ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Outcomes of laparoscopic salvage radical prostatectomy after primary treatment of prostate cancer

Raquel Catarino[1], Renán Javier Otta-Oshiro[2], Fernando Lista-Mateos[2], Jose María García-Mediero[2], Carlos Nunez-Mora[2]

[1]*Urology Department, Pedro Hispano Hospital, Matosinhos, Spain*
[2]*Urology/Oncology Urology Department, MD Anderson Cancer Center, Madrid, Spain*

Citation: Catarino R, Otta-Oshiro RJ, Lista-Mateos F, García-Mediero JM, Nunez-Mora C. Outcomes of laparoscopic salvage radical prostatectomy after primary treatment of prostate cancer. Cent European J Urol. 2022; 75: 59-64.

Article history
Submitted: Jan. 27, 2022
Accepted: March 15, 2022
Published online: March 24, 2022

Corresponding author
Raquel Catarino
Pedro Hispano Hospital
R. Dr. Eduardo Torres
Urology Department
4464-513 Senhora da Hora, Portugal
phone: 00 351 22 939 1000
raquelcatarino@gmail.com

Introduction Treatment of radio-recurrent prostate cancer (PC) is managed mainly by androgen deprivation therapy. Nonetheless, selected patients could benefit from local salvage treatment options. In this study we present our series of recurrent PC cases submitted to laparoscopic salvage radical prostatectomy (sRP) at our institution.

Material and methods A total of 29 patients with recurrent PC after primary non-surgical treatment were submitted to laparoscopic sRP at our institution, with a mean follow-up time of 7 years.

Results There were 7 post-operative complications Clavien-Dindo grade ≥2. At the end of the follow-up, 58.6% patients presented biochemical recurrence and five-year recurrence-free survival (RFS) was 50%. Positive lymph nodes, high preoperative prostate-specific antigen (PSA) and TNM stage were correlated with worse RFS. Cox regression analysis demonstrated that stage pT3b was independently associated with worse RFS in comparison with stage pT3a or less.

At 12 months, pad-free continence or mild incontinence was observed in 62% of the patients.

Conclusions sRP is a technically challenging surgery, and in our series, we were able to perform this procedure with acceptable operative time and limited blood loss.

Post-operative complications, functional results and oncological outcomes were similar to other published studies, being our series, to the best of our knowledge, the one with the longest follow-up, of 7 years.

sRP is a feasible local treatment with curative intent for radio-recurrent prostate cancer, with good oncological outcomes and reasonable continence rates in selected patients.

Key Words: recurrent prostate cancer ‹› salvage radical prostatectomy ‹› biochemical recurrence ‹› prostate cancer management

INTRODUCTION

Prostate cancer (PC) is the second most commonly diagnosed cancer in men [1]. It is expected that PC will account for 21% of all diagnosed cancers in men in 2020, with a mortality rate of 10% [2].

Most PC cases are localized at diagnosis and suitable for curative therapy. It is estimated that 20–38% of these patients are treated with radiation therapy (RT), and 22–69% of the patients treated with primary RT will undergo biochemical recurrence (BCR) [3, 4].

Salvage treatment is scarce and there is lack of controlled trials comparing oncological outcomes, thus there is no consensus regarding the best treatment option. Salvage radical prostatectomy (sRP) is a very complex surgery that is not performed very often. Studies suggest that only 2–3% of patients with BCR after RT would receive local salvage treatment [5]. Most of the patients will be treated with androgen deprivation therapy (ADT).

In this study we present our series of recurrent PC, submitted to laparoscopic sRP at our institution.

doi: 10.5173/ceju.2022.0271

MATERIAL AND METHODS

A total of 29 patients with recurrent PC after primary non-surgical treatment were submitted to laparoscopic sRP at our institution from January 2007 until September 2019.

Regarding primary treatment, 9 patients (31.0%) were treated with brachytherapy, 16 patients (55.2%) with external beam radiotherapy, 2 patients (6.9%) received cobalt therapy, 1 patient (3.4%) was treated with tomotherapy and 1 patient (3.4%) received both brachytherapy and external radiotherapy.

All patients presented histologically confirmed recurrent PC after a transrectal biopsy and metastatic disease was excluded by imaging studies, namely bone scan, computed tomography, positron emission tomography and/or magnetic resonance imaging. All patients presented a life expectancy of at least 10 years.

Laparoscopic sRP were performed by the same experienced and specialized team of surgeons, using a standardized technique [6].

Prostate-specific antigen (PSA) measurements were performed at 3, 6 and 12 months in the first year after surgery, every 6 months in the second year and yearly thereafter.

Recurrence-free survival was calculated from the time of sRP until biochemical relapse or the last available follow-up. Biochemical recurrence was defined as a PSA level >0.5 ng/ml after a subsequent confirmatory measurement.

Surgical complications within 30 days after surgery were recorded using Clavien-Dindo classification [7].

Postoperative continence was defined as pad-free, mild incontinence was classified as using less than 3 pads per day and severe incontinence with the use of 3 or more pads per day. Erectile function was queried in preoperatively potent patients.

Recurrence-free survival was estimated using the Kaplan-Meier method. Cox regression analysis was used to evaluate the impact of risk factors on biochemical recurrence after sRP. A p value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS v 24.0 for Mac (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics

The median age of the patients was 65 years (IQR 61–68). Median time from primary treatment until biochemical recurrence was 53 months (IQR 6–98) and the median PSA level before surgery was 4.60 ng/ml (IQR 2.64–8.36). Eight patients (27.6%) received androgen deprivation therapy before surgery; none of these patients were castration resistant at the time of surgery.

Tumor pathological characteristics and perioperative features

Regarding tumor stage, 10 patients (34.4%) presented pT2 (10.3% pT2a, 3.4% pT2b and 20.7% pT2c), 17 patients (58.6%) had pT3 (31% pT3a and 27.6% pT3b) and 2 patients (6.9%) presented pT4 tumor stage. Final Gleason score was 7 in 10 patients (34.5%), 8 in 3 patients (10.3%) and 9 in 10 patients (34.5%).

Median surgical time was 90 minutes (IQR 70–150) and the median blood loss was 200 ml (IQR 200–250). Median hospital stay was 4 days (IQR 3–7) and the median indwelling bladder catheter time was 10 days (IQR 7–20).

Regarding surgical margins, 8 patients (27.6%) presented positive surgical margins. Of these, the pathological study revealed that 6 had locally advanced disease (pT3), 1 pT4 and 1 pT2. Lymphadenectomy was performed in 25 (86.2%) patients and 5 (17.2%) patients presented positive lymph nodes (Table 1).

Regarding operative complications, there were 2 rectal injuries managed intra-operatively and 1 patient required a blood transfusion. There were 7 post-operative complications, namely 4 cases of Clavien-Dindo grade 2 (1 case of urinary retention after bladder catheter removal, 1 case of bladder catheter intolerance, 1 infectious complication treated with antibiotics and 1 case of deep venous thrombosis) and 3 cases grade 3b (1 case of vesicorectal fistula, and 2 cases of anastomotic stricture).

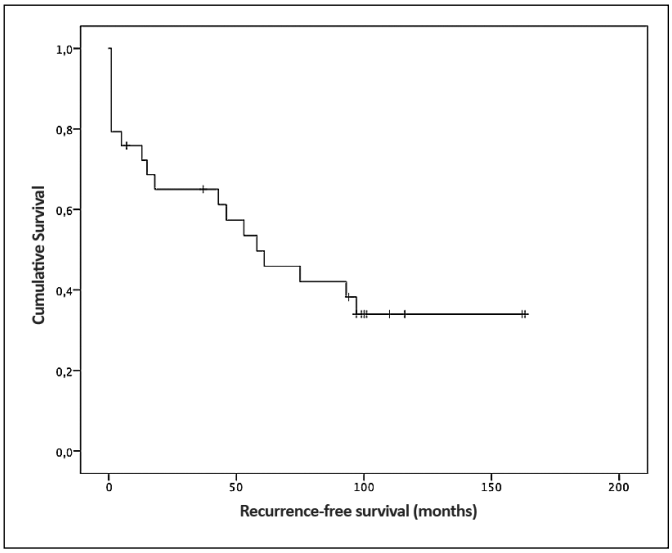

Figure 1. *Kaplan-Meier curve of recurrence-free survival of all patients submitted to laparoscopic salvage radical prostatectomy.*

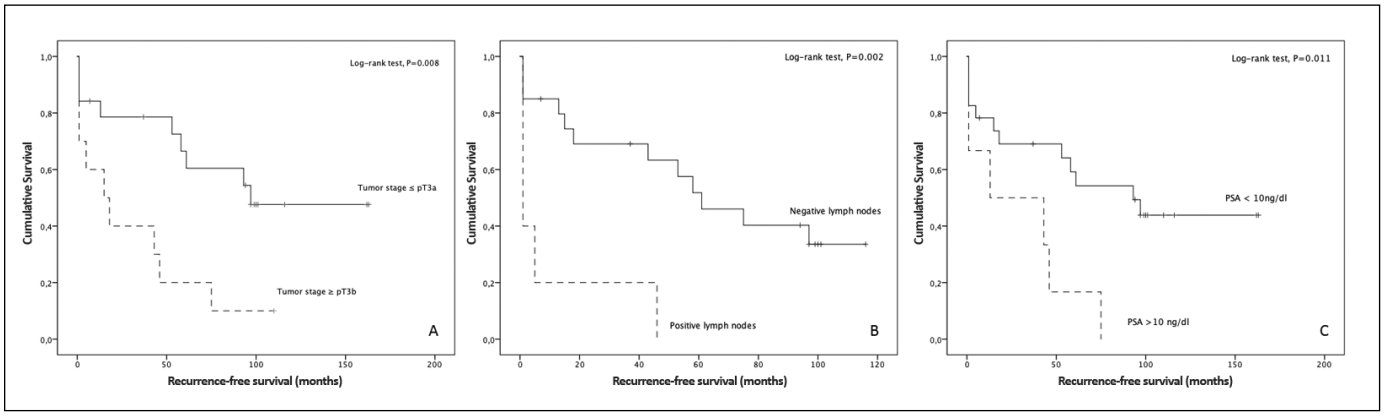

Figure 2. *Kaplan-Meier curves of recurrence-free survival according to tumor stage (A), lymph node status (B) and pre-operative prostate-specific antigen levels (C).*

Oncological results

The median follow-up time was 94 months (range 7–162). Figure 1 demonstrates the Kaplan-Meier curve of recurrence-free survival of all patients (Figure 1). Seventeen (58.6%) patients presented biochemical recurrence at the end of the follow-up and the median time to BCR was 61 months. Five-year recurrence-free survival was 50%. All recurrent cases were treated with androgen deprivation therapy.

Table 1. *Tumor characteristics, operative features and oncological results*

Tumor stage	N (%)
pT2a	3 (10.3)
pT2b	1 (3.4)
pT2c	6 (20.7)
pT3a	9 (31.0)
pT3b	8 (27.6)
pT4	2 (6.9)
Final Gleason score	N (%)
7	10 (34.5)
8	3 (10.3)
9	10 (34.5)
Unknown	6 (20.7)
Median surgical time (minutes) (IQR)	90 (70–150)
Median blood loss (ml) (IQR)	200 (200–250)
Median hospital stay (days) (IQR)	4 (3–7)
Median indwelling bladder catheter (days) (IQR)	10 (7–20)
Positive surgical margins (n)(%)	8 (27.6)
Lymphadenectomy (n) (%)	25 (86.2)
Positive lymph nodes (n) (%)	5 (17.2)
Median follow-up (months) (IQR)	94 (7–162)
BCR (n) (%)	17 (58.6)
5-year recurrence-free survival (%)	50

n – number; IQR – interquartile range; BCR – biochemical recurrence

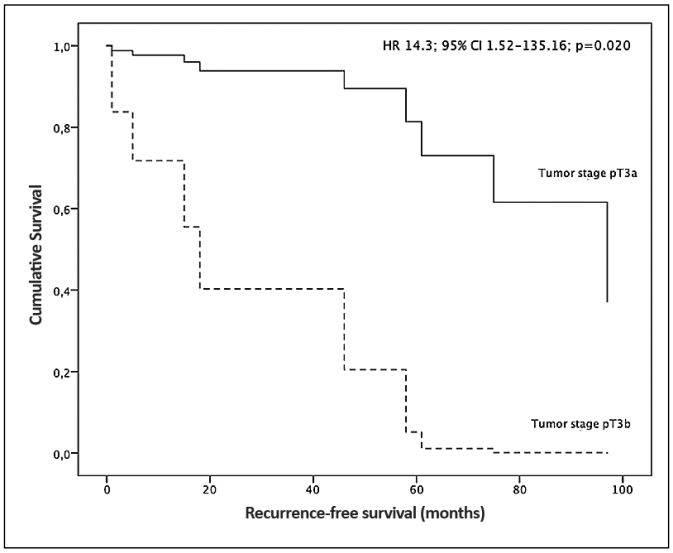

Figure 3. *Cox-regression analysis of recurrence-free survival according to tumor stage.*
HR – hazard ratio

At the end of the follow-up, there were 2 deaths, although only 1 patient died from prostate cancer.
Our results demonstrate that recurrence-free survival after sRP was statistically different according to pathological stage, with an estimated mean recurrence-free survival time of 101.1 months for patients with tumor stage ≤pT3a, comparing with 31.5 months for patients with tumor stages ≥pT3b (log-rank test, 0.008) (Figure 2A).
Positive lymph nodes were also associated with shorter recurrence-free survival, of 10.8 months, comparing with 64.7 months for negative lymph node cases (log-rank test, p = 0.002) (Figure 2B). Moreover, PSA values before surgery were also correlated with recurrence-free survival, indicating that higher PSA concentrations were associated with a worst outcome

Table 2. *Univariate Cox-regression analysis of risk factors for BCR after sRP*

Risk factor	HR (95% CI)	p value
Stage (≤pT3a vs ≥pT3b)	3.27 (1.26–8.53)	0.015
Lymph node status	4.89 (1.48–16.14)	0.009
Pre-sRP PSA (<10 vs ≥10 ng/ml)	3.35 (1.19–9.43)	0.022

BCR – biochemical recurrence; sRP – salvage radical prostatectomy; CI – confidence interval; HR – hazard ratio; PSA – prostate-specific antigen

Table 3. *Functional results at 12 months*

	N (%)
Urinary continence	
Pad-free continence	6 (20.6)
Mild incontinence	12 (41.4)
Severe incontinence	10 (34.5)
Erectile function	
Preoperative erectile function	7 (24.1)
Preserved erectile function at 12 months	1 (14.3)

(for PSA ≥10 ng/dl, mean recurrence-free survival of 29.8 months versus 91.8 months for PSA <10 ng/dl, log-rank test p = 0.011) (Figure 2C). Surgical margin status, Gleason score and pre-operative androgen deprivation therapy did not interfere with recurrence-free survival (log-rank test, p >0.05).

Univariate Cox regression analysis indicated that tumor stage (≤pT3a vs ≥pT3b) (HR 3.27, 95%CI 1.26–8.53, P = 0.015), positive lymph nodes (HR 4.89, 95%CI 1.48–16.14, p = 0.009) and high PSA values (PSA ≥10 ng/ml) (HR 3.35, 95%CI 1.19–9.43, p = 0.022) were associated with BCR (Table 2). Multivariate Cox-regression analysis did not indicate a statistically significant association between these variables and BCR (p >0.05).

Moreover, our results demonstrate that recurrence-free survival after sRP was significantly lower in patients with tumor stage pT3b, with an estimated mean recurrence-free survival time of 33.9 months, comparing with 86.8 months for patients with pT3a (log-rank test, p = 0.021). Furthermore, multivariate Cox regression analysis demonstrated that pathological stage pT3b is independently associated with worse recurrence-free survival (HR 14.3; 95%CI 1.52–135.16; P = 0.020) comparing with stage pT3a, with PSA values before surgery and lymph node involvement as covariates (Figure 3).

Functional results

Regarding continence at 12 months after surgery, pad-free continence was observed in 6 (20.6%) of the patients, mild incontinence in 12 (41.4%) patients, and severe incontinence in 10 (34.5%) patients.

Regarding erectile function, the preoperative erectile dysfunction rate was 75.9%, with 7 patients declaring potency preoperatively. Of these, 1 preserved erectile function at 12 months after surgery (Table 3).

DISCUSSION

Prostate cancer treatment has greatly advanced in the last few years. New treatment approaches have changed the outcome of this disease. Most patients have localized disease at diagnosis, suitable for a localized treatment approach. However, recurrence rates are high for intermediate and high-risk groups, leaving a substantial proportion of patients needing further management [8].

Treatment of radio-recurrent PC is managed mainly by ADT, which lacks curative intent and it is not directed to control local disease, and considering that the majority of recurrent cases after radiation therapy are localized to the prostate, these patients could benefit local salvage treatment options [8, 9, 10].

sRP is a complex surgery, historically associated with high morbidity and commonly avoided due to technical difficulties. There are a few studies evaluating the role of sRP and more recently robotic sRP [11–17]. In this study we evaluated the results of laparoscopic sRP at our institution, and to the best of our knowledge, with the longest follow-up period, with a mean follow-up of 7 years.

Considering that sRP is a complex and technically challenging surgery, in our series we were able to perform the surgery with an acceptable operative time, with a median operative time of 90 minutes and limited blood loss (Table 1). Regarding surgical complications, rectal injury is perhaps the most feared operative complication, and in our series, we present 2 cases of intraoperatively managed rectal injury (6.9%), which is in agreement with other published studies. Post-operative complications were also similar to other published studies, namely recent reports concerning robot-assisted sRP [3, 15, 16].

Regarding functional results, the literature varies widely, and we report a continence rate of 20.6% and 14.3% of preserved erectile function at 12 months (Table 2).

Our results are consistent with previous studies of sRP for radio-recurrent prostate cancer, reporting continence rates of 15–77% and potency rates of 0–20% [3, 14, 18].

Positive surgical margin rates described in the literature vary from 13% to 45%. In our series, we present a positive surgical margin rate of 27.6% [3]. We performed lymphadenectomy in the majority of the patients (86%) and 17.2% of the cases had

positive lymph nodes, which is slightly higher than other published studies [3], but still inferior to the high-risk subgroup of patients defined by Mandel and co-workers [15].

Our median follow-up time was 94 months, and at the end of the follow-up, 58.6% of the patients presented BCR, with a median time to BCR of 61 months (Table 1). Five-year recurrence-free survival was 50%, which is in agreement with other published series [3].

According to the EAU guidelines, patients with initial clinical staging ≤T2, biopsy ISUP grade ≤3, pre-operative PSA value <10 ng/ml and a life expectancy greater than 10 years could be evaluated for sRP. Mandel et al found that these patients present significantly better outcomes, with a 5-year BCR-free survival of 73.9% comparing with 11.6% for other patients [15].

Our results demonstrate that patients with tumor stages ≤pT3a present a significant increased mean recurrence-free survival time, of 101.1 months, comparing with 31.5 months for patients with tumor stages ≥pT3b (log-rank test, p = 0.008) (Figure 2A). Moreover, positive lymph nodes and high pre-operative PSA values were also correlated with worse recurrence-free survival time (Figure 2B and 2C) (Table 2). Surgical margin status and biopsy Gleason score did not interfere with recurrence-free survival in our series.

Multivariate Cox regression analysis demonstrated that pathological stage pT3b is independently associated with worse recurrence-free survival (HR 14.3; 95%CI 1.52–135.16; P = 0.020) comparing with stage pT3a, with PSA values before surgery and lymph node involvement as covariates (Figure 3).

Patient selection is vital to achieve the greatest results in the salvage setting. It is acknowledged that early salvage treatment after BCR is associated with better outcomes. Chade et al. reported that lower pre-operative PSA values and lower biopsy Gleason score after radiotherapy had the highest probability of cure from sRP, specifying that patients with a pre-operative PSA <4 ng/ml are the most favorable group for sRP [19]. This indicates that earlier recurrence detection is needed to improve oncologic outcomes in the salvage scenario. Consequently, the current BCR criteria and detection methods may not be adequate to timely detect just local recurrence. Moreover, new imaging techniques may be of great help in re-staging patients and discriminating localized disease and selecting the best candidates to salvage local treatment.

This study has several limitations, namely its retrospective nature, the heterogeneity of the patients and considering the rarity of the procedure, the sample size. Despite these limitations, this study adds more information about current oncological and functional outcomes in patients with radio-recurrent prostate cancer submitted to laparoscopic sRP.

CONCLUSIONS

sRP is a feasible local treatment with curative intent for radio-recurrent prostate cancer, with good oncological outcomes and reasonable continence rates in selected patients. However, the salvage nature of the procedure requests timely recurrence detection, in order to increase the probability of cure.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359-E386.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70: 7-30.
3. Calleris G, Marra G, Dalmasso E, et al. Is it worth to perform salvage radical prostatectomy for radio-recurrent prostate cancer? A literature review. World J Urol. 2019; 37: 1469-1483.
4. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR, Cancer of the Prostate Strategic Urological Research E. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. Cancer. 2008; 112: 307-314.
5. Golbari NM, Katz AE. Salvage Therapy Options for Local Prostate Cancer Recurrence After Primary Radiotherapy: a Literature Review. Curr Urol Rep. 2017; 18: 63.
6. Nunez-Mora C, Garcia-Mediero JM, Cabrera-Castillo PM. Radical laparoscopic salvage prostatectomy: medium-term functional and oncological results. J Endourol. 2009; 23: 1301-1305.
7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240: 205-213.
8. Grossfeld GD, Li YP, Lubeck DP, Broering JM, Mehta SS, Carroll PR. Predictors of secondary cancer treatment in patients receiving local therapy for prostate cancer: data from cancer of the prostate strategic urologic research endeavor. J Urol. 2002; 168: 530-535.
9. Zdrojowy R, Dembowski J, Malkiewicz B, Tupikowski K, Krajewski W. Salvage local therapy for radiation-recurrent prostate cancer- where are we? Cent European J Urol. 2016; 69: 264-270.
10. Gandaglia G, Fossati N, Karnes RJ, et al. Use of Concomitant Androgen Deprivation Therapy in Patients Treated with Early

Salvage Radiotherapy for Biochemical Recurrence After Radical Prostatectomy: Long-term Results from a Large, Multi-institutional Series. Eur Urol. 2018; 73: 512-518.

11. Zargar H, Lamb AD, Rocco B, et al. Salvage robotic prostatectomy for radio recurrent prostate cancer: technical challenges and outcome analysis. Minerva Urol Nefrol. 2017; 69: 26-37.

12. Eandi JA, Link BA, Nelson RA, et al. Robotic assisted laparoscopic salvage prostatectomy for radiation resistant prostate cancer. J Urol. 2010; 183: 133-137.

13. Bonet X, Ogaya-Pinies G, Woodlief T, et al. Nerve-sparing in salvage robot-assisted prostatectomy: surgical technique, oncological and functional outcomes at a single high-volume institution. BJU Int. 2018; 122: 837-844.

14. Bates AS, Samavedi S, Kumar A, et al. Salvage robot assisted radical prostatectomy: A propensity matched study of perioperative, oncological and functional outcomes. Eur J Surg Oncol. 2015; 41: 1540-1546.

15. Mandel P, Steuber T, Ahyai S, et al. Salvage radical prostatectomy for recurrent prostate cancer: verification of European Association of Urology guideline criteria. BJU Int. 2016; 117: 55-61.

16. Linares Espinos E, Sanchez-Salas R, Sivaraman A, et al. Minimally Invasive Salvage Prostatectomy After Primary Radiation or Ablation Treatment. Urology. 2016; 94: 111-116.

17. Pokala N, Huynh DL, Henderson AA, Johans C. Survival Outcomes in Men Undergoing Radical Prostatectomy After Primary Radiation Treatment for Adenocarcinoma of the Prostate. Clin Genitourin Cancer. 2016; 14: 218-225.

18. Kenney PA, Nawaf CB, Mustafa M, et al. Robotic-assisted laparoscopic versus open salvage radical prostatectomy following radiotherapy. Can J Urol. 2016; 23: 8271-8277.

19. Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol. 2011; 60: 205-210. ■