SURVIVAL OF PROSTATE CANCER PATIENTS WITH COMBINATION HORMONAL-RADIOTHERAPY BETTER THAN HORMONAL THERAPY

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ABSTRACT

Objective: *This study aims to determine the survival of prostate cancer (PCa) patients who did not undergo radical prostatectomy, but received hormonal therapy or a combination of radiotherapy and hormonal therapy.* ***Material & Methods:*** *This study was an observational analytic study with a retrospective cohort design, using secondary data to determine baseline data and diagnosis of patients, and using primary data to determine the survival of prostate cancer patients who received combination hormonal and radiotherapy therapy compared with hormonal therapy alone. The analysis was performed using chi-square and contingency coefficients to assess the relationship between survival with factors such as age, stage T, N, M, clinical stage, type of therapy, and prognosis. It also used the Kaplan Maeier curve to assess the survival picture of prostate cancer patients at Sardjito General Hospital.* ***Results:*** *79 patients met the inclusion criteria. The mean age of the patients was 68 ± 8.4 years. A total of 52 (65.8%) patients received hormonal therapy, and 27 (34.2%) patients received combination hormonal and radiotherapy. There were 41 (51.9%) patients remain life, while 38 (48.1%) of patients died during the monitoring. We found that the Gleason score, PSA level, and clinical stage were significantly associated with patient survival with p <0.005. The 5 years survival rate patient with local, locally advanced clinical stage and PSA level ≤ 20 ng/ml who received combination hormonal and radiotherapy achieved 100%.* ***Conclusion:*** *Combination of hormonal and radiotherapy was more improving patient survival compared with hormonal therapy only in patient with locally advanced clinical stage, PSA level ≤20 ng/ml and Gleason score ≤7.*

Keywords: *Radiotherapy, prostate cancer, survival.*

ABSTRAK

Tujuan: *Penelitian bertujuan untuk mengetahui ketahanan hidup pasien kanker prostat yang tidak menjalani radikal prostatektomi, namun mendapatkan hormonal terapi atau kombinasi radioterapi dan hormonal terapi.* ***Bahan & Cara:*** *Penelitian ini merupakan studi analitik observasional dengan design cohort retrospektif, menggunakan data sekunder untuk mengetahui data dasar dan diagnosis pasien, dan menggunakan data primer untuk mengetahui ketahanan hidup pasien kanker prostat yang mendapatkan terapi kombinasi hormonal dan radioterapi dibandingkan dengan terapi hormonal saja. Dilakukan analisa menggunakan uji chi-square dan koefisien kontingensi untuk menilai hubungan antara survival dengan faktor-faktor seperti usia, stadium T, N, M, stadium klinis, jenis terapi dan prognosis. Digunakan pula kurva Kaplan Maeier untuk menilai gambaran survival pasien kanker prostat di RSUP Dr. Sardjito.* ***Hasil:*** *Pada penelitian menunjukkan, ada 79 pasien yang memenuhi kriteria inklusi. Rerata usia pasien adalah 68 ± 8.4 tahun. Sebanyak 52 (65.8%) pasien mendapatkan terapi hormonal, dan 27 (34.2%) pasien mendapatkan terapi kombinasi hormonal dan radioterapi. Ada 41 (51.9%) pasien yang hidup sedangkan 38 (48.1%) pasien meninggal saat dilakukan pemantauan. Pada analisa data, gleason skor, level PSA dan stadium secara signifikan berhubungan dengan survival pasien dengan p <0.005. Pada stadium lokal, locally advanced dan level PSA ≤ 20 ng/ml angka survival 5 tahun yang mendapatkan terapi kombinasi hormonal dan radioterapi mencapai 100%.* ***Simpulan:*** *Terapi kombinasi hormonal radioterapi lebih meningkatkan survival pasien dibandingkan dengan terapi hormonal saja pada stadium locally advanced, level PSA ≤20 ng/ml, dan Gleason skor ≤7.*

Kata Kunci: *Radioterapi, kanker prostat, ketahanan hidup.*

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INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous malignancy detected in men in America, and the sixth leading cause of death in men due to cancer worldwide.[1] An estimated 230.000 American men were diagnosed as PCa in 2005. Worldwide, the incidence of PCa accounted for 11.7% of all new malignancy cases.

Data collected in the United States showed that more than 90% of PCa were found in the early and regional stages, with a 5-year survival rate approaching 100%. This figure was much better compared to 25 years ago, which only reached 69%.[2] Barnes in 1969 found a survival rate of 10 years and 15 years for early-stage PCa only by 50% and 30%.[3]

Data collected in Indonesia from Cipto Mangunkusumo National General Hospital (RSCM) and Dharmais Cancer Hospital showed an increase of patient number. The number of patient in 2001-2006 were twice compared to 1995-2000, with the average number of patients per year was 70-80 new cases/year. During the period January 1995 to December 2007, there were 610 patients with PCa in both hospitals, 110 patients receiving curative therapy. Radical prostatectomy was performed on 43 patients with a median age of 63 years, and another 67 patients with a median age of 70 years received External Beam Radiation Therapy (EBRT) therapy. Median survival was 101 months and 85 months each for patients receiving Radical Prostatectomy and EBRT. The 5-year survival rate was 68.4% and 69.2%, respectively for patients with treatment of Radical Prostatectomy and EBRT.[4-5]

Several studies of randomized control trial (RCT) showed that dose escalation (range 74-80 Gy) had a significant impact on 5-year survival without recurrence.[6-7] In low risk PCa, the total radiotherapy dose given was 74-84 Gy. In intermediate risk PCa patients, radiotherapy was given at a dose of 76-78 Gy combined with short-term ADT (4-6 months). In high risk patients with locally advanced PCa, radiotherapy was given at a total dose of 76-78 Gy and long-term ADT (2-3 years) was performed.[8]

According to Kuban et al., (2011) median survival rate of localized PCa T1-T3, N0 M0 with PSA levels of 10 ng/ml after obtaining radiotherapy 70 Gy was 9 years.[9] In another study by Dearnaley DP 2014 showed a median survival of up to 10 years in patients with PCa T1b-T3a, N0 M0 who received 74 Gy radiotherapy.[10] The combination of radiotherapy with LHRH ADT has proven its superiority compared to radiotherapy alone. The NCIC study in 2012 show that the combination of ADT and radiation therapy in locally advanced PCa T3-T4 increased overall survival 10 years to 49% - 55%.[11] Based on NCCN guideline 2015, the patient could have radiotherapy and hormonal therapy in low, intermediate, high, and very high risk condition.[12] Under metastatic conditions, there was a place for palliative radiotherapy and hormonal therapy too.[12]

OBJECTIVE

This study was conducted to determine the survival of PCa patients who did not undergo radical prostatectomy but received hormonal therapy or a combination of radiotherapy and hormonal therapy. In patients with local and locally advanced clinical stages, PSA <20 and Gleason score <7 were expected to have high survival, although did not run a radical prostatectomy procedure. This study aims to describe the survival rates in patients with PCa who receive hormonal therapy and combination radiotherapy and hormonal therapy. The survival will be described based on the clinical stage, Gleason score, and PSA level.

MATERIAL & METHODS

This study was an observational analytic study with retrospective cohort design using secondary data to identify baseline data, diagnosis of patients, and use primary data to determine the survival of PCa patients who received combination hormonal and radiotherapy compared with hormonal therapy alone. We took data from medical record such as age at diagnosis, clinical stage, TNM stage, Gleason score, hormonal therapy, and radiotherapy.

Data was collected through patient medical records. If the patient is declared dead due to PCa on medical record, then the patient is classified into the group of patients died. If the patient is declared alive from the medical record, then the patient is classified into the group of life patient. All patients with the diagnosis of prostate carcinoma and had complete medical record, were included in the study sample. Patients with localized PCa who refused radical prostatectomy procedure were also included. The diagnosis of PCa is established through histopathologic examination in the January 2009-December 2013 period, with TNM staging and

Gleason scores. Patients who died not because of PCa, but due to other causes, were excluded. In addition, patients who undergo radical prostatectomy, have not received complete radiotherapy at least one cycle and who did not get hormonal therapy were not included in this study.

Analyzes were performed using chi-square and contingency coefficients to assess the relationship between survival with analyzed factors such as age, stage T, N, M, S, clinical stage, type of therapy, and prognosis. Kaplan Meier curve is used to assess the survival of PCa patients.

RESULTS

Table 1 described descriptive data of PCa patients in 2009-2013. During the patient selection process, 79 patients met the inclusion criteria. Then we follow-up these 79 patients. The mean age of patients was 68 ± 8.4 years. A total of 38 (48.1%) of patients died during follow-up. There were 52 patients (65.8%) who receive hormonal therapy plus radiotherapy. The most common Gleason score was 8-10 for 46 (58.2%) patients. There was 27 patient (34.2%) with local stadium (T1-T2, N0, M0),

Table 1. Descriptive data of prostate cancer patients in 2009-2013.

No	Characteristics		Total
1	Survival	Yes	41 (51.9%)
		No	38 (48.1%)
2	Age	≥ 70 years	37 (45.9%)
		< 70 years	42 (57.1%)
3	Type of therapy	Hormonal	52 (65.8%)
		Hormonal + Radiotherapy	27 (34.2%)
4	Type of hormonal	Surgical	48 (60.8%)
		Medicamentosa	31 (39.2%)
5	Dose of radiation	≥ 70 Gy	17 (62.9%)
		< 70 Gy	10 (37.1%)
6	Gleason score	8-10	46 (58.2%)
		7	18 (22.7%)
		< 7	15 (18.9%)
7	PSA	< 10 ng/ml	8 (10.1%)
		10-20 ng/ml	10 (12.7%)
		> 20 ng/ml	61 (77.2%)
8	Stage	Local (T1-T2, N0, M0)	27 (34.2%)
		Locally advanced (T3-T4, N1 M0)	5 (6.3%)
		Metastase (M1)	47 (59.5%)
9	Age	68 ± 8.4 years old	
10	PSA X±SD	83 ± 66 ng/ml	

Table 2. Characteristics of patients undergoing hormonal and hormonal therapy plus radiotherapy.

No	Characteristics		Type of therapy	
			Hormonal	Hormonal and Radiotherapy
1	Stage	Local	20 (25.3%)	7 (8.8%)
		Locally advanced	3 (3.7%)	2 (2.5%)
		Metastase	29 (36.7%)	18 (22.7%)
2	Gleason score	8-10	32 (40.5%)	14 (17.7%)
		≤ 7	20 (25.3%)	13 (16.4%)
3	Age	≥ 70 years	29 (36.7%)	8 (10.1%)
		≤ 70 years	23 (29.1%)	19 (24%)

Table 3. The association of clinical variables with patient survival.

No	Variable		Survival		P	C
			No	Yes		
1	Type of therapy	Hormonal	24	28	0.631	0.054
		Hormonal + Radiotherapy	14	13		
2	Age	≥ 70 years	20	17	0.320	0.111
		≤ 70 years	18	24		
3	Gleason score	8-10	28	18	**0.007**	**0.289**
		≤ 7	10	23		
4	PSA	< 10	0	8	**0.022**	**0.382**
		10-20	2	8		
		> 20	36	25		
5	Stage	Local	6	21	**0.000**	**0.444**
		Locally advanced	0	5		
		Metastase	32	15		

Table 4. Five years survival rate based on type of therapy.

No	Variable		Hormonal alone	Hormonal plus Radiotherapy	Log Rank test
1	Overall Survival			48%	
2	Clinical stage	Local	70%	100%	P = 0.150
		Locally advanced	70%	100%	P = 0.135
		Metastase	32%	18%	P = 0.570
3	Gleason score	≤ 7	58%	61%	P = 0.226
		8-10	48%	10%	P = 0.063
4	PSA level	≤ 20 ng/ml	83%	100%	P = 0.335
		> 20 ng/ml	42%	20%	P = 0.506
5	Age	≥ 70 tahun	44%	0%	P = 0.647
		< 70 tahun	60%	32%	P = 0.530

Locally advanced (T3-T4, N1 M0) was 5 patients (6.3%), and metastasis was 47 patients (59.5 %). From this data, we found that the highest percentage is patient with metastasis stage so that the survival rate becomes lower.

Table 2 described the characteristics of patients undergoing hormonal therapy and hormonal plus radiotherapy. The distribution of PCa patients undergoing hormonal therapy as well as hormonal plus radiotherapy is divided based on stage, Gleason score, and age. It showed that most patients in metastatic stage receive both hormonal therapy and hormonal plus radiotherapy. A total of 29 (36.7%) patients received hormonal therapy, as many as 18 (22.7%) patients received hormonal plus radiotherapy. Patients with Gleason score 8-10 score divided into two groups. There were 32 patients (40.5%) receive hormonal therapy alone while 14 patient (17.7%) received hormonal and radiotherapy.

Based on the relationship between survival of patients with the type of therapy, age, Gleason score, and clinical stage, there was a significant correlation between Gleason score, PSA level and clinical stage with $p<0.05$. With the value of the contingency coefficient respectively 0.289, 0.382, and 0.444 (Table 3).

The Kaplan Meier curve (Figure 1-4) obtained a 5-year survival rate in PCa patients at Sardjito General Hospital is 48% (Table 4). The value is an overall survival without consider the patient's treatment. Then we performed survival comparison in patients who received hormonal therapy alone compared with hormonal plus radiotherapy. The comparison was performed by grouping patients based on patient's clinical stage, Gleason score, and age. Kaplan Meier curve based on

Table 5. Descriptive data of prostate cancer patients in 2009-2013.

No	Characteristics		Total
1	Survival	Yes	41 (51.9%)
		No	38 (48.1%)
2	Age	≥ 70 years	37 (45.9%)
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3	Type of therapy	Hormonal	52 (65.8%)
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		>20 ng/ml	61 (77.2%)
8	Stage	Local (T1-T2, N0, M0)	27 (34.2%)
		Locally advanced (T3-T4, N1 M0)	5 (6.3%)
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9	Age	68 ± 8.4 years old	
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Table 6. Characteristics of patients undergoing hormonal and hormonal therapy plus radiotherapy.

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		≤ 7	20 (25.3%)	13 (16.4%)
3	Age	≥ 70 years	29 (36.7%)	8 (10.1%)
		≤ 70 years	23 (29.1%)	19 (24%)

clinical stage local and locally advanced show that 5-year survival patients who receive combination hormonal and radiotherapy is higher than survival patient who receives hormonal therapy alone.

However, 5-year survival of patients with metastase is higher in the group who receive hormonal therapy alone. Kaplan Meier curve based on Gleason score show that the survival patients with Gleason score of 8-10 was lower compared with Gleason score ≤ 7. This condition can be seen from patients receiving either hormonal only or hormonal plus radiotherapy. In the PSA group ≤ 20 ng/ml, the 5-year survival of patients was higher in the group receiving hormonal plus radiotherapy, but these results were opposite to the PSA group >20 ng/ml. In the age group, patients with age ≥70 years, the 5-year survival rate of patients receiving hormonal therapy was better than those receiving hormonal plus radiotherapy. This finding also applied to the patient with age <70 years.

Table 7. The association of clinical variables with patient survival.

No	Variable		Survival		P	C
			No	Yes		
1	Type of therapy	Hormonal	24	28	0.631	0.054
		Hormonal + Radiotherapy	14	13		
2	Age	≥70 years	20	17	0.320	0.111
		≤70 years	18	24		
3	Gleason score	8-10	28	18	**0.007**	**0.289**
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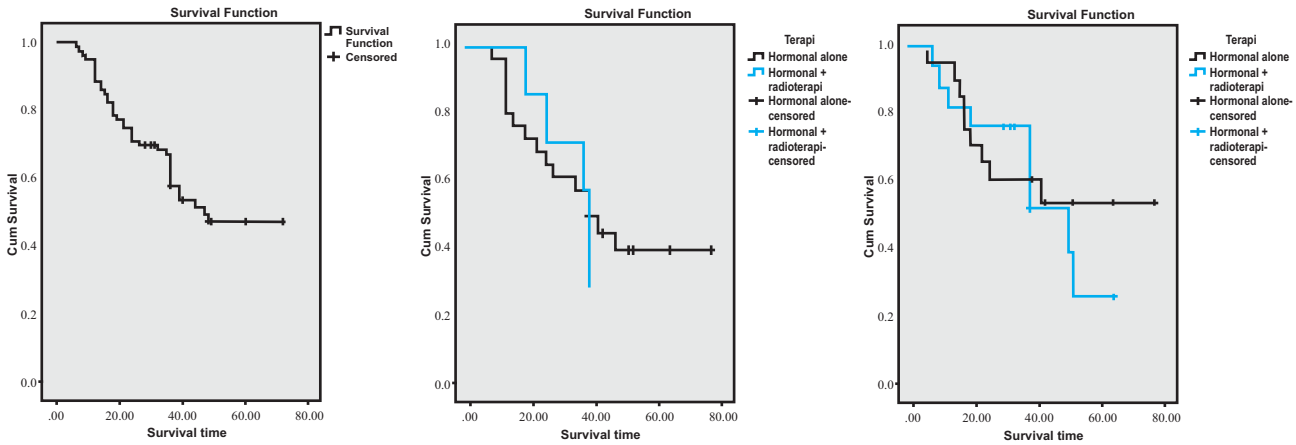
4	PSA	<10	0	8	**0.022**	**0.382**
		10-20	2	8		
		>20	36	25		
5	Stage	Local	6	21	**0.000**	**0.444**
		Locally advanced	0	5		
		Metastase	32	15		

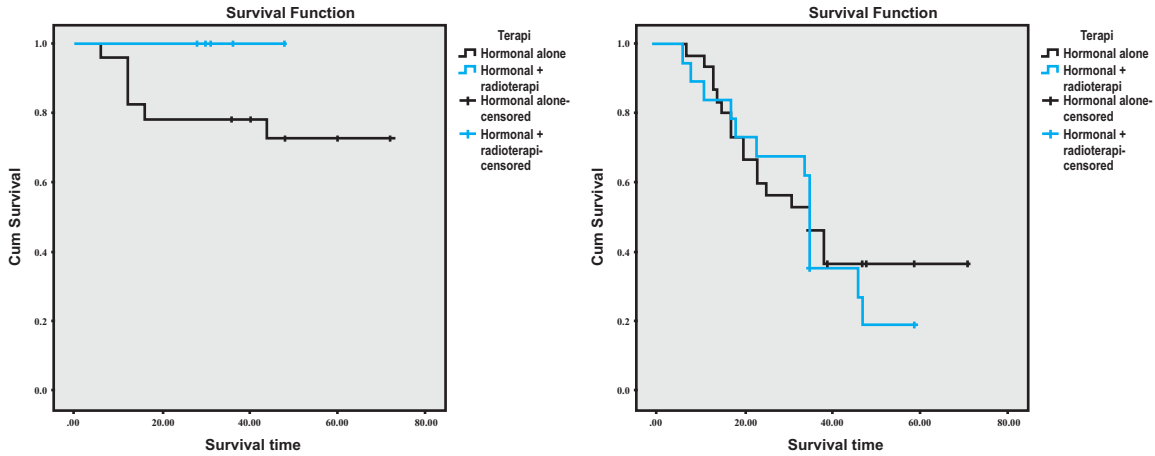


Overall survival prostate cancer patient

age > 70 years

age < 70 years

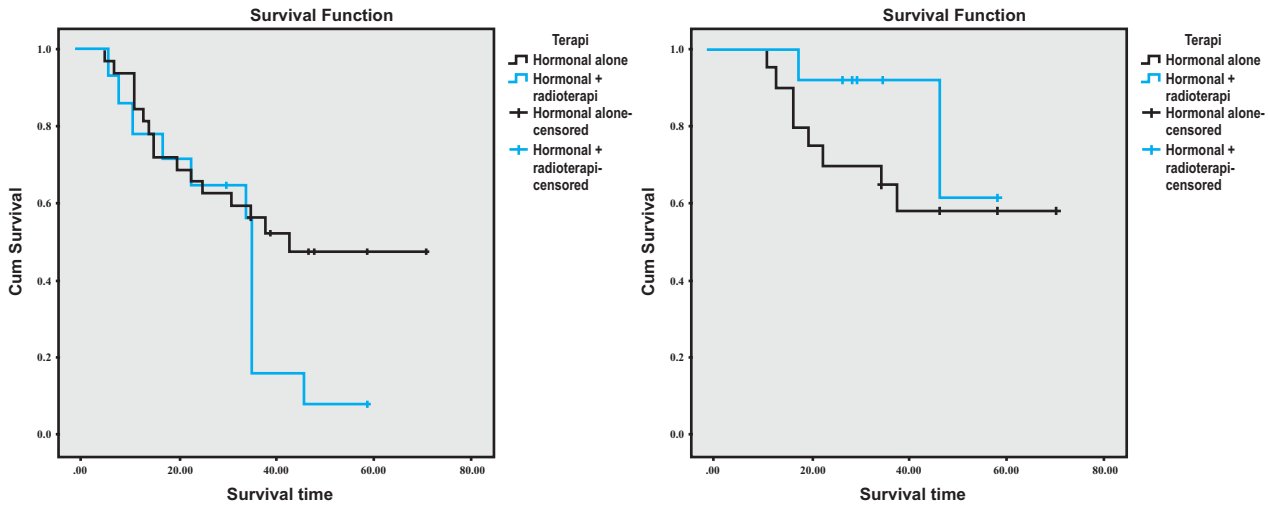
Figure 1. Kaplan Meier curve overall survival and influenced the aging factor.



Local and locally advanced stage

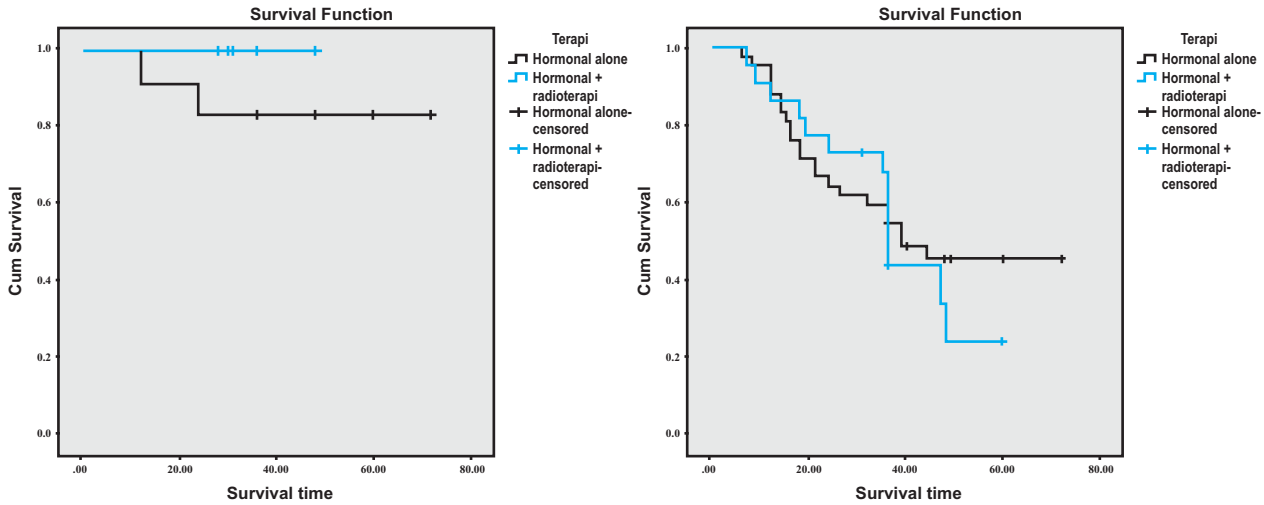
Metastatic stage

Figure 2. Kaplan Meier curve based on clinical stage.



Gleason score 8-10 Gleason score ≤ 7

Figure 3. Kaplan Meier curve based on Gleason score.



PSA ≤ 20 ng/ml PSA > 20 ng/ml

Figure 4. Kaplan Meier curve based on PSA level.

Table 8. Five years survival rate based on type of therapy.

No	Variable		Hormonal alone	Hormonal plus Radiotherapy	Log Rank test
1	Overall Survival			48%	
2	Clinical stage	Local	70%	100%	P = 0.150
		Locally advanced	70%	100%	P = 0.135
		Metastase	32%	18%	P = 0.570
3	Gleason score	≤7	58%	61%	P = 0.226
		8-10	48%	10%	P = 0.063
4	PSA level	≤20 ng/ml	83%	100%	P = 0.335
		>20 ng/ml	42%	20%	P = 0.506
5	Age	≥ 70 tahun	44%	0%	P = 0.647
		< 70 tahun	60%	32%	P = 0.530

DISCUSSION

In this study patient who underwent combination hormonal and radiotherapy as many as 27 (34.2%) patients. This result was still quite low, in line with national data showing radiotherapy modality in PCa in Indonesia performed as much as 6% of cases.[13] The most stages found in this study were metastatic stages 47 (59.5%) patients. It was also in line with national data showing the highest stage is metastatic stage 50.5%.[13]

Clinical variables correlated significantly with deaths in PCa patients were Gleason score, PSA level and clinical stage with $p < 0.05$ and contingency coefficients respectively 0.289, 0.382, and 0.444. In some studies, it was also mentioned that Gleason scores, PSA level and clinical stages are prognostic and predictive factors for the outcome of PCa patients.[3,14,15]

The overall 5 years survival rate of PCa patients in this study was 48%. In another study in Japan by Nakamura et al. Overall 5 years survival rate is 93%. A 5-year survival rate in this study was lower for several reasons. First, in this study, we could find a high proportion of patients with high risk PCa, with the percentage of patients with Gleason score >7, PSA level >20 and PCa who have metastasis more than 50%.[16] In Asia, advanced PCa is more common in developing countries such as Indonesia compared to developed countries such as Japan and South Korea.[3] Another factor that also contributes to the survival of PCa patients is the low survival rate of men in Indonesia. In addition, the low percentage of patients undergoing radiotherapy, and less optimal radiation doses administered to patients resulted in lower patient survival.[17]

In this study, 5 years survival rate of patients at locally advanced stage and better than in metastatic stage. Based on the type of therapy at various stages, the combination of hormonal radiotherapy given to local and locally advanced patients showed excellent results. The 5 years survival rate reached 100% vs 70% compared with patients who only got hormonal therapy alone. Radiotherapy is an effective therapy modality for locally advanced and locally advanced PCa in Indonesia. Radiotherapy combined with adjuvant hormonal therapy significantly improved patient survival.[17] The advantages of radiotherapy combined with hormonal therapy versus hormonal alone in locally advanced PCa patients were previously published with two randomized controlled trial studies by Widmark et al and Warde et al. Based on the study, 10 years cancer specific mortality in the hormonal therapy group itself was 23.9% compared with 11.9% in the combined group hormonal plus radiotherapy.[10,16] The combination of radiotherapy and hormonal therapy increased the 7 years overall survival by 74% compared with 66% in hormonal therapy itself.[18] Similar to those studies in the seventh year, there was an 8% overall survival benefit in the combination group of hormonal plus radiotherapy versus the hormonal therapy group itself.[11]

Patients who have metastatic stage of PCa have a poor outcome. In this study, the 5-year survival rate of PCa patients who had metastasis was 32% with hormonal therapy alone, and 18% in group who received combination hormonal and radiotherapy. The radiotherapy indication in patients with metastatic prostate cancer was palliative radiotherapy.[12] However, hormonal therapy itself showed better results. James in 2014 revealed that the median survival of PCa patients who had metastasis was 42 months. Androgen deprivation therapy (ADT) is a gold standard for metastatic PCa therapy.[7]

Based on previous research by Scosyrev et al., the 5 years cumulative incidence of death in PCa patients increased 3%-4% at age <75 years and increased to 30% at age ≥90 years.[19] Although there was an increased risk of death from other causes, age >75 years still contribute to 47% of deaths from PCa. Low survival in PCa patients aged >70 years as significantly associated with clinical staging and high Gleason scores, as well as more aggressive PCa properties.[20] The explanation of why PCa is more aggressive in advanced age is because of age-related changes in testosterone, and its natural course of undiagnosed disease.[21] The results of previous research were in line with this study that the survival rate of patients <70 years better than patients aged >70 years. But combination hormonal and radiotherapy is not better than hormonal therapy itself. This is because patients who receive combination therapy are predominantly PCa patients at high risk and have metastasis.

There are several treatment modality options for localized PCa: prostatectomy radicals, brachytherapy, external beam radiation therapy, hormonal and active monitoring. The choice of therapy was then adjusted in stadium, Gleason score, life expectancy, comorbid and patient expectations.[21] Radiotherapy is an alternative therapy in addition to curative surgery. Radiotherapy is a treatment option

for patients who resist surgery, a life expectancy of less than 10 years, and high-risk Pca.[22,12] According to this result, at local and locally advanced stage the 5-year survival rate patient who got radiotherapy and hormonal combination therapy were good, achieved 100%. Similarly, in patients who had PSA level ≤ 20 ng/ml the 5-year survival rate achieved 100%. These results suggested that combination therapy of radiotherapy and hormonal therapy might be considered in patients who rejected radical prostatectomy procedure, with good survival rates and done in the early stage.

This study had several limitations. First, in our center radical prostatectomy procedure was rare. Some patients were eligible and indications for radical prostatectomy but patients refused. Second, this study had fewer samples compared with the others. Owing to small numbers of patients in our data sets, we were unable to assess for other clinically relevant endpoints. However, this study showed that without radical prostatectomy the outcome and patient survival in the local, locally advance stage and PSA level ≤ 20 ng/ml group was good enough. This was the strength of our study.

CONCLUSION

This study shows that 5 year survival rate of patients with PCa at Sarjito General Hospital was 48%. Gleason's score, PSA level and clinical stage of PCa were significantly associated with the survival of PCa patients. Combination of hormonal and radiotherapy was more improving patient survival compared to hormonal therapy in patient with locally advanced clinical stage, PSA level ≤ 20 ng/ml and Gleason score ≤7.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ref: KE/FK/429/EC/2016.

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