



Minimally Invasive Radical Prostatectomy after Previous Bladder Outlet Surgery: A Systematic Review and Pooled Analysis of Comparative Studies

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Purpose: Prostate cancer surgery after previous bladder outlet surgery of benign prostate hypertrophy is an uncommon yet challenging scenario. We performed a systematic review and pooled analysis of comparative studies on laparoscopic and robotic minimally invasive radical prostatectomy after bladder outlet surgery.

Materials and Methods: We searched the literature on PubMed®, Embase® and Web of Science™ up to February 2019 according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement to identify eligible studies. Surgical, oncologic and functional outcomes in patients who underwent minimally invasive radical prostatectomy after bladder outlet surgery were compared to those without a history of bladder outlet surgery. Sensitivity analysis was done according to surgical technique (laparoscopic or robotic). RevMan 5.3 was used for statistical analysis.

Results: A total of 12 comparative studies were included in analysis. Patients who underwent minimally invasive radical prostatectomy after bladder outlet surgery were older ($p \leq 0.00001$) and had a smaller prostate ($p = 0.04$) and lower prostate specific antigen ($p = 0.003$). The previous bladder outlet surgery group had lower odds of nerve sparing procedures, longer operative time, a higher rate of bladder neck reconstruction (each $p < 0.0001$) and longer catheter time ($p = 0.03$). They were at higher risk for intraoperative ($p = 0.001$), overall ($p < 0.00001$) and major complications ($p = 0.0008$), a higher positive surgical margin rate ($p = 0.0005$) and biochemical recurrence ($p = 0.05$). Moreover, potency ($p = 0.03$) and continence recovery ($p = 0.007$) at 12 months were lower in men with previous bladder outlet surgery. Robotic surgery seemed to offer better outcomes than laparoscopy.

Abbreviations and Acronyms

BOS = bladder outlet surgery

BPH = benign prostate hypertrophy

LRP = laparoscopic radical prostatectomy

MIRP = minimally invasive radical prostatectomy

OT = operative time

PICO = Population, Intervention, Comparator, Outcome

PSA = prostate specific antigen

PSM = positive surgical margin

RARP = robot-assisted radical prostatectomy

TURP = transurethral prostate resection

WMD = weighted mean difference

Accepted for publication April 12, 2019.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

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Editor's Note: This article is the ●●● of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions ●●● and ●●●.

Conclusions: Minimally invasive radical prostatectomy after previous bladder outlet surgery represents a challenging surgical task with a higher risk of complications and higher odds of worse functional and oncologic outcomes. Patients should be aware of these drawbacks and these factors should be considered during patient counseling. When surgery is pursued, robot-assisted radical prostatectomy should be preferred over laparoscopic radical prostatectomy since it can offer superior outcomes. The overall literature on this topic is of low quality and further efforts should be made to obtain higher levels of evidence.

Key Words: prostatic neoplasms, urinary bladder neck obstruction, prostatectomy, robotic surgical procedures, laparoscopy

In the last decade laparoscopic or robotic MIRP has gradually replaced open radical prostatectomy as the gold standard surgical treatment of prostate cancer. This paradigm shift was mainly fueled by the rapid implementation of robot-assisted laparoscopy.¹ Indeed, RARP has proved to provide better intraoperative and postoperative results than its open counterpart² but with comparable oncologic and functional outcomes.³ Standard LRP is still performed at centers where robotic technology is not available and laparoscopic expertise is present.⁴

MIRP after BOS of BPH has been reported and it can represent a challenging surgical task.⁵ However, the literature remains sparse and there is a lack of robust evidence on this subject. Our aim was to perform a systematic review and a pooled analysis of studies comparing the outcomes of MIRP in patients treated with BOS vs those in patients without a history of previous BPH surgery.

MATERIALS AND METHODS

Literature Research Strategy

Two of us independently assessed the literature on MIRP after BOS and another of us screened the results. We queried the PubMed®, Embase® and Web of Science™ search engines up to February 2019. Supplementary figure 1 (<https://www.jurology.com>) shows the research strategy. During the literature search studies were filtered to exclude nonEnglish language articles, congress abstracts, letters to the editor, editorial comments and studies published before 2000. A reference list of each study eligible for analysis was reviewed to avoid missing articles.

Study Selection

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement^{6,7} served as the guideline for study selection. The study design was established according to the PICO process.⁸ Eligible studies had to include patients with prostate cancer who underwent MIRP (Population) with (Intervention) or without (Comparator) a history of BOS so that surgical, oncologic and functional outcomes (Outcome) could be compared. The first step was to assess study titles to exclude those inconsistent with the PICO question. After this first screening the abstract of each potentially eligible study was carefully evaluated and those fully

compatible with the PICO process were included in the meta-analysis.

Data Extraction

Certain data were included in the meta-analysis. The baseline features were patient age, body mass index, prostate size, PSA, mean Gleason score, Gleason score 7 or less and greater than 7, and pathological extension. Data on surgical outcomes included nerve sparing procedures; estimated blood loss; operative and catheter times; the bladder neck reconstruction and transfusion rates; intraoperative, postoperative and major complications; anastomotic leakage; and stricture. The oncologic outcomes were pathological extension, PSMs, the mean Gleason score, Gleason score 7 or less and greater than 7, and biochemical recurrence. The functional outcomes were potency and complete continence at 12 months of followup.

Study Quality Assessment

All included reports were stratified according to the level of evidence as described by the Oxford Level of Evidence Working Group 2011.⁹ Study quality was established according to the NOS (Newcastle-Ottawa Assessment Scale) for nonrandomized controlled trials.¹⁰ Given the mean quality level of analyses, scores of 5, 6 or 7 and 8 or 9 were considered low, intermediate and high, respectively. The study quality evaluation was completed using the CCRBT (Cochrane Collaboration Risk of Bias Tool)¹¹ to account for bias.

Data Analysis

Analysis was performed on continuous and dichotomous variables. The inverse variance WMD was applied to summarize continuous variables and the Mantel-Haenszel test was used to calculate the OR and 95% CI of binary values. Heterogeneity among studies was assumed not to be influenced by sample size only and a random effects model was used to establish I^2 .¹² The heterogeneity level was stratified as low—25% or less, intermediate—25% to 50% and high—greater than 75%.

We used the Hozo formula¹³ to convert comparable data reported as the median and range to the mean \pm SD. The grand mean was used to calculate overall mean of data on inherently the same variable but split into 2 groups. In addition, we assessed patient subcategories according to the surgical procedure. Then we performed sensitive analysis of studies comparing outcomes of interests for laparoscopic and robotic procedures.

Meta-analysis was performed with RevMan, version 5.3 (<https://community.cochrane.org/help/tools-and-software/revman-5>). Statistical significance was considered at $p < 0.05$.

RESULTS

Study Features

Supplementary figure 1 (<https://www.jurology.com>) shows the study selection PRISMA flow chart. The literature search identified 12 comparative studies which were deemed eligible for meta-analysis.^{14–25} All studies were retrospective, including 7 retrospective cohort analyses,^{14–23} 4 matched paired analyses^{15–24} and 1 case series.¹⁸ Further stratification was done according to surgical technique. Six reports described laparoscopic surgery in a total of 2,334 patients, including 365 treated and 2,215 not treated with BOS,^{14–25} and 6 described inherent robotic surgery in a total of 3,425 patients, including 247 treated and 3,178 not treated with BOS.^{17–24} Overall the meta-analysis included 5,969 patients, including 612 and 5,357 treated and not treated with BOS, respectively (supplementary table 1, <https://www.jurology.com>).

Overall Analysis

Baseline Features. The BOS group presented at an older age (WMD 2.25 years, 95% CI 1.23–3.27, $p < 0.0001$) with a smaller prostate size (WMD -9.30 ml, 95% CI -18.18 – -0.43 , $p = 0.04$) and lower PSA (WMD -1.33 ng/dl, 95% CI -2.19 – -0.46 , $p = 0.003$). No difference was found between the groups in the remaining baseline characteristics (supplementary table 2, <https://www.jurology.com>).

Operative Outcomes. There were higher odds of undergoing a nerve sparing procedure in the BOS naïve patient group (OR 3.83, 95% CI 2.66, 5.52, $p < 0.00001$, supplementary fig. 2, <https://www.jurology.com>). Longer OT (WMD 22.51 minutes, 95% CI 11.64–33.37) and a higher rate of bladder neck reconstruction (OR 21.04, 95% CI 5.00–88.49, each $p < 0.0001$) were found in the BOS group. Moreover, the BOS group had longer catheter time

(WMD 0.96 days, 95% CI 0.10–1.81, $p = 0.03$), a higher complication rate intraoperatively (OR 8.22, 95% CI 2.28–29.65, $p = 0.001$) and overall post-operatively (OR 3.10, 95% CI 2.28–4.21, $p < 0.00001$), and a higher major complication rate (WMD 2.87, 95% CI 1.55–5.31, $p = 0.0008$). In the BOS group there was also a higher risk of anastomotic leakage (OR 2.48, 95% CI 1.42–4.34, $p = 0.001$) and post-operative stricture (OR 4.88, 95% CI 2.66–8.95, $p < 0.00001$, supplementary table 3, <https://www.jurology.com>).

Oncologic and Functional Outcomes. The PSM rate was higher in the BOS group (OR 1.52, 95% CI 1.20–1.93, $p = 0.0005$), as was the risk of biochemical recurrence (OR 1.84, 95% CI 1.00–3.39, $p = 0.05$). No difference was found between the 2 groups in pathological extension or the Gleason score (supplementary table 4, <https://www.jurology.com>). There was a significant difference in potency recovery between the 2 groups with a lower rate in the BOS group (OR 1.80, 95% CI 1.04–3.09, $p = 0.03$). The rate of complete recovery of continence was similarly lower (OR 1.61, 95% CI 1.14–2.27, $p = 0.007$, see table).

Sensitivity Analysis of Laparoscopic or Robotic Surgical Technique

Baseline Features. In the BOS group patients who underwent LRP or RARP were older ($p = 0.0004$ or 0.007 , respectively). Those treated with LRP presented with a smaller prostate (WMD -14.53 ml, 95% CI -29.14 – 0.07 , $p = 0.05$) and lower PSA (WMD -1.70 ng/dl, 95% CI -2.57 – -0.83 , $p = 0.0001$). However, there was no difference between the 2 study groups in patients treated with RARP (supplementary table 2 and fig. 3, <https://www.jurology.com>).

Operative Outcomes. RARP was associated with a higher incidence of bladder neck reconstruction in the BOS group ($p = 0.0003$). However, these data were not assessable for LRP. Catheter time was longer in the BOS group in patients who underwent LRP (WMD 4.87 days, 95% CI 0.30–9.43, $p = 0.04$) but there was no difference in those treated with RARP. For LRP the rate of intraoperative complications were higher in the BOS group (OR 11.69, 95% CI

Study group functional outcomes

| 12-Mo Outcomes | No. Studies | No. Bladder Outlet Surgery/Total No. | | T ² | Chi-Square | Degrees of Freedom | p Value | % I ² | OR (95% CI) | p Value |
|----------------------|-------------|--------------------------------------|-------------|----------------|------------|--------------------|---------|------------------|------------------|---------|
| | | Yes | No | | | | | | | |
| Potency: | | | | | | | | | | |
| Overall | 6 | 28/259 | 567/1,766 | 0.19 | 9.12 | 5 | 0.10 | 45 | 1.80 (1.04–3.09) | 0.03 |
| Laparoscopic | 2 | 23/144 | 402/1,442 | 0.44 | 3.75 | 1 | 0.05 | 73 | 2.01 (0.69–5.82) | 0.20 |
| Robotic | 4 | 55/115 | 165/324 | 0.29 | 5.35 | 3 | 0.15 | 44 | 1.60 (0.70–3.63) | 0.26 |
| Complete continence: | | | | | | | | | | |
| Overall | 7 | 246/339 | 1,943/4,411 | 0.00 | 3.46 | 6 | 0.75 | 0 | 1.61 (1.14–2.27) | 0.007 |
| Laparoscopic | 3 | 133/169 | 1,293/1,467 | 0.00 | 0.05 | 2 | 0.98 | | 1.89 (1.23–2.89) | 0.003 |
| Robotic | 4 | 174/243 | 650/2,944 | 0.00 | 1.66 | 3 | 0.65 | | 1.15 (0.68–1.97) | 0.60 |

1.88-72.70, $p = 0.008$). Higher risks of anastomotic leakage (OR 2.86, 95% CI 1.41-5.74, $p = 0.03$) and stricture (OR 6.35, 95% CI 3.28-12.32, $p < 0.00001$) were associated with LRP in the BOS group but no statistical differences were found for RARP (supplementary table 3 and fig. 3, <https://www.jurology.com>).

Oncologic and Functional Outcomes. LRP and RARP carried a higher risk of PSM in the BOS group ($p = 0.02$ vs 0.006). The 2 groups overlapped in regard to the other oncologic outcomes (supplementary table 4, <https://www.jurology.com/>, and fig. 1). Complete continence was lower in the previous surgery LRP group than in the robotic LRP group ($p = 0.03$ vs 0.60, see table and fig. 2).

Publication Bias

Each bias risk assessment revealed a high risk of selection, performance and detection bias with a fair level of uncertain bias. We found no obvious high risk of attrition, reporting or other bias in most studies (supplementary figs. 4 and 5, <https://www.jurology.com>).

DISCUSSION

To our knowledge we report the first systematic review and pooled analysis of comparative studies on MIRP after BOS. Several findings in this large sample of more than 5,000 cases are worth discussing. Collectively MIRP in patients with previous BOS was confirmed to be a challenging procedure,

given the potential for worse surgical, oncologic and functional outcomes compared to MIRP under standard conditions. In addition, our sensitivity analysis suggests that in this scenario a robotic procedure can offer better outcomes than laparoscopy.

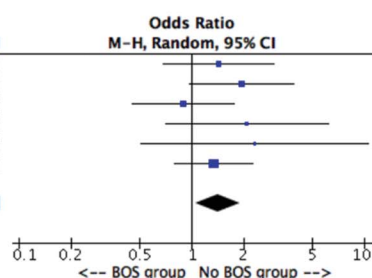
Not surprisingly patients who had undergone BOS were older than those in the surgery naïve group. This finding is consistent with previous literature. A case series study in a cohort of 135 patients who underwent RARP after previous prostate surgery indicated that this patient subset was more likely to be older.²⁶ The same data were mentioned in a recent report in a large cohort of patients who underwent open or robotic radical prostatectomy after TURP.⁵ We equally expected to find lower prostate size and PSA in the BOS group. Indeed, resection, excision or vaporization of the prostate adenoma directly impacts the serum PSA level and prostate size.²⁷

In terms of operative outcomes, longer OT of about 22 minutes was found in the BOS group. One might speculate that this may have been the consequence of more difficult dissection secondary to tissue reaction due to previous surgery since prior surgery might have caused cautery artifacts. Moreover, there was a more frequent need for bladder neck reconstruction in BOS cases, meaning that there was an additional surgical step to add and ultimately additional OT. Notably this specific parameter (bladder neck reconstruction) was available only in RARP studies and it was not assessed in LRP studies.

Laparoscopic radical prostatectomy

Positive surgical margins

| Study or Subgroup | BOS group | | No BOS group | | Weight | Odds Ratio | |
|---|-----------|------------|--------------|-------------|---------------|---------------------|---------------------|
| | Events | Total | Events | Total | | M-H, Random, 95% CI | M-H, Random, 95% CI |
| [14] Eden CG et al | 10 | 42 | 100 | 558 | 16.6% | 1.43 | [0.68, 3.01] |
| [15] Jaffe J et al | 26 | 119 | 15 | 119 | 18.9% | 1.94 | [0.97, 3.88] |
| [16] Menard J et al | 12 | 46 | 168 | 594 | 19.6% | 0.89 | [0.45, 1.77] |
| [21] Yang Y et al | 12 | 35 | 7 | 35 | 7.8% | 2.09 | [0.71, 6.16] |
| [22] Pastore A et al | 6 | 25 | 3 | 25 | 4.0% | 2.32 | [0.51, 10.54] |
| [25] Verze P et al | 20 | 98 | 136 | 848 | 33.2% | 1.34 | [0.79, 2.27] |
| Total (95% CI) | | 365 | | 2179 | 100.0% | 1.42 | [1.05, 1.92] |
| Total events | 86 | | 429 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.46, df = 5 (P = 0.63); I ² = 0% | | | | | | | |
| Test for overall effect: Z = 2.28 (P = 0.02) | | | | | | | |



Robotic radical prostatectomy

Positive surgical margins

| Study or Subgroup | BOS group | | No BOS group | | Weight | Odds Ratio | |
|---|-----------|------------|--------------|-------------|---------------|---------------------|---------------------|
| | Events | Total | Events | Total | | M-H, Random, 95% CI | M-H, Random, 95% CI |
| [17] Hampton JL et al | 18 | 51 | 18 | 102 | 23.9% | 2.55 | [1.18, 5.48] |
| [18] Gupta NP et al | 5 | 26 | 17 | 132 | 11.6% | 1.61 | [0.54, 4.84] |
| [19] Zugar V et al | 6 | 80 | 4 | 80 | 8.3% | 1.54 | [0.42, 5.68] |
| [20] Hung GF et al | 7 | 16 | 74 | 184 | 13.3% | 1.16 | [0.41, 3.24] |
| [23] SU YK et al | 15 | 49 | 554 | 2644 | 37.3% | 1.66 | [0.90, 3.08] |
| [24] Tugcu V et al | 3 | 25 | 4 | 36 | 5.6% | 1.09 | [0.22, 5.36] |
| Total (95% CI) | | 247 | | 3178 | 100.0% | 1.70 | [1.17, 2.47] |
| Total events | 54 | | 671 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 1.93, df = 5 (P = 0.86); I ² = 0% | | | | | | | |
| Test for overall effect: Z = 2.76 (P = 0.006) | | | | | | | |

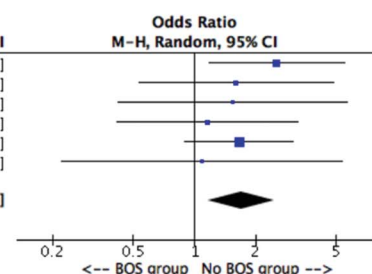
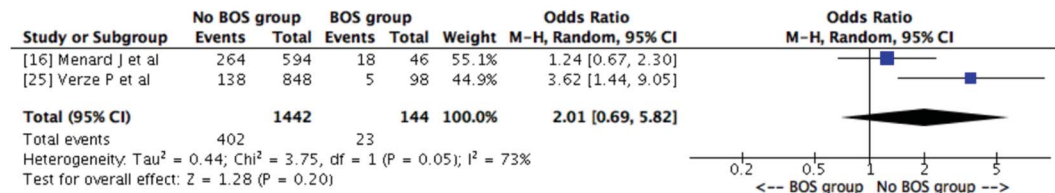


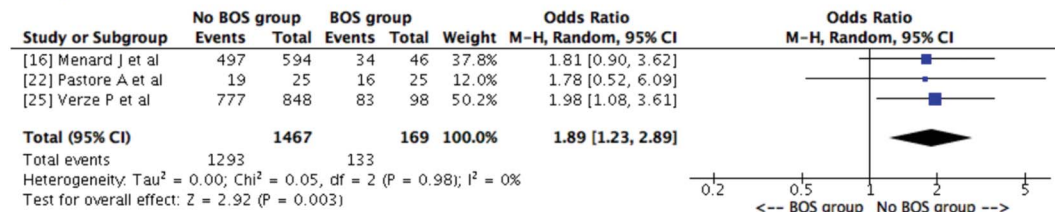
Figure 1. Comparison of oncologic outcomes. M-H, Mantel-Haenszel test.

Laparoscopic radical prostatectomy

Potency at 12 months

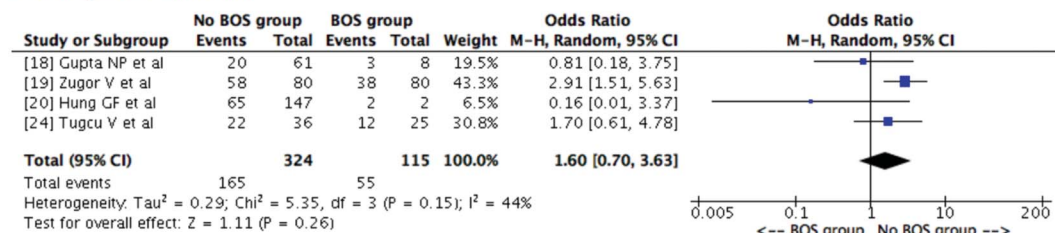


Complete continence at 12 months



Robotic radical prostatectomy

Potency at 12 months



Complete continence at 12 months

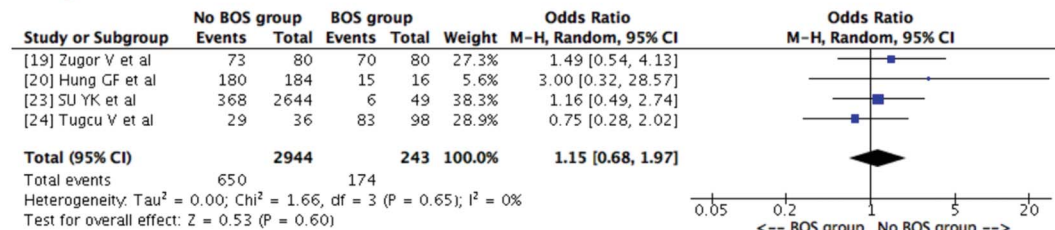


Figure 2. Comparison of functional outcomes. M-H, Mantel-Haenszel test.

Given these findings, MIRP following BOS is more challenging and it requires more caution. Indeed, the odds of intraoperative and postoperative complications were higher in the BOS group. Notably the intraoperative complication rate was higher in the laparoscopic series but this was not the case when considering RARP. This finding confirms that the robotic platform facilitates the surgeon in these challenging cases due to its well-known features such as enhanced vision, improved surgical dexterity and increased range of motion compared to standard laparoscopy. Nevertheless, LRP and RARP showed higher postoperative and major complication rates in the BOS group. In addition, all studies included in this meta-analysis

described high postoperative and major complications rates in patients with previous BOS.^{14–25}

In terms of postoperative complications the BOS group was at overall higher risk for anastomotic leakage after LRP (OR 2.86). This was not the case for RARP, which seems to enable better preservation of the anatomical mechanisms involved in urinary continence. In the largest meta-analysis Tewari et al noted that RARP provides better outcomes than open and laparoscopic techniques.²⁸ In that series RARP provided certain advantages, especially in terms of the hospital readmission rate, injury to nerves, the ureter and the rectum, deep vein thrombosis, pneumonia, hematoma, lymphocele, anastomotic leak, fistula and wound infection.

Moreover, catheter time was longer (about 5 days) in patients who underwent BOS and LRP while again such a difference was not found in those treated with RARP. While this difference could in part be explained by a change in practice patterns with time, it may also be speculated that during RARP the surgeon can achieve a better (more watertight) vesicourethral anastomosis, ultimately allowing for earlier removal of the urethral catheter.

A study evaluating complications of vesicourethral anastomosis demonstrated that prolonged urinary leakage as well as a history of BOS increased the odds of anastomotic stricture.²⁹ Thus, patients treated with BOS might present with bladder neck stricture before radical prostatectomy, making reconstructive time difficult. In fact, in our meta-analysis patients in the BOS group showed a higher overall anastomotic stricture rate, mostly after a laparoscopic procedure.

Oncologic outcomes revealed a higher overall PSM rate in the BOS group. A reasonable explanation could be the surgical difficulties encountered in these patients. Menard et al described the difficulties during posterior bladder neck incision, posterior plane dissection and apical section.¹⁶ In 2 studies the PSM location was recorded at a higher rate at the bladder neck and apex levels in patients undergoing RARP after TURP.^{14–25} Consequently patients with BOS might be at higher risk for biochemical recurrence, as suggested by our pooled analysis (OR 1.84, $p = 0.05$).

Functional outcomes revealed worse results in the BOS group. Indeed, the potency rate at 12 months was lower in these patients. Verze et al noted similar findings and explained it by the lower rate of nerve sparing procedures in patients with a history of BPH surgery.²⁵ This was also the case for LRP and RARP in our pooled analysis. In addition, erectile dysfunction has a multifactorial etiology and potency might already have been harmed in patients who underwent BOS. A higher rate of impaired continence overall and for LRP was recorded in the BOS group at 12 months of followup while there was no difference for the robotic surgery.

The better functional outcomes for RARP were in line with those observed by Tugcu et al, who reported more than 90% complete continence recovery at 1 year.²⁴ Recently Pavlovich et al pointed out that meticulous nerve sparing and preservation of the surrounding prostate structures could result in better functional outcomes.³⁰ In our subset of patients the repercussions of BOS, the surgical challenges and the older age of patients did not enable these structures to be preserved, resulting in worse outcomes. In addition, angiogenesis cessation secondary to previous BPH and scarring reactions after BOS could be responsible for the decompensation of bladder function.

Our analysis is not devoid of limitations. 1) Because the included studies were retrospective and of low-intermediate quality, they were affected by selection bias and unmeasurable confounders. 2) The low number of studies and the low performance of MIRP after BOS did not allow us to include a large sample in the BOS group. Nevertheless, to our knowledge our study represents the largest comparative analysis ever reported. 3) In most studies TURP was the only procedure done for BPH. Only 4 reports included other BOS techniques (bladder neck incision, simple prostatectomy and holmium laser enucleation of the prostate) but no subgroup analysis was done based on the specific procedure. 4) The heterogeneous definitions of continence and potency adopted by the different authors should be considered when assessing functional outcomes.

CONCLUSIONS

MIRP after previous BOS can be offered but it represents a challenging surgical task with a higher risk of complications and higher odds of worse outcomes. Patients should be aware of this and these factors should be considered in the equation during patient counseling. When surgery is pursued, a minimally invasive approach can be offered and RARP should be preferred over LRP. The overall quality of the literature on prostate cancer surgery after previous BOS remains low and further effort should be made to obtain higher levels of evidence.

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