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Correlation of Radiation Dose and PSA Blood Level in the Radiotherapy of Prostate Cancer: A retrospective case series

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Abstract

Background: The objective of this study was to analyze the correlation of radiation dose and Prostate-Specific Antigen (PSA) blood level following radiation therapy in prostate cancer.

Methods: The study population was serial of 13 patients with histologically proven T1b-T4, any N, M0 prostate adenocarcinoma, having any Gleason score with any PSA before and after complete EBRT (external beam radiotherapy), from January 2009 to December 2010 and evaluated for PSA decrease post-EBRT.

Results: Out of 13 patients, one patient received 62 Gy, one patient received 72 Gy, and 11 patients received 80 Gy. PSA blood level was decreased (median 5.4, 9.43 and 25.27, respectively) in all patients.

Conclusion: This case series results were consistent with the results of previous studies that a higher radiation dose will have a higher PSA decrease with a tolerable side effect.

Keywords: Prostate cancer, PSA, EBRT, radiation dose

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Background

Based on the latest data from Globocan 2018, prostate cancer is the most cancer in men in the world with a prevalence of 96.7 per 100,000 population. In Indonesia, prostate cancer is the fourth most cancer in men, with a prevalence of 29.8 per 100,000 population. This number has the potential to continue to increase along with the increasing life expectancy of the population.¹ In western countries, prostate cancer is the most primary cancer in men, causing 94,000 deaths in Europe in 2008 and more than 28,000 deaths in the United States in 2012. Overall, over the past decade, the relative 5-year survival percentage for prostate cancer continues to increase from 73.4% in 1999-2001 to 83.4% in 2005-2007.²

In the ProtecT study by Hamdy et al. investigating the five years and ten years specific survival of prostate cancer in local prostate cancer patients who performed active monitoring, surgery and radiation showed that the particular survival of 5-year prostate cancer was 99.4% in the active monitoring group, 100% in the

surgery group, and 100% per cent in the radiation group ($p = 0.48$). In the ten years specific survival of prostate cancer, 98.8% were found in the active monitoring group, 99% in the surgery group and 99.6% in the radiation group. Significant findings were only seen in the clinical progression of 1,000 patients per year as many as 22.9, 8.9, 9.0 in that group respectively ($p < 0.001$) and also significant in metastasis of 1,000 patients per year as many as 6.3, 2.4, 3 in that group respectively ($p = 0.004$).³ PSA level is one of the indicators used to predict prognosis in prostate cancer and also used to evaluate response to therapy. In this case series, we analyze the correlation between radiation dose and PSA blood level after completing radiotherapy, where decreased PSA level was a good prognosis for prostate cancer patients.

Methods

This study was retrospective, nonrandomized, single-centre case series. patients with complete data of PSA

blood level before and after complete EBRT were analyzed. Diagnostic confirmation was made by histology of prostate adenocarcinoma. Patients were given radiation dose based on the clinical decision by the medical doctor according to the guideline at the department of radiotherapy. Data were analyzed using SPSS version 20.0 for windows.

to define the shape and location of the prostate with CT and MRI simulations. Although usually sufficient for the management of T1 and T2a tumors, field reconstruction using CT clearly shows that a field size of 8 x 8 cm will not be sufficient to cover almost the entire prostate in advanced local prostate cancer, especially if the seminal vesicle is at risk.⁴

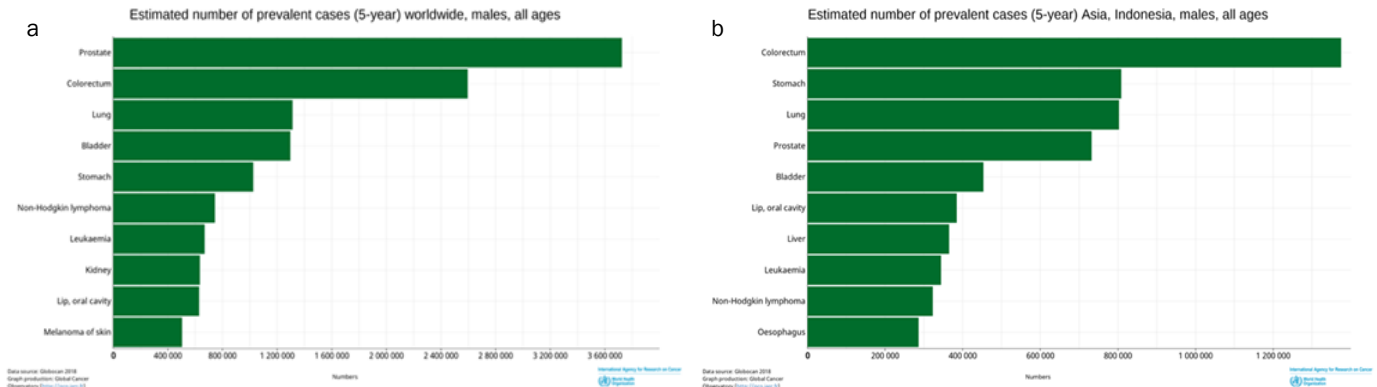


Figure 1. (a) Cancer Prevalence in men worldwide (b) Cancer Prevalence in men in Indonesia

Source: Reference no. 1 and 2

Results

A total of 13 patients selected was treated from January 2009 to December 2010 in the Radiotherapy Department Cipto Mangunkusumo Hospital (RSCM), detail of patients data shown at **Table 1**.

Group 1, patient treated with total dose 62 Gy

Prostate cancer patients aged 59 years with T1N0M0, Gleason Score 3 + 3. The pre and post complete treatment, PSA blood level was 5.4 and 1.1 ng/mL respectively, the absolute decrease of PSA was 4.3.

Group 2, patient treated with total dose 72 Gy

A 77 -year-old patient with diagnose T2N0M0 intermediate risk prostate cancer, Gleason score 4 + 3, initial PSA 9.43 ng/mL. The Post-EBRT PSA of this patient was 0.009 ng/mL so the absolut PSA level decreased value was 9.24 ng/mL.

Group 3, patient treated with total dose 80 Gy

Eleven localized prostate cancer patients with T, and N, risk stratification as seen in table 1 received 80 Gy EBRT. The median pre-EBRT PSA level was 32.29 ng/mL, median post-EBRT PSA level was 3.34 ng/mL, the median PSA decrease was 28.95.

In the 11 patients the PSA decreased were shown in the boxplot

Discussion

Radiation techniques for prostate cancer patients was improved from conventional EBRT techniques that use estimation of prostate anatomic boundaries based on plain radiographs and digital rectal examination. This technique is suboptimal compared to the current ability

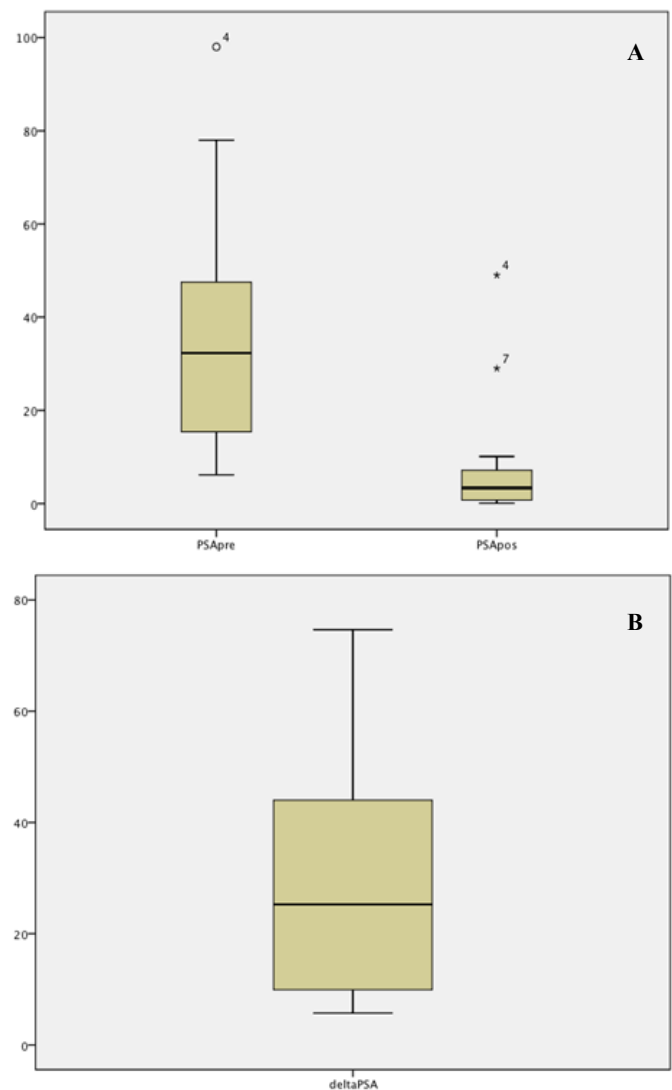


Figure 2. A) Pre and post EBRT PSA level of 11 patients. B) PSA decreased in 11 patients following 80 Gy EBRT (median 25.27, mean 28.41)

Table 1. Characteristic of EBRT prostate cancer patients

Total dose EBRT		62 Gy	72 Gy	80 Gy
Age (years old)		(n)	(n)	(n)
	45 - 59	1		2
	60 - 69			3
	70 - 79		1	5
	≥80			1
Pre-EBRT PSA	Mean	5.4	9.43	37.89
	Median			32.29
	Range			91.85
Post-EBRT PSA	Mean	1.1	0.09	9.48
	Median			3.34
	Range			48.95
PSA decrease	(median)	4.3	9.24	25.27
Combined Gleason				
	2 – 6	1		3
	7		1	4
	8 – 10			4
T				
	T1	1		3
	T2		1	3
	T3			3
	T4			2
	Unkown			2
N	N0	1	1	9
	N1			1
	Unkown			2
Risk Stratification	Low			
	Intermediate	1	1	
	High			4
	Very High			7

More precise radiation makes it possible to provide a higher radiation dose. The Three-Dimensional Conformal Radiation Therapy (3D-CRT) radiation technique uses computer software to integrate CT images of the patient's internal anatomy in an anatomic position, which allows higher cumulative doses to be given with a lower risk of further effects. The second generation of 3D techniques, Intensity Modulated

Radiotherapy (IMRT) is increasingly being used. IMRT reduces the risk of gastrointestinal toxicity and the rate of salvage therapy.⁵ IMRT is the current standard EBRT for prostate cancer. After an initial single institutional report on the increasing efficacy and therapeutic ratio by Hanks et al, the dose escalation strategy has become an important focus of research on prostate cancer. The presence of 3D-conformal and the

emergence of IMRT show increased biochemical control and decreased toxicity compared to the 2D approach.

In this case series there was a decrease in PSA in all three groups. The PSA decrease were 5.4, 9.43, and 25.27 (median) in 62 Gy, 72 Gy, and 80 Gy respectively. In group 3 with total radiation dose of 80 Gy, the median Pre-EBRT PSA level was 32.29 and median post-EBRT PSA was 3.34 and median PSA decrease was 25.27. Of the three groups, the most decrease occurred in the 80 Gy radiation group.

This result is consistent with result of studies about dose escalation for prostate cancer. A randomized trial study by comparing the results of 5 years of prostate cancer patients receiving 70 Gy and 80 Gy radiation of a total 306 patients with local prostate cancer were randomized. The final outcome assessed was biochemical recurrence according to the modified 1997-American Society for Therapeutic Radiology and Oncology and Phoenix definitions. Toxicity was assessed using the 1991 Radiation Therapy Oncology Group and late effects on normal tissue - subjective, objective, management, and analytical scale with LENT-SOMA scales. The quality of life of patients was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire which consisted of 30 specific questions about cancer and 25 specific questions about prostate. The results show that high radiation doses provide better 5-year biochemical results with slightly higher toxicity.⁶

Doses of 70 Gy and 78 Gy were compared by Kuban et al in 301 patients with 4-field box technique and 3D-CRT and a median follow-up of 8.7 years showed biochemical control of 59% at 70 Gy and 78% at 78 Gy ($p = 0.004$). With a median follow-up of 8.9 years Zietman et al compared biochemical controls in 393 patients given doses of 70.2 Gy and 79.2 Gy with a 4-field box technique and photon booster and then obtained biochemical control of 67.6% at 70.2 Gy and 83.3% at 79.2 Gy ($p < 0.0001$). Al-mamgani et al irradiated patients with 3D technique then compared the administration of 68 Gy and 78 Gy doses to 669 patients with a median follow-up of 5.8 years obtained 45% biochemical control for 68 Gy doses and 71% for 78 Gy doses ($p = 0.03$).⁷

Comparing 74 Gy and 64 Gy was also become the a long-term randomized controlled study by David P Dearnaley et al, in local prostate cancer patients.

Results from the study with a median follow-up of 10 years, escalation-dose conformal radiotherapy with neoadjuvant androgen deprivation therapy (ADT) showed benefits of biochemical progression-free survival (PFS), but these benefits did not apply to overall survival.⁸ RTOG 0126 (ASCO 2015) by Michalski et al. biochemistry in 1,499 patients who were given radiation doses of 70.2 and 79.2 Gy with 3D or IMRT techniques and a median follow-up of 7 years and obtained biochemical control at a dose of 70.2 Gy as much as 55% and at a dose of 79.2 Gy as much as 70%.⁸

Another study investigating doses in prostate cancer patients in local prostate cancer radiation with a randomized phase III study from a multicenter in the Netherlands comparing radiotherapy doses of 68 Gy with 78 Gy in 3D-CRT radiotherapy techniques. Studies followed by patients with stage T1b-4 prostate cancer show a significant increase in freedom from failure (FFF) in prostate cancer patients given higher doses of radiotherapy.⁹ Higher radiation doses in the treatment of local prostate cancer were also analyzed by meta-analysis in a randomized controlled study by Gustavo Arruda Viani et al., Of seven randomized controlled studies with a total patient population of 2812 fulfilling the criteria, the results showed that high dose radiotherapy was superior to conventional dose radiotherapy in prevent biochemical failure for all patients, regardless of risk status.¹¹ Studies that look at long-term failure patterns and survival with a random dose escalation test in prostate cancer by Deborah A. Kuban et al conclude that moderate dose escalation 78 Gy decreases biochemical failure, clinical failure and death from prostate cancer in patients with PSA before treatment > 10 ng / ml or high risk diseases.¹⁰

A meta-analysis of long-term follow-up after administering high-dose radiation and conventional doses to prostate cancer patients was conducted to see the efficacy and toxicity between high-dose radiotherapy and conventional dose radiotherapy by collecting studies with long-term follow-up taken from Ovid MEDLINE, ovid EMBASE, Cochrane Library, Science Citation Index (Web of Science) and ClinicalTrial.gov for the following: biochemical failure (BF), overall survival (OS), prostate cancer-specific survival (PCSS) and side effects. The meta-analysis was performed using Review Manager 5.2 and stata version 12.0. with results expressed as odds ratios (OR) with 95% confidence intervals. Results from 6 randomized controlled studies, with a total population

of 2,822 were eligible. In terms of the 10-year relative efficacy of conventional dose radiotherapy, high doses are almost equivalent to overall survival (73.4 vs. 74.3%, OR 1.05, 95% CI 0.86-1.28; $p = 0.64$) and prostate cancer-specific survival (90.7 vs. 91.6 %, OR 1.11, 95% CI 0.83–1.49; $p = 0.47$) but a significant reduction in biochemical failure (34.0 vs. 24.7%, OR 0.61, 95% CI 0.51–0.74; $p < 0.00001$). In terms of toxicity, high-dose radiotherapy significantly increases grade 2 or greater gastrointestinal late toxicity (28.0 vs. 18.6%, OR 1.72, 95% CI 1.42–2.08; $p < 0.00001$) and genitourinary toxicity of grade 2 or more (22.6 vs. 19.5 %, OR 1.24, 95% CI 1.01-1.52; $p = 0.04$). In group analysis, patients with or without ADT both showed a significant reduction in biochemical failure over 10 years. Taking into account quality of life, there was no significant difference between conventional dose radiotherapy and high dose radiotherapy ($p > 0.05$).¹¹

For early-stage prostate adenocarcinoma a randomized trial comparing conventional high-dose radiotherapy in the long term to find out whether increasing the radiation dose in patients with early-stage prostate cancer improves clinical outcomes. The study shows long-term cancer control in patients receiving high doses of radiation compared to conventional doses.¹² While for prostate cancer patients without metastasis another study assessed at the relationship between dose escalation and overall survival. The study was conducted retrospectively, and not randomly comparing the effectiveness of EBRT escalation doses and standard doses in prostate cancer patients diagnosed from 2004 to 2006 using the National Cancer Database (NCDB), there were three cohorts evaluated, low risk prostate cancer patients (NCDB) $n = 12,229$, intermediate risk ($n = 16,714$) or high risk ($n = 13,538$). Patients were classified into two treatment groups, EBRT with standard doses (from 68.4 Gy to 75.6 Gy) or escalation doses (from 75.6 to 90 Gy), compared to overall survival of the two groups, using the Cox proportional hazard model. The results of the study show that EBRT with doses escalation is associated with increased survival in the intermediate risk group and high risk group but not in the low risk group. For each additional dose of about 2 Gy, there is a 7.8% and 6.3% reduction in hazard of death for intermediate and high risk patients.¹³

Conclusions

As life expectancy increases, and the development of early detection and diagnosis methods for prostate cancer, the prevalence of prostate cancer continues to increase. Management of prostate cancer can be done

with several modalities according to the stage and risk stratification. The role of radiation can be started from curative to palliative, as a post-prostatectomy adjuvant or as a salvage. At present the administration of radiation doses in prostate cancer leads to dose escalation due to the existence of IMRT as a new technique. This case series results are consistent with the results of previous studies that a higher radiation dose will reduce more PSA level and is a good prognosis in prostate cancer patients.

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