Original Article

The Oncological Outcomes of Adjuvant Radiotherapy in Laparoscopic Extraperitoneal Radical Prostatectomy

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Objective: To study the oncological outcome of adjuvant radiotherapy after extra-peritoneal laparoscopic radical prostatectomy (ELRP).

Materials and Methods: From 2008 to December 2016, 112 patients underwent ELRP for localized prostate cancer by the same urologist (SP). We analyzed the patient demographics, perioperative outcomes, and compared the oncological outcomes between patients, with and without adjuvant radiotherapy, by biochemical failure.

Results: The median follow-up time in the present study was 35 months (IQR: 26 to 64). Due to indications of high risk, the adjuvant radiotherapy rate after ELRP was 20.5% (23/112 cases). The biochemical failure rate in this group was 8.7%. In non-adjuvant radiotherapy patients, the biochemical failure, salvage radiation and the overall survival rates were 28.1% (25/89 cases), 14.6% (13 cases), and 92.1% (82/89), respectively. Interestingly, there was no significant difference in either biochemical progression free survival (p = 0.051) or overall survival (p = 0.787), with or without adjuvant RT. However, biochemical control tended to be better in patients who received adjuvant radiotherapy.

Conclusion: The present study indicated the positive oncologic outcome of adjuvant radiotherapy after ELRP radiotherapy in terms of biochemical failure. Further prospective study design with longterm follow-up is needed to draw a conclusion.

Keywords: Adjuvant Radiotherapy, Extra-peritoneal laparoscopic radical prostatectomy, Prostate cancer, Biochemical failure

J Med Assoc Thai 2019;102(Suppl.2): S38-42
Website: http://www.jmatonline.com

Laparoscopic extraperitoneal radical prostatectomy (LERP) has advantages over the transperitoneal approach, such as shorter operation time, catheterization time, hospitalization time and time to oral diet. Also, the biochemical progression-free survival and local control of both techniques remain similar[1].

However, the rate of positive surgical margins (PSMs) is still high, especially in pT3 lesions. McNeill et al showed overall rates of PSMs as high as 23.5% and up to 40.5% in pT3 disease[2]. Also, Tomasz et al reported overall rates of PSMs as 29.15% and 67.4% in pT3 lesions[3]. Kupelian et al reported that the pre-treatment PSA and positive surgical margin are independent predictive factors for biochemical progression-free survival[4]. D'Amico et al found that pre-treatment PSA, staging and Gleason score were predictive factors for PSA failure in post-treatment prostate cancer[5].

As a result, compared to salvage radiotherapy, adjuvant post radical prostatectomy radiotherapy provides benefit in post radical prostatectomy patients with postoperative adverse factors such as, positive margin, seminal vesicle invasion, extracapsular extension, or detectable PSA after radical prostatectomy[6]. Also, Chin et al reported that the post-prostatectomy radiotherapy had tolerable ill effects, with regard to genitourinary (GU) and gastrointestinal (GI) toxicity[7].

Thus, this study reviewed the outcome of adjuvant post-operative radiotherapy following LERP in organ confined prostate cancer patients and compared the oncologic outcomes between patients, with and without adjuvant radiotherapy, by biochemical failure.

Materials and Methods

This descriptive study included the medical records of patients who underwent ELRP by a single surgeon followed by adjuvant RT during 2008 to 2016. The case was excluded if completed medical records could not be obtained or patient contact was lost during follow-up. As a result, 112 medical records were included.

The radiotherapy technique: Intensity Modulated Radiotherapy (IMRT) was used. The total radiation dose

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How to cite this article: Lowanichkiattikul C, Sawangsilp T, Permpongkosol S. The Oncological Outcomes of Adjuvant Radiotherapy in Laparoscopic Extraperitoneal Radical Prostatectomy. J Med Assoc Thai 2019;102;Suppl.2: S38-42.

ranged from 66 to 78 Gy in conventional fractionation. In addition, the Clinical Target Volume (CTV), and either prostate only RT or additional pelvic RT was used. The CTV delineation method was detailed as RTOG contouring atlas for both pelvic RT and tumor bed RT. The radiotherapy treatment planning was generated by Eclipse™ (Varian Medical Systems, Inc.) and the treatment was delivered by RapidArc® (Varian Medical Systems, Inc).

The PSA assessment was obtained pre-operatively, before radiotherapy, then at 3 to 4- month intervals after completion of radiotherapy. The definition of biochemical failure after adjuvant radiotherapy used is the recommendation from the RTOG-ASTRO PHOENIX consensus conference that: 1) A rise of 2ng/ml or more above the nadir PSA be considered the standard definition for biochemical failure after external beam radiotherapy (EBRT) with or without hormonal therapy (HT). 2) The date of failure is determined "at call" (not backdated)[8]. Biochemical failure after radical prostatectomy is defined as either: 1) Those whose PSA failed to decrease to undetectable levels after RP (persistent disease), or 2) Those who achieve undetectable PSA after RP with a subsequent detectable PSA level that increased on 2 or more subsequent laboratory determinations (recurrent disease), or 3) Those with low detectable, persistent PSA (no exact definition, but PSA greater than 0.2 or 0.4 were used as the cutoff points)[9]. The present study used a PSA cutoff point of 0.2 ng/ml.

Statistical analysis

Patient baseline characteristics are reported by mean with SD or median with interquartile range. In addition, the potential risk factors were calculated with the Cox proportional hazard model to find the association with biochemical progression-free survival. The Kaplan-Meier curve was used to demonstrate the biochemical progression-free survival and overall survival using STATA version 14.

Results

Patients' characteristics

A hundred and twelve medical records were reviewed in this study, 23 of 112 received adjuvant post-operative RT. The median follow-up time was 35 (IQR: 21 to 64) months. A summary of enrolled cases is presented in Figure 1.

The mean age of the patients was 68.9±8.3 years. The median pre-operative PSA level was 8.8 (IQR: 5.5 to 15.8) ng/ml. The T-staging was 7% (pT1), 54% (pT2), 38% (pT3) and 2% (pT4). The number of patients grouped by Gleason score was 39 (35.1%) in lower than 7, 52 (46.9%) in equal to 7 and 20 (18%) in the more than 7 points group. The D'Amico risk categorization was 15 (13.4%), 41 (36.6%) and 56 (50%) in low, intermediate and high risk, respectively. The pathological extracapsular extension was 24.1% (27/112). The seminal vesicle invasion was found about 4.5% (5/112). The positive surgical margin rate was 32.1% (36/112). A summary of patients' characteristics is shown in Table 1.

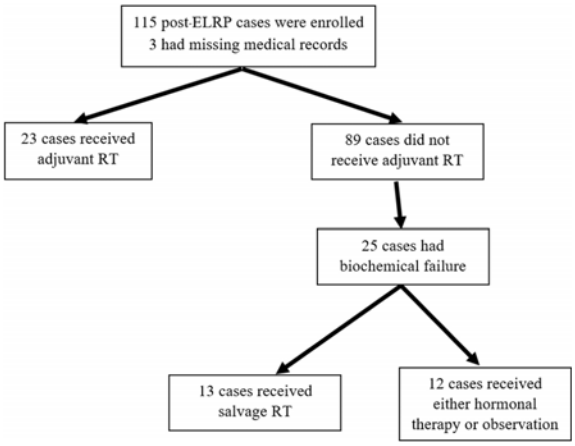

Figure 1. Overview of cases receiving adjuvant RT or not, after ELRP.

Adjuvant radiotherapy patients

The mean age of the patients was 67.2±8.4 years and the median of pre-operative PSA level was 20.6 (IQR: 10.9 to 38). The T-staging was 8.7% (2/23), 26.1% (6/23), 60.9% (14/23) and 4.4% (1/23) in pT1 to pT4, respectively. Furthermore, the D'Amico risk was 4.4% (1/23), 21.7% (5/23) and 73.9% (17/23) for low, intermediate and high risk, respectively. Also, the adverse pathological features were 43.5% for ECE, 8.7% for SVI and the PSMs rate was 47.8%. The mean total radiation dose was 61.3±9.4 Gy in conventional fractionation. Radiation complications were observed in 3 cases. Two reported radiation cystitis during the radiation course at 40 and 44 Gy, both patients refused to receive further radiation. Another patient reported radiation proctitis 3 years after completing the radiation course (70 Gy in 35 fractions). There was biochemical failure in 2 patients with the biochemical progression-free survival as 3 and 22 months.

Non-adjuvant radiotherapy patients

The mean age of the patients was 69.4±8.3 years, comparable to the adjuvant RT patients. The median of pre-operative PSA level was 7.77 (IQR: 5.3 to 11.2) ng/ml. The T-staging was pT1 5.6% (5/89), pT2 53.9% (48/89), pT3 27% (24/89) and pT4 1.1% (1/89). The D'Amico risk categorization was 15.7% (14/89), 40.5% (36/89) and 43.8% (39/89) for low, intermediate and high risk, respectively. Also, the pathologic adverse features were 19.1% for ECE, 3.4% for SVI and PSMs rate was 28.1%.

Almost all of the poor prognostic factors were statistically significantly lower in non-adjuvant RT patients such as pre-operative PSA level (p<0.005), T-staging (p = 0.005), D'Amico risk (p = 0.044), ECE (p = 0.026) and SVI (p = 0.033). Also, the PSMs rate was lower but not statistically significant.

A total of 89 cases did not receive adjuvant post-operative RT. Twenty-five cases experienced biochemical

Table 1. Patients' characteristics

Characteristics	Adjuvant RT (%)	Non-adjuvant RT (%)	*p*-value
n	23	89	
Age (years; mean ± SD)	67.2±8.4	69.4±8.3	0.267
Preoperative PSA level (ng/ml) median (IQR)	20.62 (10.88 to 38)	7.77 (5.32 to 11.24)	<0.005
<10	5 (21.7)	58 (65.2)	
10 to 20	6 (26.1)	20 (22.5)	
>20	11 (47.8)	10 (1.1)	
T-Staging, n (%)			0.005
pT1	2 (8.7)	5 (5.6)	
pT2	6 (26.1)	48 (53.9)	
pT3	14 (60.9)	24 (27.0)	
pT4	1 (4.4)	1 (1.12)	
Pathologic Gleason score, n (%)			0.009
<7	4 (17.4)	35 (39.8)	
7	10 (43.5)	42 (47.7)	
>7	9 (39.1)	11 (12.5)	
D'Amico risk, n (%)			0.044
Low	1 (4.4)	14 (15.7)	
Intermediate	5 (21.7)	36 (40.5)	
High	17 (73.9)	39 (43.8)	
Pathological findings, n (%)			
ECE	10 (43.5)	17 (19.1)	0.026
SVI	2 (8.7)	3 (3.4)	0.033
PSMs	11 (47.8)	25 (28.1)	0.083
Incontinence, n (%)	16 (69.6)	50 (56.2)	0.225

failure, of which the median of biochemical progression-free survival was 12 (IQR: 8 to 21) months. Of the 25, 13 cases underwent salvage RT as detailed above and the others refused salvage RT, instead, receiving androgen deprivation therapy either GNRH-agonist or bilateral orchiectomy. Note that, no biochemical failure was reported in any of the salvage RT cases.

Biochemical progression-free survival

The overall biochemical failure rate was 24.1%. In non-adjuvant RT patients, the biochemical failure rate was 28.1% (25/89) and 8.7% (2/23) in adjuvant RT patients, with a median follow-up time of 35 (IQR: 21 to 64) months. There was no statistically significant difference in biochemical progression-free survival, whether or not the patient received adjuvant RT (p = 0.051) as shown in Figure 2.

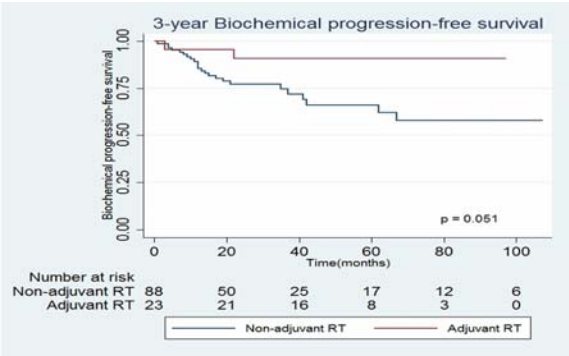

Figure 2. 3-year biochemical progression-free survival between adjuvant and non-adjuvant patients.

Overall survival rate

After three years follow-up, the overall survival rate was 91.1%.There was no difference in overall survival between adjuvant RT and non-adjuvant RT patients (p = 0.787) (Figure 3).

Complications

The post-treatment urinary incontinence rate was 58.9%, which was higher in adjuvant RT patients: 69.6% (16/23) vs. 56.2% (50/89); but not statistically significant (p = 0.225).

In adjuvant radiotherapy patients, acute radiation cystitis was observed in two patients and late radiation proctitis was found in one patient.

Discussion

Although, the ELRP technique can avoid injury to intraperitoneal organs and results in decreased complications, this technique is more complex and requires a long learning curve to achieve comparable oncological results[1,10]. This study is limited in that the data were collected retrospectively and the patients were not randomized for study. A disproportionately high number of patients with more

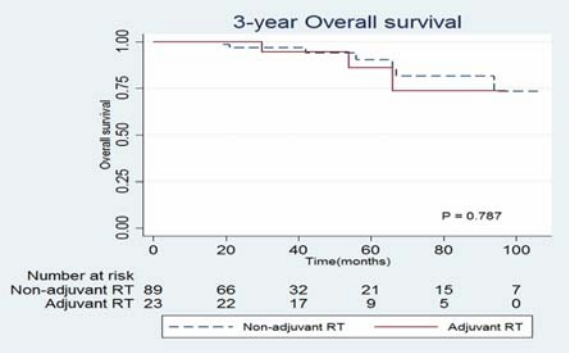

Figure 3. 3-year overall survival between adjuvant and non-adjuvant patients.

aggressive, intermediate and high-risk tumors might be included in our study. In this study, the rate of positive surgical margins is about 32%. This may be related to the fact that in approximately 35% of patients the disease had progressed to stage pT3 or higher which tends to lead to a higher incidence of positive surgical margins as reported in many studies.

Post-operative adjuvant radiotherapy after radical prostatectomy has been shown to increase progression-free survival and local control in cases that had such adverse pathologic features as positive surgical margins, seminal vesicle invasion and extracapsular extension[6,11,12]. In this study, only 26.8% (11/41) of patients who had adverse pathologic features received adjuvant RT. This was due to the fact that most of the patients refused radiation and preferred both observation and hormonal therapy. As a result, the biochemical failure in non-adjuvant RT was relatively high at 28.1% when compared to historical data. However, some patients, who had biochemical failure, received salvage RT and no biochemical failure was observed in 3 years of follow-up. Thus, whether patients received adjuvant RT or not, there was no difference in overall survival. Nevertheless, a longer follow-up time needs to be observed.

In adjuvant RT patients, the biochemical failure rate was 8.7%, which tends to suggest better biochemical progression-free survival, but this was not statistically significant. This study had a retrospective design with a relatively short follow-up time and a small sample size.

Urinary incontinence occurs in radical prostatectomy, especially in cases involving bladder neck injury, and bladder neck preservation can result in more positive surgical margins. Early adjuvant radiotherapy after surgery is a further cause of urinary incontinence. In this study, the rate of urinary incontinence was 58.9% (66/112). The incontinence rate in previous studies was around 16 to 38%[3,10]. In several studies, the patient's age was a relatively strong predictive factor for urinary incontinence, especially for patients >70 years-old[13-15]. As above, the mean age of the patients in this study was 69.4±8.3 years-old, so we could expect high incidence of incontinence. However, the incontinence rate could be affected by other risk factors such as BMI, prior bladder neck treatment and prostate weight, which are not included in this study.

Conclusion

Adjuvant radiotherapy after extraperitoneal laparoscopic radical prostatectomy does not show a statistically significant difference of biochemical progression-free survival but tends to have benefits. A further prospective study designed with long term follow-up is needed to draw a more reliable conclusion.

What is already known on this topic?

Although the role of adjuvant post-radical prostatectomy radiotherapy in prostate cancer have been well established by many published papers but most of them used an rather old-fashion techniques for either surgical or radiotherapy techniques. This paper reported the result of adjuvant radiotherapy in newly innovative approach extraperitoneal laparoscopic radical prostatectomy which proved not only still offer comparable disease control but also less invasive technique.

What this study adds?

This paper reported the result of adjuvant radiotherapy in newly innovative approach extraperitoneal laparoscopic radical prostatectomy which proved not only still offer comparable disease control but also less invasive technique.

Acknowledgements

We wish to thank Mr. Terry King for English proof-reading.Miss Kornkanok Somboonpun for help with data search and Pattawia Choikrua for data analysis.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Akand M, Erdogru T, Avci E, Ates M. Transperitoneal versus extraperitoneal robot-assisted laparoscopic radical prostatectomy: A prospective single surgeon randomized comparative study. Int J Urol 2015;22:916-21.
2. McNeill SA, Good DW, Stewart GD, Stolzenburg JU. Five-year oncological outcomes of endoscopic extraperitoneal radical prostatectomy (EERPE) for prostate cancer: results from a medium-volume UK centre. BJU Int 2014;113:449-57.
3. Golabek T, Jaskulski J, Jarecki P, Dudek P, Szopinski T, Chlosta P. Laparoscopic radical prostatectomy with bladder neck preservation: positive surgical margin and urinary continence status. Wideochir Inne Tech Maloinwazyjne 2014;9:362-70.
4. Kupelian PA, Katcher J, Levin HS, Klein EA. Stage T1-2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys

1997;37:1043-52.
5. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999;17:168-72.
6. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-9.
7. Chin S, Aherne NJ, Last A, Assareh H, Shakespeare TP. Toxicity after post-prostatectomy image-guided intensity-modulated radiotherapy using Australian guidelines. J Med Imaging Radiat Oncol 2017;61:804-11.
8. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
9. Koulikov D, Mohler MC, Mehedint DC, Attwood K, Wilding GE, Mohler JL. Low detectable prostate specific antigen after radical prostatectomy—treat or watch? J Urol 2014;192:1390-6.
10. akobczyk B, Wrona M, Wrona-Lis M, Oszukowska E, Lipinski P, Szewczyk M, et al. Endoscopic extraperitoneal radical prostatectomy: An initial report following the first 30 cases. Cent European J Urol 2017;70:48-52.
11. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018-27.
12. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow-up of a randomized clinical trial. J Urol 2009;181:956-62.
13. Mochtar CA, Kauer PC, Laguna MP, de la Rosette JJ. Urinary leakage after laparoscopic radical prostatectomy: a systematic review. J Endourol 2007;21:1371-9.
14. Kumar A, Samavedi S, Bates AS, Coelho RF, Rocco B, Palmer K, et al. Continence outcomes of robot-assisted radical prostatectomy in patients with adverse urinary continence risk factors. BJU Int 2015;116:764-70.
15. Lee DJ, Cheetham P, Badani KK. Predictors of early urinary continence after robotic prostatectomy. Can J Urol 2010;17:5200-5.