Original Article

Long term outcomes between adjuvant radiotherapy and combined radiotherapy with hormonal treatment after radical prostatectomy in high risk prostate cancer

Chalermchai Kiatbamrungpunt, Chaiyong Nualyong, Sittiporn Srinualnad, Sunai Leewansangtong, Tawatchai Taweemonkongsap, Bansithi Chaiyaprasithi, Ekkarin Chotikawanich, Kittipong Phinthusophon, Siros Jitpraphai, Patkawat Ramart, Chalairat Suk-ouichai,Varat Woranisarakul

Division of Urology, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Keywords:
Prostate cancer, locally advanced, high risk, adjuvant radiotherapy, combined treatment, hormonal treatment

Abstract

Objective: To determine the oncological outcome of adjuvant treatment between radiotherapy (RT) alone and combined radiotherapy with androgen deprivation therapy (ADT) in high risk prostate cancer patients after radical prostatectomy (RP).

Materials and Methods: All medical records of high risk-prostate cancer patients (including PSA > 20 ng/ml, pT3-pT4 or Gleason score 8-10) who underwent RP in Siriraj Hospital between 2000 and 2016 were retrospectively reviewed. Demographic data, pathological staging, types of adjuvant treatment, time to follow up and time to biochemical recurrence (BCR) were analyzed.

Results: Undetectable PSA after RP was achieved in 1009 out of 1221 high risk prostate cancer patients who had been followed up at least 6 months after surgery. Pathological staging pT2, pT3, pT4 and N1 was 23.8%, 73%, 0.8% and 4.7%, respectively. Forty one percent received adjuvant treatment (41 adjuvant RT alone, 74 combined adjuvant RT and ADT, 303 ADT alone). Median follow up time in the adjuvant RT group and combined treatment group was 63.8 months (8.9 - 210.7). BCR rates were 22% (9 of 41) for adjuvant RT and 12.2% (9 of 74) for adjuvant combined treatment. 10-year BCR-free survival in the two groups was 70.2% and 83.8%, respectively. There was no statistical difference between adjuvant RT and adjuvant combined treatment in terms of survival benefit (Hazard Ratio 0.40; p = 0.057).

Conclusion: Adjuvant radiotherapy after radical prostatectomy increases long term survival outcomes for high risk prostate cancer patients. This study shows that combined adjuvant RT and ADT may improve BCR-free survival.

Insight Urol 2021;42(1):7-12. doi: 10.52786/isu.a.16

Corresponding author: Varat Woranisarakul

Address: Division of Urology, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

E-mail: varatmd@gmail.com

Manuscript received: April 20, 2020

Revision received: May 2, 2021

Accepted after revision: May 2, 2021

Introduction

Radical prostatectomy (RP) is one of the standard treatments in localized high-risk prostate cancer patients. Between 25 and 40 percent of patients who undergo RP have biochemical recurrence or disease progression, especially patients with adverse pathological features which include extracapsular extension, a positive surgical margin and seminal vesicle involvement[1,2]. Several trials have shown that adjuvant radiation therapy (ART) after RP conferred benefits with regard to long-term biochemical progression-free survival (PFS) and metastasis-free survival (MFS)[2-5]. On the contrary the data from two large randomized trials (RTOG 96-01 and GETUG-AFU 16) indicated that salvage radiation therapy (SRT) combined with short or long term of androgen deprivation therapy (ADT) was advantageous and improved PFS and MFS in patients with disease recurrence. However, at the start of this investigation there was no consensus regarding the role and duration of ADT in combination with ART or SRT in post RP patients[6-8]. Therefore, this study was conducted to determine the oncological outcome of adjuvant treatment between ART alone and combined radiotherapy with androgen deprivation therapy (ART plus ADT) in high risk prostate cancer patients after RP.

Materials and Methods

All charts of patients who were diagnosed with high risk prostate cancer and underwent radical prostatectomy with pelvic lymphadenectomy at Siriraj Hospital between 2000 and 2016 were retrospectively reviewed. All patients had pathological confirmation of adenocarcinoma with a Gleason score of 8-10, pathological staging T3-T4 or preoperative PSA > 20 ng/ml with adverse pathological features (positive surgical margin, bladder neck involvement or seminal vesicle invasion). Patients who had postoperative detectable PSA (PSA > 0.2 ng/ml) or a follow up time of less than 6 months were excluded. Eligible patients were categorized into two groups: the adjuvant radiation therapy group including patients who received postoperative radiotherapy alone without any ADT and patients who received combined radiation therapy with ADT (Figure 1).

Both groups underwent external beam radiation therapy (EBRT) at the Radiation Oncology Division, Department of Radiology, Faculty of Medicine Siriraj Hospital. Most of these were given three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) within the 12 months after surgery. The radiation doses ranged from 66 to 72 Gray (Gy) given in 33 to 36 daily fractions at the surgical bed. ADT was given including a GnRH agonist,

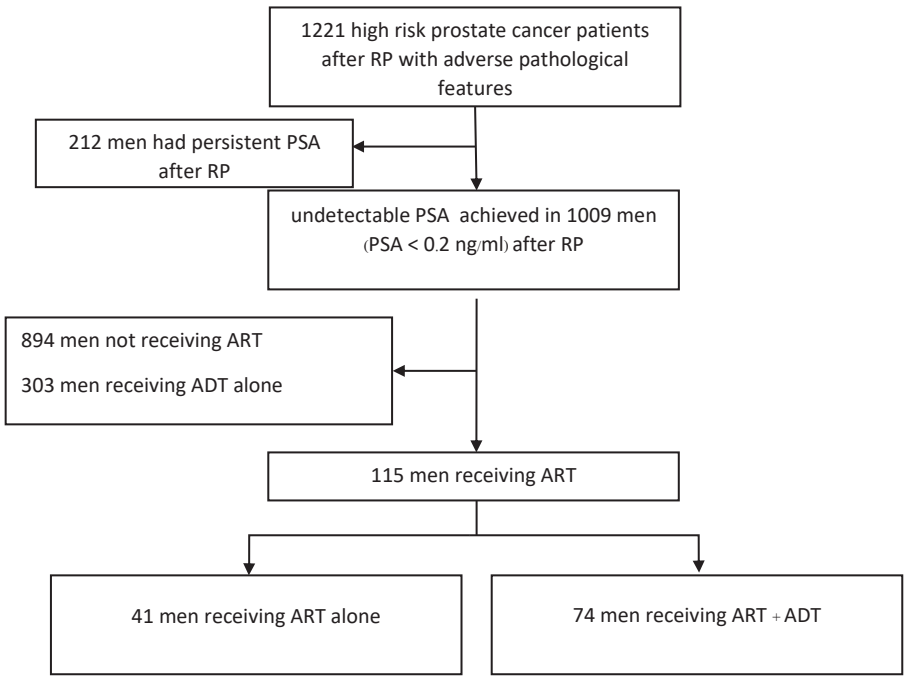

Figure 1. Study design

an antiandrogen and a bilateral orchiectomy. The period of ADT in patients who underwent a bilateral orchiectomy was recorded to the last follow up time or biochemical recurrence occurred. Demographic data, tumor characteristics and types of adjuvant treatment were reviewed. Time to events were calculated starting from date of operation to the documented time of recurrence or metastasis. Biochemical recurrence was defined by two consecutive PSA values of increases of more than 0.2 ng/ml[9]. Distant metastasis was evaluated using CT and bone scans. The primary outcome was biochemical recurrence-free (BCR) survival between the two groups of adjuvant treatment after RP. The secondary outcome was metastasis-free survival.

Statistical analysis was carried out using SPSS version 21.0. Demographic data are showed as mean and median. The Kaplan-Meier method was used to analyze survival time. A log-rank test was used to compare the two groups. Quantitative data was analyzed using a Mann Whitney U test and independent t-tests, and a Chi-square test was used for categorical data.

Results

Undetectable PSA after RP was achieved in 1009 out of 1221 high risk prostate cancer patients who had been followed up at least 6 months after surgery. One hundred and fifteen men received ART regardless of adjuvant ADT, 41 patients (35.7%) underwent ART alone, 74 patients (64.3%) received a combination of ART plus ADT.

Demographic data and tumor characteristics in both groups are shown in Table 1. A comparison between the ART alone group and the combined treatment group showed there was no statistical difference in age, preoperative PSA level or pathological staging. Mean age in both groups was 65 years. Median preoperative PSA levels were 19 ng/ml in both groups. Median follow up time was 56.7 months (Range 9.5 to 154.9) and 73.7 months (Range 8.9 to 210.7) in the ART alone group and combined group respectively. Positive surgical margin rates were 70.7% vs 81.1%, BCR rates were 22% vs 12.2%, distant metastasis rates were 2.4% vs 2.7%, between ART alone group and combined group respectively. Four patients in the adjuvant combined treatment group had regional lymph node metastasis (pN1).

Survival analysis is shown in Figure 2. Ten year BCR-free survival of adjuvant RT alone and the combined treatment group was 70.2% and 83.8% respectively (Hazard ratio 0.40; 95% confidence interval 0.16 to 1.03, p = 0.057). Ten

Table 1. Demographic data and tumor characteristics

Characteristics	Adjuvant RT alone (n = 41)	Adjuvant RT + ADT (n = 74)	P-value
Age (years)	65.3 ± 6.6	65.4 ± 8.7	0.923
PSA (ng/ml)	19.15 (5 to 60)	19.0 (2 to108)	0.28
Follow up time (months)	56.7 (9.5 to 154.9)	73.7 (8.9 to 210.7)	0.01
Gleason grade group (N = 109) n (%)	n = 38	n = 71	0.089
1	1 (2.6)	1 (1.4)	
2	11 (28.9)	12 (16.9)	
3	11 (28.9)	11 (15.5)	
4	8 (21.1)	18 (25.4)	
5	7 (18.4	29 (40.8)	
Surgical margin status			0.204
Positive n (%)	29 (70.7)	60 (81.1)	
Pathological staging n (%)			0.696
pT2	3 (7.3)	7 (9.5)	
pT3	38 (92.7)	67 (90.5)	
Node n (%)			0.111
pN1	0 (0)	4 (6)	
Biochemical recurrence n (%)	9 (22)	9 (12.2)	0.166
Metastasis n (%)	1 (2.4)	2 (2.7)	0.932

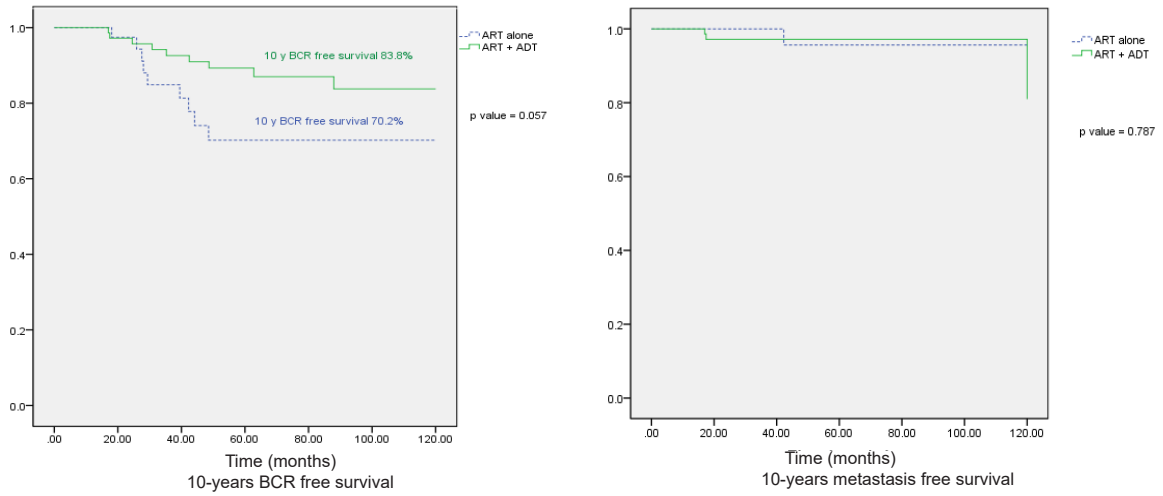

Figure 2. Kaplan-Meier curves of biochemical recurrence free survival and metastasis free survival

Table 2. Details of comparative analysis

Study	Siriraj study	GETUG-AFU-16	RTOG 9601
Years (no. of patients)	2000-2016 (115)	2006-2010 (743)	1998-2003 (760)
Inclusion criteria	pT2-T4 preop PSA > 20 ng/ml Gleason grade group 4-5 Adverse pathologic features	PT2-T4a Pre SRT PSA 0.2-2.0 ng/ml Undetectable PSA postop	pT3N0 or T2 with positive margin Pre SRT PSA 0.2-4.0 ng/ml
Treatment arms	ART vs ART + ADT	SRT vs SRT + ADT	SRT vs SRT + ADT
RT dose (Gy)	66-72	66	64.8
Hormone therapy type	GnRH agonist; Antiandrogen Bilateral orchiectomy	GnRH agonist (goserelin)	Antiandrogen (bicalutamide)
ADT duration (mo)	28	6	24
Median follow-up (yr)	5.3	9.3	13
High-risk features (%)	T3 : 91.3 SM+ : 77.4 Persistent PSA : 0	T3 : 46 SM+ : 51 Persistent PSA : 0	T3 : 67 SM+ : 75 Persistent PSA : >12
Biochemical control (%)	9.8 improvement (10 yr)	17 absolute improvement (9.3 yr)	24 absolute improvement (12 yr)
Distant metastasis (%)	No significant improvement	7 absolute improvement (9.3 yr)	9 absolute; improvement (12 yr)

years metastasis-free survival was 95.7% and 81% respectively (p = 0.787).

Discussion

Locally advanced prostate cancer with high risk features is a complex condition which needs a multidisciplinary approach to increase a positive outcome. Long term ADT plays a major role in combination with radiotherapy as an effective primary treatment which improves survival in high risk prostate cancer patients with intact prostate[10-12]. By contrast, surgical treatment alone may be insufficient in long life expectancy patients. Previous randomized studies demonstrated the benefits of adjuvant radiotherapy alone after RP in high risk pathological cases. Unfortunately, there is no strong evidence to support the benefits of additional ADT in patients who underwent radical prostatectomy.

Bolla et al. and Wiegel et al. reported biochemical recurrence rates of about 40% in cases where ART alone was given after a 10-year follow up[2-4]. RTOG 9601 and GETUG-AFU 16 reported that a combination of SRT with ADT increased PFS and MFS in patients with BCR after RP[7,8]. The duration of ADT in these trials was 24 months of bicalutamide and 6 months of goserelin respectively. A comparative analysis is shown in table 2. This study shows a 9.8% improvement in biochemical control after 10 years of follow up whereas 24% and 17% absolute improvement were discovered in RTOG 9601 and GETUG-AFU 16 respectively. The 10-year PFS in GETUG-AFU 16 was 64% for patients in the radiotherapy plus goserelin group. Our results emphasize that a combination of ART plus ADT improved BCR-free survival in high risk patients with adverse pathological features after RP (70.2% vs 83.8% in ART alone vs ART plus ADT). Some recent data showed an overall survival improvement after a combination of ART plus ADT vs observation or ADT alone in high risk and node-positive patients after RP (HR 0.77, 95% CI 0.64-0.94; p = 0.008)[13]. This may guide us how to improve survival rates in the context of adjuvant combination therapy after RP in men with adverse pathological features.

Major limitations of this study include its retrospective nature which can lead to a selection bias and lack of matched controls causing a level of variation in types and duration of ADT in the combination treatment cohort. Phase III AFU-GETUG-20 (NCT01442246) and ERADICATE trials (NCT04484818) will help us to understand the benefits and the optimum duration of hormonal treatment in adjuvant therapies.

Conclusion

Multimodality treatment increases long term survival rates for high risk prostate cancer patients. A combination of radiotherapy and hormonal treatment after radical prostatectomy appears to improve biochemical recurrence-free survival in patients with adverse features when compared with adjuvant radiation therapy alone.

Acknowledgement

The authors would like to thank Ms. Jitsiri Chaiyatho and all coordinators at the Siriraj Hospital for their important contributions to this study.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Stephenson AJ, Bolla M, Briganti A, et al. Postoperative radiation therapy for pathologically advanced prostate cancer after radical prostatectomy. Eur Urol 2012;61:443-51.
2. 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). The Lancet 2012;380:2018-27.
3. 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 followup of a randomized clinical trial. J Urol 2009;181:956-62.
4. Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 2014;66:243-50.
5. Woranisarakul V, Leewansangtong S, Dankulchai P, Apiwarodom N, Srinualnad S, Taweemonkongsap T, et al. Oncological Outcomes of Radiotherapy after Radical Prostatectomy in Thai Patients with Prostate Cancer. J Med Assoc Thai 2017;100:S179-85.
6. Boonyapanichskul P, Leewansangtong S, Srinualnad S, Nualyong C, Taweemonkongsap T, Woranisarakul V. Outcome of Adjuvant versus Salvage Androgen Deprivation Therapy (ADT) with/without Radiotherapy Following Radical Prostatectomy for Prostate Cancer Patients with Adverse Pathologic Feature(s) or with Positive Regional Lymph Node Metastasis. J Med Assoc Thai 2020;103:75-80.
7. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417-28.
8. Carrie C, Magne N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange J, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019;20:1740-49.
9. Cookson MS, Aus G, Burnett AL, Canby-Hagino

ED, D'Amico AV, Dmochoski RR, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540-5.

10. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff R, Storme G, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066-73.
11. Pilepich MV, Winter K, Lawton CA, Krisch R, Wolkov HB, Movsas B, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005;61:1285-90.
12. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008;26:2497-504.
13. Mohit G, Hiten D P, Zeyad R S, Tran PT, Partin AW. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int 2019;123:252-60.