RADICAL ROBOT PROSTATECTOMY: ONCOLOGICAL OUTCOMES.

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Summary.- OBJECTIVES: To review the current literature on oncologic outcomes following robot-assisted laparoscopic radical prostatectomy.

METHODS: A systematic MEDLINE search was performed to retrieve articles relating to oncologic outcomes with robot-assisted laparoscopic prostatectomy. Two reviewers independently selected studies, assessed their methodological quality and extracted data.

RESULTS: Positive surgical margin rates in RALP are commensurate to contemporary open and standard laparoscopic series. Surgical experience and refinement of technique helped decrease positive margins. Long-term biochemical disease-free survival (PSA <0.1 ng/ml) following RALP is currently unknown, with only 2 series reporting data with >12 month follow-up.

Keywords: Robot-assisted. Laparoscopic radical prostatectomy. Oncological outcomes. Surgical margins. PSA recurrence.

CONCLUSIONS: RALP is a safe and reproducible treatment modality for organ-confined prostate cancer and provides excellent short-term oncological control. Larger studies with long-term oncologic follow-up are needed to establish the efficacy compared to more traditional surgical approaches.

INTRODUCCIÓN

Prostate cancer is the second most frequent cause of cancer death in men and it accounts for nearly 10% of all male cancers (1). Today, radical retropubic prostatectomy (RRP) remains the gold standard treatment for localized disease. With the anatomical dissection described by Walsh in the 1980’s, the morbidity of RRP has declined, while functional and oncological outcomes have improved (2,3). To further reduce morbidity and improve convalescence, there is increasing interest for minimally invasive treatments in oncology.

The first laparoscopic radical prostatectomy (LRP) was reported in 1992 (4). Initial experience with 9 cases demonstrated no functional or oncological benefits compared to open prostatectomy (5). With technological advancements and surgical refinement, in the following years several institutions popularized the laparoscopic approach by demonstrating decreased postoperative narcotic use, less blood loss, fewer minor complications, improved cosmesis, and similar
continence and potency outcomes compared with the open RRP (6-11). However, a standard LRP is technically challenging even for experienced laparoscopists. To overcome the limitations of standard laparoscopy, robotic systems which use magnified three-dimensional imaging, full-range motion surgical arms, articulating instruments with 7-degrees of freedom, filtered tremor, and intuitive movements have been introduced. Although originally developed for performing battlefield operations with the surgeon controlling the tele-manipulators in a console from a remote distance (12), robotic systems have been adapted in civilian hospitals and are effective in cardiac surgery and other medical procedures (13-15).

The first robot-assisted laparoscopic prostatectomy (RALP) was performed in 2000 (15), and since more than 50000 procedures have been performed worldwide. Robot-assistance technology has generated much enthusiasm among urologists, particularly for non-laparoscopically trained surgeons who can now more readily offer their patients minimally invasive treatments. Given the growing number of RALPs being performed worldwide, it is imperative to establish safety, reproducibility and efficacy, and compare functional and oncologic outcomes to present day open radical prostatectomy. Only then will robot-assistance be accepted universally as an alternative modality in the surgical pantheon. We performed a systematic literature review on oncological outcomes with RALP and compared it to contemporary open and standard laparoscopic series.

MATERIALS AND METHODS

We identified published and unpublished series evaluating oncological outcomes after RALP by systematically searching major electronic databases (MEDLINE, EMBASE, Cochrane Library, Web Science). We searched the reference lists of included studies and identified papers and abstract books of recent major international urology conferences. Additionally, selected websites were also searched for eligible, evidence-based reports. Two of the authors independently selected the relevant manuscripts and retrieved the data into an electronic database. Details of the search strategy and list of selected websites are available upon request.

RESULTS

1) Positive surgical margins

Twenty manuscripts with >15 patients were identified which discussed oncological outcomes with robot-assisted prostatectomy (Table I). Oncologic outcomes in selected large contemporary open and standard laparoscopic prostatectomy series were reviewed for comparison (Table II). Positive surgical margin rates with RALP are commensurate with contemporary open and standard laparoscopic outcomes (Table II). In most series surgical specimen sampling and pathologic review methodology were not described in detail.

2) PSA recurrence

Data on >6 month biochemical disease-free survival (PSA <0.1 ng/ml) was limited to 6 studies, with only 2 series having >12 month follow-up (Table I). Follow-up ranged between 7-36 months with biochemical disease-free survival rates between 95-96.7%.

DISCUSSION

The introduction of robotic technology allows open and laparoscopic novice surgeons to perform complex minimally invasive urologic procedures which previously required extensive laparoscopic expertise. Radical prostatectomy is the most common robot-assisted oncologic procedure being performed worldwide. However, new interventions must not compromise the cornerstone oncologic principle which is eradication of all cancer cells. Radical prostatectomy offers the advantage of precise staging and grading and facilitates the confirmation of disease eradication or recurrence via PSA nadir or PSA rise over non-extirpative treatment modalities. Cancer control can then be assessed by surgical specimen margin status and presence of biochemical recurrence.

Although the true impact of a positive surgical margin (PSM) remains controversial, many authorities agree it's an independent poor prognostic indicator and may ultimately result in higher biochemical recurrence and decreased cancer-specific survival (16-21). The reported five-year biochemical failure risk for PSM is between 42%-64%, which is significantly higher than for patients with negative surgical margins (NSM) (20). Scardino and colleagues recently reviewed their experience with 1389 RRPs for clinical stage T1-T3 prostate cancer (18). The overall PSM rate was 12.9%, with 6.8% for T2 and 23% for T3. At a 50-month median follow-up, the probability of being PSA progression-free was 58% vs. 81% for PSM and NSM, respectively. This translated into a relative failure risk of 1.2-2.7 with PSM. The investigators concluded that a positive margin increased the risk of recurrence even after adjusting for concurrent risk factors (pretreatment PSA, Gleason grade, and clinical and pathologic stage). In another large study of 2500 RRPs, Blute and co-workers demonstra-
### TABLE I. ROBOT-ASSISTED LAPAROSCOPIC PROSTATECTOMY SERIES: ONCOLOGIC OUTCOMES.

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<th>Authors</th>
<th>Nº</th>
<th>Age (yrs)</th>
<th>F/U, (mo)</th>
<th>% PSA Free*</th>
<th>pT2 (%)</th>
<th>pT3a (%)</th>
<th>pT3 (%)</th>
<th>pT3b (%)</th>
<th>Overall PSM Rate (%)</th>
<th>PSM pT2 (%)</th>
<th>PSM pT3a (%)</th>
<th>PSM pT3 (%)</th>
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Surgical Margins

Oncologic results from selected large contemporary open (retropubic and perineal) and standard laparoscopic radical prostatectomy series are listed in Table II (7,11,22-28). Positive margin rate ranged from 12.8%-24%. The largest series from Johns Hopkins, had 9035 RPPs with 14.7% positive margins (22). The selected laparoscopic series with over 2100 patients had 15.7%-19.2% positive margins. In their literature review, Wieder and Soloway noted a wide range of PSMs in open RRP series from 0% to 77%, with an average of 36% (19). By stage, average PSMs were 17% for T2a disease, 36% for T2b, and 53% in T3 disease.

There are few published RALP studies with long-term follow-up (29-48). The overall PSM rate in robotic series with at least 15 patients ranged from 2.6%-36% (Table I), which is commensurate to the open literature. By stage, positive margins ranged from 2.4%-12.7% for pT2 disease, and 23%-67% for pT3. In the largest single center experience, Menon and colleagues reported an overall PSM rate of 13% in 2652 cases (47). A multi-institutional review of 1130 combined RALPs by Ahlering, Patel and Lee demonstrated similar favorable surgical margin rates (48). A positive margin was strictly defined as cancer cells at any inked margin. Mean values for relevant clinical data from all 3 institutions were: age (60.6 years), preoperative PSA (7.0 ng/ml), clinical stage T1c (82%), cT2 (16%) and cT3 (2%). The mean PSMs were: overall 13.3%, pT2 5.2% and pT3 37.6%.

An important aspect of radical prostatectomy is the reduction of iatrogenic positive margins in otherwise organ-confined disease. Surgical experience inversely correlated with positive margins. Patel and associates noted a decline in PSMs from 13% in the first 100 cases to 8% in the subsequent 100 (37). Similarly, in a multi-institutional review of 1130 RALPs, the positive margin rate decreased following 150-200 cases, with an overall rate of <10% and a pT2 margin rate of <5% (48).

In addition to surgical experience, several technique refinements were effective in reducing positive margins. Ahlering and co-workers (33) described important technical points to aid in the apical dissection: removal of all fat overlying the dorsal venous complex (DVC) and prostate, full dissection of the levator fibers to expose and increase the DVC length, division of the puboprostatic ligaments, and division

<table>
<thead>
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<th>Author</th>
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<th>Positive Margins (%)</th>
<th>Mean Follow-up (months)</th>
<th>PSA progression-free (%)</th>
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of the DVC using a laparoscopic vascular stapler (Figure 1). The overall PSM in their initial 50 cases when two sutures were used to control the DVC was 36%, which they attributed to poor visualization from fat bundles obscuring the apex. With this modified apical dissection, in their next 200 consecutive cases overall PSMs declined from 36% to 16.7% and pT2 cases from 27% to 4.7%.

Subsequently, Ahlering’s group described a second modification to the apical dissection which further reduced PSMs (49). Evaluation of 200 consecutive cases (group 1) revealed that 75% of PSMs were focal and located at the apex. Assessment of urethral length demonstrated that patients with very short urethral stumps which retracted below the urogenital diaphragm requiring perineal pressure during the vesico-urethral anastomosis had equivalent time to continence and overall continence rates compared to patients with readily accessible long urethral stumps (Figure 2). After careful clinical and pathological review of this group their point of urethral transection was altered to include 3-6 mm more of urethra (Figure 3). Positive margin status and time to continence (no-pad) using validated questionnaires for the ensuing 100 cases (group 2) was prospectively followed to evaluate this new technical modification. The overall PSM rate for group 1 was 17.6% versus 6% for group 2. By stage, pT2 decreased from 7.3% to 2.4, while pT3/4 declined from 50% to 26.7% (Table III). Kaplan-Meier time-to-continence curves were not significantly different at 3 and 6 months with continence rates of 73% and 89% in group 1 vs. 61% and 95% for group 2.

Menon and colleagues recently published their experience with 2652 cases (47). They described their current technique in detail, and pointed out several technical modifications which improved functional and oncological outcomes. With bulk ligation of the DVC the positive margin rate at the apex was 12% in their first 100 cases. When bulk ligation was replaced with suture ligation of the individual vessels
after removal of the prostate, the apical PSM rate decreased to 1.5% in patients with T2 disease.

Caution is advised when interpreting surgical margins between series as they are greatly subjective and not standardized between institutions. Margin positivity is generally assessed by inking the margins of the specimen. However, the majority of the series reviewed did not describe specimen sampling and pathologic review methodology in detail. Additionally, some authors reported margin status based on intraoperative biopsies and not the inked specimen margin (30, 50). Furthermore, surgical margin status is also affected by clinical stage, serum PSA and biopsy Gleason score (51). When stratified by PSA level, investigators at Henri Mondor reported positive margins in 20.6% of patients with PSA<10ng/ml, versus 25% overall rate (52,53). Similarly, when pa-

**FIGURE 3.** Change in technique of urethral transection.

Old incision at prostatourethral junction resulted in 18% rate of positive margins with 74% at the apex. By incising 3-7 mm distally (New), positive margin rate decreased to 5.7% without any compromise in continence. (Borin J, Ahlering TE, Skarecky DW, 2006).

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**TABLE III.** COMPARISON OF POSITIVE MARGIN RATES FOR PATIENTS UNDERGOING ROBOT-ASSISTED RADICAL PROSTATECTOMY PRIOR AND SUBSEQUENT TO AN INTERIM ANALYSIS AND CHANGE IN TECHNIQUE. SM+, POSITIVE SURGICAL MARGIN. *TWO-SIDED FISHER’S EXACT TEST. BORIN J, AHLERING TE, SKARECKY DW, 2006.

<table>
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<th>Stage</th>
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<th>After interim analysis (N=70)</th>
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<td>SM+ at Apex</td>
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<tr>
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<td>(7.2%)</td>
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<tr>
<td>Overall</td>
<td>18%</td>
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patients with favorable characteristics were considered (PSA < 10 ng/ml, cT1c disease, and Gleason score ≤7). Ahlering and colleagues showed a decrease in overall positive margins from 36% to 17% (33). In summary, surgical margin comparisons should only be performed after adjustment of relevant covariates.

Biochemical recurrence

Assessment of long-term biological progression (PSA) after RALP is unknown at this time considering the relatively short follow-up of reported series. Data with > 6 month biochemical disease-free survival (PSA < 0.1 ng/ml) was limited to 6 studies, with only 2 studies reporting > 12 month follow-up (Table I). In all, follow-up ranged from 7-36 months with biochemical disease-free survival rates between 95%-96.7%. Patel reported a 95% biochemical disease-free survival in 200 patients with a mean follow-up of 9.7 months (37). Similarly, Mikhail and colleagues noted a 96% biochemical disease-free survival in 100 patients with a median follow-up of 12 months (43). The largest and longest biochemical recurrence results were provided by Menon and colleagues (47). Of 1142 patients, 26 (2.3%) had a biochemical recurrence at a medium follow-up of 36 months (range 12-66). The predicted 5-year PSA recurrence rate was calculated to be 8.4%. Although promising, these results need to be considered early.

CONCLUSION

With the introduction of the da Vinci robot we are witnessing an unprecedented shift from open to laparoscopic prostatectomy as the procedure of choice at many centers. Early studies indicate that robotic prostatectomy has equal short-term outcomes in sexual function and continence compared to open surgery, and potentially favorable outcomes in blood loss, transfusion rates, minor complications, narcotic use, convalescence and length of hospital stay. However, laparoscopic prostatectomy, whether performed using standard laparoscopic instruments or robot-assisted is in its infancy compared to open prostatectomy. Contemporary results of experienced open prostatectomy surgeons have set high standards in oncologic and functional outcomes. Initial short-term oncologic data with RALP is very promising and at least comparable to the open approach. However, in order for RALP to gain widespread acceptance as an alternative minimally invasive treatment to the current gold standard, oncologic outcomes must not be compromised. Longer follow-up with larger numbers and standardized review methods will help confirm the efficacy of robot-assistance in treating prostate cancer.

REFERENCES AND RECOMMENDED READINGS

(* of special interest, ** of outstanding interest)


