

Profile of Radiation Therapy after Radical Prostatectomy: Experience in a Tertiary Hospital in Jakarta, Indonesia

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ABSTRACT

Background: Despite the high recurrence rate, radical prostatectomy (RP) remains as a preferable surgical treatment of localized prostate cancer. Adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) are available approaches in preventing biochemical progression after RP. We aim to investigate the use of radiotherapy, both ART and SRT, in those who underwent RP.

Methods: We used a retrospective cohort study design, with samples recruited from prostate cancer patients who underwent RP between January 2008 and December 2016. Patients who had undergone RP at Cipto Mangunkusumo Hospital, Jakarta, Indonesia were included in the present study. More in detail, three and five subjects were treated with ART and SRT, respectively. We only included those who had a minimum of one year of follow-up. Variables including age, preoperative prostate-specific antigen (PSA), clinical staging, pathological staging, Gleason score, and death were recorded. We analyzed the overall survival time using the Kaplan-Meier method.

Results: From 34 patients included in the study, 26 underwent RP alone, while 5 patients underwent adjuvant radiotherapy and 3 patients underwent salvage radiotherapy after RP. The mean ages in the three groups were 61.46 ± 5.76 , 58.2 ± 4.86 and 62.67 ± 7.5 , respectively. The preoperative PSA value was above 10 mg/dL in 61.5% in patients without RT, 100% in patients with ART after RP, and none in SRT. 17 (51.5%) out of 33 subjects were $\geq T2$ clinical stage and 24/30 (80%) subjects were $\geq pT2$. Timing for ART and SRT ranged from 1.07 to 6.3 and 5.27 to 21.43 months after RP, respectively. The 10-year survival rates were 84.6% in patients with RP alone, 80% in patients with ART+RP, and 66.7% in patients with SRT+RP. The average survivals of those who had RP alone as well as ART and SRT were 44.56 ± 32.64 , 46.79 ± 24.02 , and 71.71 ± 38.74 months.

Conclusions: The average survival of those who received SRT is better than those who underwent ART and RP alone. Prospective studies with larger samples are needed to evaluate the efficacy of radiation therapy after radical prostatectomy.

INTRODUCTION

Prostate cancer (PC) is one of the most frequently occurring male neoplasms, with 241,740 new cases diagnosed in the United States in 2012 [1]. In Indonesia, PC is ranked as the 6th highest number of cancer cases in males [2]. Radical prostatectomy (RP) acts as the standard treatment for localized PC; it cures approximately two-thirds of men with PC. However, up to one-third of patients develop recurrence in 10 years [1]. To make matters worse, recurrence will result in elevated prostate-specific antigen (PSA) in 15 to 50% within 10 years after RP [4,5]. The risk of recurrence tends to be higher in patients with abnormal pathology, including positive surgical margins (SM), seminal vesicle invasion (SVI), extra-prostatic extension, higher Gleason scores, high serum PSA level before surgery, and persistently elevated PSA after RP [1,4–6]. If left untreated, up to nearly half

of these patients are at risk of dying from such disease within the 15 years of biochemical progression (BCP) [7]. To date, there have been two types of radiotherapy available for treatment and prevention of such progression after RP, which are: immediate postoperative adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) [3]. ART refers to the postsurgical radiotherapy given to patients who are at the high risk for recurrence but lack measurable disease, and SRT refers to radiotherapy given to patients with clinical evidence of residual or recurrent disease after surgery.

Adjuvant radiotherapy in high-risk patients was shown to increase local control rates and disease-free survival. The positive effect of ART for survival in patients diagnosed with PC is highly influenced by tumor characteristics. The fundamental premise underlying ART is that local recurrence comes first before systemic, metastatic spread occurs in the majority of those in whom RP failed [8].

Thus, it might be better to administer ART after RP. According to the National Comprehensive Cancer Network (NCCN), the indications of ART include those with pT3, positive SMs, Gleason scores of 8 to 10, or SVI. Usually, ART is administered within a year after surgery and once there is an improvement of the side effects of RP [9]. Recurrence, often defined as PSA values of at least ≥ 0.2 after RP [10], is also an indication for ART.

Salvage radiotherapy is defined as radiotherapy to the prostatic bed and surrounding tissues in patients with biochemical recurrence (BCR) following RP without showing signs of distant metastases [1]. Theoretically, SRT reduces the expenses and adverse effects of ART to individuals with adverse pathologies but who have a low risk of recurrence after surgery [11–13]. To this date, there are no studies regarding the use of radiotherapy in those who underwent RP in our hospital. The present study aims to investigate the average survival of the patients who underwent ART and SRT compared to those who underwent RP but didn't get the radiotherapy.

METHODS

Participant

This was a retrospective cohort study on prostate cancer patients who underwent RP with or without additional radiation therapy during the period of January 2008 to December 2016 at Cipto Mangunkusumo

Hospital, Jakarta, Indonesia with the ethic committee approval number 1140/UN2.F1/ETIK/2018.

The sample size was initially measured using the mean survival between two groups and there are two different type groups, namely, ART and SRT groups, which were being compared with the patients without the radiation group as the control group. Since patients recruited within the study period were only 34 samples, the statistical analysis was not done due to inadequate data. Thus, a descriptive report was presented. Patients who had sufficient data and a minimum of one-year follow-up were included in the present study. Variables including age, preoperative PSA, clinical stage, pathological stage, Gleason score, and death were recorded.

Statistical Analysis

The average survival and overall survival (OS) from ART and SRT groups were calculated from the date of RP to the date of death or the last follow-up and were compared with the control. Since the number of recruited samples were inadequate for the statistical analysis, a descriptive report was done. The survival rate was estimated by using the Kaplan-Meier analysis.

Average survival is defined as mean survival time since the commencement of therapy (RP) until the death of each sample presented as months. Overall survival is defined as the percentage of samples who are still found to be alive after the period of follow-up.

RESULTS

Table 1. Characteristics of the subjects

Characteristics	Without radiotherapy (N=26)	With adjuvant radiotherapy (N=5)	With salvage radiotherapy (N=3)
Age			
Mean \pm SD	61.46 \pm 5.76	58.2 \pm 4.86	62.67 \pm 7.5
Median (range)	62 (44-69)	55 (54-64)	63 (55-70)
Preoperative PSA			
<10	10 (38.5%)	0 (0%)	2 (66.7%)*
≥ 10	16 (61.5%)	5 (100%)	0 (0%)
Mean \pm SD	28.19 \pm 59.3	64.48 \pm 66.58	6.62 \pm 3.87
Median (range)	14 (0.48-308.65)	32.56 (12.05-170)	6.62 (3.88-9.36)
Clinical stage			
T1	13 (49.1%)*	3 (60%)	0 (0%)
$\geq T2$	12 (46.2%)	2 (40%)	3 (100%)
Pathological stage			
T1	6 (23.1%)**	0 (0%)	0 (0%)*
$\geq T2$	17 (65.4%)	5 (100%)	2 (66.7%)
Gleason score			
≤ 7	17 (65.2%)*	3 (60%)	2 (66.7%)
≤ 8	8 (30.7%)	2 (40%)	1 (33.3%)
Average survival (months)	44.56 \pm 32.64	46.79 \pm 24.02	71.71 \pm 38.74

*One subject was missing

**Three subjects were missing

A total of 34 subjects who underwent RP were recruited for this study. Twenty-six subjects did not receive additional radiotherapy, while five and three subjects had ART and SRT, respectively (Table 1). SRT was initiated in patients with PSA levels of 0.15, 0.06, and 3.9 ng/mL, and ART was initiated at PSA levels of 4.28, 0.16, 0.206, and 0.007 ng/mL (one subject was missing).

The average survival of the group without radiotherapy, ART group, and SRT group were 81%, 48%, and 65% respectively. The average survival of SRT is the highest with a mean survival of 71.71 ± 38.74 months, followed by the ART group with a mean survival of 46.79 ± 24.02 . The control group (without radiotherapy) had the lowest average survival with a mean survival of 44.56 ± 32.64 . The Kaplan-Meier analysis of the survival function of the subjects is presented in Figure 1. A total of six subjects died during the follow-up period.

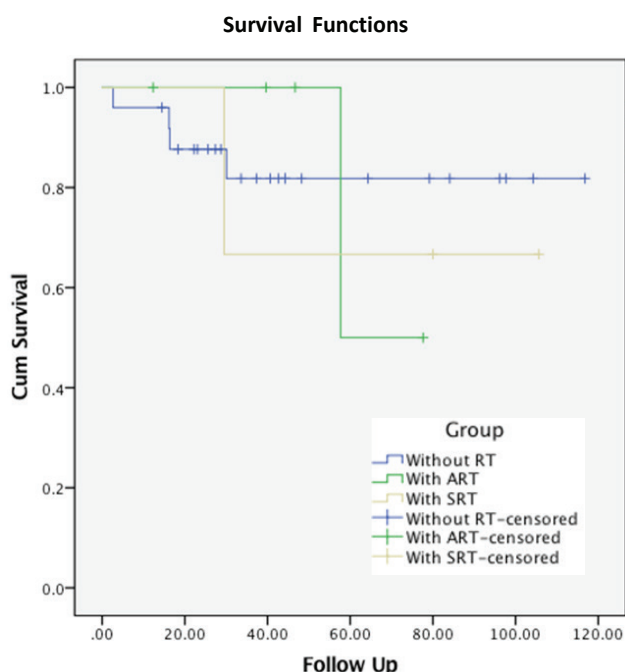


Figure 1. Kaplan-Meier analysis of the survival function of the subjects

DISCUSSION

Despite being a standard treatment for post-op RP BCR, there is currently no consensus with regard to the optimal timing of SRT [14]. Moreover, controversy remains concerning when ART should be given after surgery [15–18]. In the present study, the timing for ART and SRT ranged from 1.07 to 6.3 and 5.27 to 21.43 months after RP, respectively.

In this study, the three subjects that received SRT had pre-RT PSA levels of 0.06, 0.15, and 3.9 ng/mL. King suggested that SRT should be initiated at the lowest possible PSA [19]. In a study comparing the outcomes

of different timings of the administration of SRT after postoperative BCR with the median follow-up of 70 months, Taguchi et al. [14] found that four (20%), nine (23), and seven (44%) patients had biochemical failure in ultra-early SRT (given before the patients meet criteria of two consecutive PSA values ≥ 0.2 ng/mL). Early SRT administered at pre-radiation PSA ≤ 0.5 ng/mL and delayed SRT given after PSA reached 0.5 ng/mL groups. There was no survival benefit of ultra-early SRT compared to early SRT. However, delayed SRT was associated with poorer prognosis. Stephenson et al. [20] reported that the 6-year BCR-free survival rates were between 50% and 18% among patients with PSA levels of ≤ 0.5 and >1.5 ng/ml at the initiation of RT, respectively. Another study that included individuals receiving only early SRT, defined as post-operative RT at PSA values ≤ 0.5 ng/ml, showed a 5-year BCR-free survival rate of approximately 75% [21]. However, whether early SRT has similar efficacy as ART after RP should be further investigated in prospective RCTs. A multicenter retrospective study reported that the initial observation followed by early SRT showed a comparable BCR-free survival to ART in men with pT3N0 disease using a matched-controlled approach [13]. The investigators, however, failed to show any difference in the 5-year recurrence-free survival rates between the two groups in an approximately 1000 patient population with aggressive pathologic characteristics. (78.4 vs 81.8% for adjuvant vs. observation eventually followed by SRT, respectively) [13].

Despite the fact that administering ART in all men had no justification, the existing evidence demonstrates those with men with positive SMs and pT3 PC have more than 50% risk of biochemical within 10 years after RP [22-24]. Thus, those with such diseases are considered suitable candidates for undergoing ART. A Cochrane review study of 3 RCTs with 1.815 high-risk patients at the time of surgery (e.g., SVI) showed that ART improved biochemical progress-free survival (PFS) in comparison to RP alone at 5 and 10 years (risk difference at 5 years: -0.16; 95% CI: -0.21 to 0.11 and at 10 years: -0.29; 95% CI: 0.39 to 0.19) (49) [25]. According to the NCCN, the indications of ART include pT2 disease, positive SMs, Gleason scores of 8 to 10, or SVI. ART is usually given within a year after RP and once there is an improvement of any side effects of RP [9,26,27].

Other findings also suggest that ART may reduce the BCR hazard ratio [HR] significantly in the presence of adverse pathology after RP, despite lower RT doses than usual [28–31]. However, these studies contained major contamination biases; such as 30–35% of the included subjects had detectable PSA and thus received SRT rather than ART. These make the efficacy data questionable. The use of postoperative RT might increase the risks of toxicities in both short and long terms, which may impair patients’ quality of life. In the SWOG

8794 trial, those who received ART developed a rectal complication, urethral stricture, and urinary incontinence compared to controls [32]. The EORTC 22863 trial also showed that the incidence of genitourinary toxicity and other late adverse events, during 10 years of follow-up, were higher among patients treated with immediate postoperative RT [15]. A systematic review involving three RCTs revealed that ART increased the risk of acute and late gastrointestinal problems, urinary stricture, and worse continence recovery rates [33]. Whereas, retrospective studies focusing on patients treated with SRT showed that this radiotherapy might lead to grade 2 or higher genitourinary toxicities in up to 20% of the patients [34,35]. In addition, previous studies that compared the safety profile of postoperative ART and SRT failed to show significant differences between both approaches [35,36].

The advantages of administering ART immediately are more evident from three RCTs. These trials demonstrated that those who underwent ART achieved 20% higher biochemical control at 5 years compared to those undergoing SRT [15,32,37,38]. Nevertheless, it should be considered that in two out of three RCTs, more than a quarter of the included subjects had PSA levels higher than 0.2 ng/mL at the time RT began. This corresponds to a “salvage-like” situation [15,32]. Our study was limited by the small number of post-RP patients receiving ART or SRT.

CONCLUSIONS

The highest average survival group was SRT with a mean survival of 71.71 ± 38.74 months, followed by ART group with a mean survival of 46.79 ± 24.02 . The control group (without radiotherapy) had the lowest average survival with a mean survival of 44.56 ± 32.64 . Patients who underwent SRT have better average survival than those undergoing RP alone or ART. Further studies with prospective study design and larger samples are needed to evaluate the efficacy of radiation therapy after radical prostatectomy.

DECLARATIONS

Competing of Interest

The author(s) declare no competing interest in this study.

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