The Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) is a retrospective study including individual patient-level data from patients with muscle-invasive or advanced urothelial carcinoma or non-urothelial histology who have received any systemic therapy during their disease course. This contemporary database includes data gathered from hospitals in the United States, Europe, Israel, and Canada. The RISC study was approved by the ethics committee at each participating institution.

In July 2016, data were extracted to select patients who fulfilled the following characteristics: bladder tumor primary site, any tumor histology (i.e. pure or prevalent urothelial carcinoma or non-urothelial variant histologies), administration of cisplatin- or carboplatin-containing neoadjuvant and/or adjuvant chemotherapy, and performance of radical cystectomy as either RARC or ORC. Data analysis was performed externally by a senior statistician (GP).

*Statistical analyses:*

The study objective was to determine whether differences existed in surgical performance or oncological outcome measures between RARC and ORC groups. The endpoints of surgical quality consisted in the following parameters: number of removed lymph-nodes, rate of pathologically-assessed positive surgical margins, and frequency of performed neobladder diversion type. Survival endpoints like RFS and OS, as well as the time from neoadjuvant chemotherapy to surgery, and from surgery to the start of adjuvant chemotherapy, were aimed at assessing oncological outcomes. Patients who were operated from January 2000 to July 2013 were included for analysis. Patient, disease, and outcome characteristics were summarized using descriptive statistics with frequencies and percentages used for categorical variables and medians and inter-quartile range (IQR) for continuous variables. Fisher’s exact tests, χ2 tests, and Wilcoxon rank sum tests were used to examine if factors were different between patients undergoing ORC or RARC. Logistic regression (for dichotomous outcomes) and Cox regression analyses (for time-to-event outcomes) were performed to evaluate potential prognostic factors. Complete case analysis was performed and no imputation was performed for missing data. However, to account for the substantial missing data which occurred due to the retrospective nature of this analysis, multiple supportive models were constructed for each outcome to explore the robustness of effects. Additionally, multivariable models were based on pre-specified factors that were hypothesized to be clinically important. All tests were two-sided and statistical significance was defined as a p-value of 0.05 or less. All analyses were performed in SAS version 9.2.

**Results:**

*Patient, disease, treatment characteristics and outcomes*:

The study flow chart is presented in Figure 1. Of 3,024 registered cases, 729 patients were initially identified. Of these, 41 patients were excluded due to missing information, leaving 688 patients (85 in the RARC group and 603 in the ORC group, respectively), treated from January 2000 to July 2013 from 28 contributing centres, were suitable for analyses. Summary statistics, which describe respondent characteristics, are presented in Table 1. Almost half of the patients from the RARC group (49.4%) came from 2 centers (i.e., City of Hope Comprehensive Cancer Center [COH] and Fox Chase Cancer Center), otherwise, there were no statistically significant differences between the groups according to the other analysed factors.

Tables 2 and 3 present the distribution of key factors between the two groups. Overall, the number of removed lymph nodes was greater with RARC than with ORC: 21 (IQR: 14-34.5) vs 13 (8-21, p<0.001, Figure 2A). The difference remained significant in subgroup analysis. Conversely, no difference was found in the rate of positive surgical margins (overall, p=0.59) and neobladder (p=0.33, Figure 2B). These results remained consistent across patient subgroups.

Among the survival outcomes, no statistically significant differences were found in the median time from end neoadjuvant chemotherapy to cystectomy (3.68 months for RARC vs 3.52 months for ORC, p=0.51) and from cystectomy to initiation of adjuvant chemotherapy: 1.9 months (range 0.4-4.2) for RARC and 1.9 (0.07-5.7) for ORC (p=0.98). The number of removed lymph nodes did not significantly change during the years (i.e. 2000 to 2006, 2007-2010, and ≥2011) in both groups: for RARC, Spearman correlation coefficient=0.075, p-value=0.50; for ORS, Spearman correlation coefficient=0.03, p-value=0.56. Finally, there were no significant differences in survival outcomes: 1-year and 5-year RFS were 70.3% (95%CI: 59-79.1) and 52.1% (95%CI: 39-63.7) in the RARC group and 68.3% (95%CI: 64.3-72) and 32.2% (95%CI: 27.4-37.1) in the ORC group, respectively (p=0.31). As for OS, 1-year and 5-year estimates were 86% (95%CI: 76.2-92) and 48.4 (28.4-65.8) for RARC and 84.7% (95%CI: 81.4-87.4) and 44.3% (95%CI: 38.9-49.5) for ORC (p=0.33).

*Results of univariable and multivariable analyses*:

Logistic regression analyses are presented in Table 3. No factor was statistically significant as prognostic for having positive surgical margins in the multivariable model. Notably, all patients from COH were missing the Charlson comorbidity index. Hence, for multivariable analyses, it was not possible to include the three-site grouping and Charlson index in the model.

As for the rate of urinary diversion type, increasing age and higher Charlson index were less likely to be associated with neobladder (p=0.002 both) while the administration of neoadjuvant chemotherapy was significantly associated to the chances of having a neobladder (OR: 2.42, 95%CI: 1.38-4.27, p=0.002). Surgical modality was not associated with any outcome. No interaction effect was observed to be statistically significant between age, Charlson index and neoadjuvant therapy. Cox regression analyses are shown in Supplementary Table 1. Multivariably, there were no differences in both RFS and OS between the two groups, as also shown in Supplementary Figure 1A,B.

**Discussion**:

We have provided results from one of the few studies assessing surgical and oncological outcomes between RARC and ORC in the context of multidisciplinary patient management in UBC, and by analysing data from a multicentric international database. In the context of a recommended partnership between surgical and medical disciplines, the advances in technique of surgical resection did not result to significanlty affect key oncological parameters.

Since a few years ago, there is an ongoing debate among surgical urology specialists as to whether improvements in technology with the use of robot-assisted cystectomies may lead to a change in the standard indication for cystectomy in UBC. A huge amount of data is already available that compares robotic vs. open surgical procedures, mainly focusing on immediate and long-term morbidity issues.[15-23] Results from almost all these studies are retrospective in nature, and the level of evidence is usually low for RARC data. Trend are for longer operating time and hospital stays for RARC but less intraoperative blood loss compared to ORC, and substantial overlapping in mixed post-surgical quality of life parameters may be noted, although these outcomes are highly-dependent on the surgical volume of each center. Of note, similar findings were prospectively reported in a United States pivotal, randomized study comparing RARC with ORC. After the inclusion of 118 patients, the investigators found no significant reduction in perioperative complications with RARC as compared with ORC (with the use of extracorporeal urinary diversion in both cases), and the trial was closed in advance for futility reasons.[24,25]

Additionally, contradictory results have been presented by multiple authors in regards to the relative costs of each surgical procedure. In principle, it will remain very hard to compare the performance of RARC and ORC. In fact, RARC use is continually being boosted by technological improvements, and as a result is being increasingly used in many centers worldwide. Hence, it is likely that robotic technology use will eventually become more frequent than open procedures in referral centers, although current data have not sufficiently proven the advantages or disadvantages of either technique for oncological and functional outcomes.

In the present analysis, two key oncological findings do not seem to be negatively affected by robotic surgical technique: i.e. the number of lymph nodes removed (otherwise referred to as lymph node yield) and the frequency of positive surgical margins in the radical cystectomy specimens. As for the former, we observed a significantly higher median number of lymph nodes in the surgical specimens of RARC group, although the inherent bias of center selection and the different sample size between the two groups may account for this result. Yet these findings confirm that extended lymph node dissection is possible during RARC,[18,19] the number of lymph nodes removed was high independent of the time of data collection, and the analysis further support patient centralization in high-volume centers whenever RARC is planned, especially for combination with chemotherapy. Of course, an adequate pathological assessment is always implied when dealing with the number of lymph nodes removed at the time of radical cystectomy, and the lack of information on such assessment should be recognized as another inherent bias when interpreting results. Another important limitation in evaluating the number of lymph nodes refers to the pathologist judgement that may vary across the centers worldwide.

In regard to the frequency of tumor positive surgical margins, we found again substantial overlap between the surgical techniques, as it was observed in an analysis from the International Robotic Cystectomy Consortium (IRCC) database.[26]

The above outcomes, added to the comparable number of neobladder diversions in the two groups, were also found in subgroup analyses from patients with more advanced and high risk disease, such as those with high T and N stage. As expected, increasing age and Charlson comorbidity index were inversely associated with the probability of performing a neobladder diversion in both univariable and multivariable analyses. Conversely, the administration of neoadjuvant chemotherapy seemed to be associated with the possibility to perform neobladder reconstruction. In referral centers, urologists tend to counsel almost all patients under the age of 70 toward neoadjuvant chemotherapy, and tend to also counsel them toward the neobladder urinary diversion. Hence the observed association may be ultimately the product of the belief that younger, healthier patient is a better candidate for neoadjuvant chemotherapy and neobladder urinary diversion.

Of course, the presence of certain biases may have affected other results. Most of these limitations ultimately refer to the nature of our data. First, the RISC database was aimed to collect information on the outcomes of different systemic therapies in UBC (i.e. from neoadjuvant therapy to salvage therapy after chemotherapy failure): for this reason, it is plausible that a selection of patients trending to worse outcomes is generally seen when analysing surgical outcomes, that usually refer to the early stages of disease. However, despite retrospective nature of this study, it is likely that this bias is equally distributed in the two groups. Second, despite the large numbers overall, the number of RARC cases was not so high to allow for highly powered analyses, and this bias may further affect the results of the subgroup analyses. Also, RARC cases were contributed by a limited number of centers, emphasizing that complex surgical techniques are usually provided by selected high-volume centers, either inside or outside of clinical trials. Third, we were unable to provide data about safety outcomes, because these data were not captured in the RISC database. Robust literature is already available on this issue in general, either from the surgical and the oncological viewpoint, yet prospective reporting of side effects after chemotherapy plus robotic surgery are warranted.

In the field of robotic surgery, enormous efforts are being made to enhance the urologists’ learning curve as well as to lower the incidence of postoperative complications and shorten the length of hospital stay and patient recovery.[27] In our study we were able to provide information on one very important safety parameter that also yields oncological value, i.e., the time from cystectomy to initiation of adjuvant chemotherapy, and no difference between the groups was observed.

Finally, as an observation outside of the aim of this study, increasing Charlson comorbidity index was strongly associated with both worse RFS and OS. The incorporation of this still underused factor into new decision-making tools, before administering perioperative chemotherapy, is encouraged as outlined in recent guidelines.[28] Additional prognostic factor analyses are suggested to compare the prognostic utility of Charlson index with other comorbidity scores.

**Conclusions**:

In summary, we presented the results of a retrospective analysis comparing key oncological outcomes between RARC and ORC in patients with muscle-invasive UBC who received complementary neoadjuvant or adjuvant chemotherapy. Results showed a substantial overlap in all these parameters irrespective of the type of surgery the patients received. Our study provides further evidence supporting robot-assisted procedure and discussion in multidisciplinary setting, although the issues related to cost-effectiveness balance when performing robotic procedure remain open to debate.

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**Legend to figures**:

**Figure 1**: Study flow chart, with counts and reasons for patient selection.

**Figure 2**: Box plots showing the overall comparison of robot-assisted and open radical cystectomy groups according to the number of removed lymph-nodes (Panel A), and according to the rate of positive surgical margins and neobladder urinary diversions (Panel B).

**Supplementary Figure 1A,B**: Kaplan-Meier curves of relapse-free survival (A) and overall survival (B) in the overall population according to the type of radical cystectomy.

*Legend*: black line: open radical cystectomy; red line: robot-assisted radical cystectomy.