

A RETROSPECTIVE STUDY ON SURVIVAL ANALYSIS AND ITS PROGNOSTIC FACTORS OF PROSTATE CANCER PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

DR AHMAD FIRDAUS BIN AHMAD LUTFI

Dissertation Submitted in Partial Fulfillment of The Requirements for The

Degree of Master of Surgery

UNIVERSITI SAINS MALAYSIA

2020

ACKNOWLEDGEMENTS

In the first place, I would like to thank my supervisor Associate Professor Dr. Andee Dzulkarnaen Bin Zakaria together with my co supervisor Dr. Mohamed Ashraf Bin Mohamed Daud and Dr. Nik Mohd Hafizi Bin Nik Anuar for their support and encouraging contribution at the very outset of this study. Without their support and motivation this study may not have been done.

I also sincerely thank the department head and all the lecturers of the Surgery Department of Hospital Universiti Sains Malaysia, who participated in this study directly and indirectly.

I would also like to express my gratitude, for their support and contribution in data collection in this report, to my fellow colleagues and colleagues.

Last but not least, I want to thank my friends and family who helped me during the course and gave me the motivation I needed before this thesis was over.

TABLE OF CONTENTS

Contents
ACKNOWLEDGEMENTSII
TABLE OF CONTENTS III
LIST OF ABBREVIATIONS
ABSTRAK
ABSTRACT VIII
CHAPTER 1: INTRODUCTION 1
1.0 Introduction
1.1 Literature Review
1.2 Justification of Study
1.3 Research Question
1.4 Research Objectives
1.5 Research Hypothesis
1.6 Conceptual Framework7
CHAPTER 2: STUDY PROTOCOL
2.0 Research Methodology
2.1 Research Design
2.2 Sampling Design

2.2.1	Study Area	9
2.2.2	Study Population	9
2.2.3	Study Duration	9
2.2.4 S	Subject Criteria	9
2.2.5 S	Sampling Technique	9
2.2.6 S	Sample Size Calculation	. 10
2.3. Data	Collection	. 11
2.4 Opera	ational Definition	. 11
2.5 Statis	stical Data Analysis	. 12
2.6 Ethica	al Consideration	13
2.6.1 S	Subject vulnerability	13
2.6.2 E	Declaration of absence of conflict of interest	.13
2.6.3 P	Privacy and confidentiality	.13
2.6.4 C	Community sensitivities and benefits	.13
2.6.5 H	Honorarium and incentives	.13
2.7 Study	Flow Chart	. 14
2.8 Gantt	t Chart	15
2.9 Refer	rences	16
3.0 Appe	ndix	. 18

CHAPTER 3.0 MANUSCRIPT
3.1 Title Page
3.2 Abstract
3.3 Introduction
3.4 Methodology
3.5 Results
3.6 Discussion
3.7 Conclusion 39
3.8 Acknowledgment 40
3.9 References
3.10 Figures and Tables
3.11 Journal Format
CHAPTER 4: APPENDICES

LIST OF ABBREVIATIONS

ED	Emergency Department
FAST	Focused Assessment with Sonography in Trauma
СТ	Computed Tomography
USG	Ultrasonography
HUSM	Hospital Universiti Sains Malaysia

ABSTRAK

Latar belakang: Kanser prostat adalah penyebab utama morbiditi dan kematian lelaki di peringkat global dan di Malaysia. Oleh itu, penyelidikan ini akan menilai faktor kelangsungan hidup selama lima tahun dan faktor prognostik di kalangan pesakit kanser prostat di HUSM, Kelantan.

Metodologi: Kami mengkaji 150 rekod perubatan pesakit yang didiagnosis dengan kanser prostat, dari tahun 2009 hingga 2014. Waktu bertahan dianalisis untuk demografi pesakit, skor Gleason, klasifikasi ASA, skor ECOG, tahap PSA, sejarah keluarga, tahap kanser, parameter hematologi yang berkaitan dengan kanser, dan kaedah rawatan. Model kelangsungan hidup Kaplan-Meier dan model bahaya berkadar Cox telah digunakan dalam analisis ini.

Hasil: Kadar kelangsungan hidup lima tahun kanser prostat adalah 84.5%. Keseluruhan keluk survival Kaplan-Meier menunjukkan masa bertahan rata-rata yang baik. Analisis regresi univariate menunjukkan faktor prognostik yang signifikan termasuk umur (HR = 1.06, 95% CI: 1.00, 1.11, p = 0.034), klasifikasi ASA 3 (HR = 3.72, 95% CI: 1.38, 10.00, p = 0.009), skor ECOG 2 (HR = 17.98, 95% CI: 3.98, 81.1, p <0.001), ECOG 3 (HR = 33.94, 95% CI: 7.41, 150.0, p <0.001), anemia (HR = 9.07, 95% CI: 3.33, 24.6, p <0.001), LDH Tinggi (HR = 5.37, 95% CI: 1.80, 15.90, p = 0.003), ALP Tinggi (HR = 8.94, 95% CI: 3.31, 24.1, p <0.001), Pementasan nodular (HR = 5.87, 95% CI: 1.74, 19.85, p = 0.004), Metastasis (HR = 3.48, 95% CI: 1.28, 9.44, p = 0.014), Terapi Kekurangan Androgen (HR = 0.29, 95% CI: 0.08, 0,99, p = 0,05) dan Kemoterapi (HR = 4,57, 95% CI: 1,79, 11,6, p = 0,001).

Kesimpulan: Kadar kelangsungan hidup pesakit HUSM selama lima tahun yang dirawat untuk kanser prostat adalah baik. Namun, kadar survival menurun dengan ketara disebabkan oleh faktor prognostik seperti usia, klasifikasi ASA, skor ECOG, beberapa parameter hematologi, tahap kanser dan kemoterapi. Akan tetapi, pesakit yang menerima rawatan ADT mempunyai kadar kelangsungan hidup yang lebih baik, yang menunjukkan peranan utama awal terapi dalam meningkatkan kelangsungan hidup pesakit.

Kata kunci: Kanser Prostat, Kelangsungan Hidup, Faktor Prognostik

ABSTRACT

Background: Prostate cancer is a leading cause of male morbidity and mortality globally and in Malaysia. This study assessed the five-year survival and prognostic factors among prostate cancer patients in Hospital USM, Kelantan.

Methodology: We reviewed 150 medical records of patients diagnosed with prostate cancer, from 2009 to 2014. Survival time was analyzed in relation of patient demographics, Gleason score, ASA classification, ECOG scores, PSA level, family history, cancer staging, cancer-related hematological parameters, and treatment method. Kaplan-Meier survival curves and Cox proportional hazards models are used for the analysis.

Results: The prostate cancer five-year survival rate was 84.5%. Overall Kaplan-Meier survival curve showed good median survival times. Univariate regression analysis revealed significant prognostic factors including age (HR=1.06, 95% CI:1.00, 1.11, p=0.034), ASA 3 classification (HR=3.72, 95% CI:1.38, 10.00, p=0.009), ECOG score 2 (HR=17.98, 95% CI:3.98, 81.1, p<0.001), ECOG 3 (HR=33.94, 95% CI:7.41, 150.0, p<0.001), anemia (HR=9.07, 95% CI:3.33, 24.6, p<0.001), High LDH (HR=5.37, 95% CI:1.80, 15.90, p=0.003), High ALP (HR=8.94, 95% CI:3.31, 24.1, p<0.001), Nodular staging (HR=5.87, 95% CI:1.74, 19.85, p=0.004), Metastasis (HR=3.48, 95% CI:1.28, 9.44, p=0.014), Androgen Deprivation Therapy (HR= 0.29, 95% CI:0.08, 0.99, p=0.05) and Chemotherapy (HR=4.57, 95% CI:1.79, 11.6, p=0.001).

Conclusion: The five-year survival rate of HUSM patients treated for prostate cancer was 84.5%. The survival rate reduces significantly due to prognostic factors like age, ASA classification, ECOG score, some hematological parameters, cancer staging and chemotherapy. However, patients received the ADT have a better survival rate, which suggests the main role of prompt initiation of the therapy in improving patient survival.

Keywords: Prostate Cancer, Survival, Prognostic Factors

CHAPTER 1: INTRODUCTION

1.0 Introduction

Cancer is one of the world's leading causes of premature mortality and the prevalence is rising. About 14.1 million of new cancer cases with 8.2 million death due to cancer reported in 2012 (1) and the prevalence in 2015 was measured at 17.5 million and accounted for 8.7 million deaths worldwide (2). In term of new cases and death in the world due to cancer, lung cancer is the highest followed by breast cancer, colorectal, prostate, stomach and liver cancer. In 2012, it is reported that about 55% of global incidence burden is due to all the six cancers which are lung, breast, colorectal, prostate, stomach and liver (1). However, in 2016, the prostate cancer became the most common and fifth leading cause of male cancer deaths in the world, with more than 1.44 million patients, 381,000 deaths and an estimated 6.1 million disability-adjusted life years (DALYs) (2). While cancer was historically identified as a rich-born disease, it became apparent that in low- and medium-income countries it is also a public health issue. This may be attributed to changes in lifestyle, rapid urbanization, cultural transformation and increased life expectancy in the countries. Moreover, the burden of prostate cancer in low-income countries is underestimated, due to inadequate testing and screening procedures, minimal treatment choices, insufficient study and training and limited population-based cancer registration (1, 3).

1.1 Literature Review

Epidemiology of Prostate Cancer

Prostate cancer is the most prevalent cause of male malignancy in the Western world and the second-largest cause of cancer death. Western men have a greater risk of developing prostate cancer than men in other parts of the world. The epidemiological environment has however, shown an annual rise in incidence patterns in countries in Asia that previously recorded the world's lowest prostate cancer rates (4). More patients with prostate cancer are currently being diagnosed in Asia in early stages than they were 10 years ago. In the year 2000, South-East Asia reported a total of 11,152 incidents (5). Prostate cancer is one of the most common cancers of males in Malaysia including colorectal, pulmonary, nasopharyngeal and lymphoma (6, 7). Prostate cancer was listed as the third most common cancer in men with an age standardization rate of 6.6 per 100,000 population. Chinese men (ASR 9.0/100,000), followed by Indians (ASR 6.1/100,000) and Malays (ASR 5.3/100,000) (7) were the most frequently recorded incidence. The growing incidence of prostate cancer globally, including Malaysia, may be due to increased Prostate Specific Antigen (PSA) measures and demographic factors, particularly the rise of the elderly population (2).

Survival Rate of Prostate Cancer

The five-year survival rate of prostate cancer is better than in other cancers. Asia has demonstrated a substantial difference in outcomes for men with prostate cancer in the Asia-Pacific region. In New Zealand, Australia, Japan, Singapore and South Korea, the five-year relative survival figures were 85% and higher. This compares with the approximate five-year survival rates in areas of China and Thailand between 30 and 40 percent (8).

The stage or severity and spread of the disease upon diagnosis is one of the major prognostic factors in prostate cancer, with survival rates much higher for those diagnosed with a localized disease relative to advanced cancer. For example, in Japan, 5-year relative survival ranged from almost 100 percent of locally occurring disease to 87 percent of regional disease (cancer that developed from surrounding lymph nodes or organs and tissues outside the initial tumor) and 40 percent of cancer that had spread to distant lymph nodes and organs (9). This contrasts 83%, 43% and 23% of the comparable 5-year survival rate estimated in Singapore for localized, regional and distant cancer of the prostate (10). Meanwhile in Malaysia, the five-year overall survival rate for prostate cancer patients is 73%. Malaysia also do better when compared to the survival rate according to the localized, regional and distant cancer with 97.3%, 92.1% and 43.2% respectively. This is comparable to other developed Asia-Pacific countries (6).

Prognostic Factors of Prostate Cancer.

Prognostic factors in organ confined prostate cancer will reflect survival after surgical radical prostatectomy. Determining prognostic factors is important in learning about the history of the disease and factors that influence the outcome, and in selecting the best treatment methods for the patient. Patients' social and clinical characteristics would have important effect on prognosis. Social characteristics including kind of race, marital status, living in rural or urban places, education level, family income, and percentage of poor people in city. Some research reported that married individuals would enjoy lower mortality and longer overall survival compared to those who were single, separated, widowed, or divorced persons (11, 12). Men living in urban areas were likely to receive definitive treatment for their early-stage prostate cancer than those who living in rural areas (13). Education level and neighborhood socio-economic status were independently associated with risk of advanced prostate cancer (14). The effect of age as a

prognostic factor has been studied extensively and the risk for developing prostate cancer increases with age, beginning to be significant at the age of 50 (4, 15). Men with a family history of prostate cancer have a significantly greater risk of developing prostate cancer than those with no such family history (16). The pooled relative risk (RR) in first degree relatives was 2.5. It was highest in relatives of cases diagnosed before 60 years old and the RR declined with age. The risk increases to 3.5-fold with two affected relatives. Relative risk to sons of cases appeared to be lower than in brothers (17).

Meanwhile, patients' clinical characteristics that proved to be a significant prognostic factors are prostate-specific antigen (PSA) level, Gleason scores, histological grade, clinical stage, TNM stage, baseline hemoglobin, lactate dehydrogenase, albumin, alkaline phosphatase, treatment therapy and metastasis status (18, 19). Prostate cancer patient is usually presented as an asymptomatic patient in the early stages and, thus, may not be diagnosed until later stages. In Malaysia, about 43% of cases of prostate cancers are diagnosed in stage 4, and metastatic prostate cancer has not a favorable prognosis. While 16% was diagnose as first stage, 24% stage two and 19% are stage 3 (7). Late diagnosis, localized tumors, metastatic and active treatments (radical prostatectomy and radiotherapy) were significant predictors of good survival (18-20).

1.2 Justification of Study

Contrary to high-income nations, where patients enrolling in health screening and early treatment contributes to greater chance of survival, patient health care is predicted to be late in low-middleincome countries like Malaysia, with very lower life expectancy. Treatment targets include minimizing further the risk of recurrence of cancer, reducing residual physical and psychological side effects of medication and improving longevity. To measure the efficacy and quality of the patients' treatment it is important to predict the survival rate. While several studies have identified the prevalence of the condition, the survival rate and prognostic determinants in patients with prostate cancer in Malaysia are scarce. Survival tests provide significant clinical importance for patients and clinicians in recognizing how the prognosis improves over time and in assessing better care choices. It also makes it possible for practitioners in public health to consider the quality and effectiveness of services and procedures applied to increase survival and quality of life (21). In comparison, prostate cancer mortality has disproportionate consequences on low- and middle-income countries with 165,000 mortality compared to 142,000 deaths in high-income countries (2). Early diagnosis and progressive cancer therapy would have a positive effect on the chance of survival.

1.3 Research Question

- 1. What is the five years survival rates of prostate cancer patients in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014?
- 2. What are the prognostic factors affecting survival rates of prostate cancer patients in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014?

1.4 Research Objectives

1.4.1 General Objective

To determine the survival rates and prognostic factors of prostate cancer patients in Hospital Universiti Sains Malaysia between 2009 until 2014.

1.4.2 Specific objective

- To determine the five years survival rate of prostate cancer patients in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014.
- 4. To identify the prognostic factors affecting survival rates of prostate cancer patients in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014.

1.5 Research Hypothesis

- 1. There is a significant five years survival rate of prostate cancer patients in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014.
- There are significant prognostic factors in determining survival of prostate cancer patients in in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan in between 2009 until 2014.

1.6 Conceptual Framework



CHAPTER 2: STUDY PROTOCOL

2.0 Research Methodology

The main objective of this research is to determine the survival rate and prognostic factors of prostate cancer patients in Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan in between 2009 until 2014. Several approaches and mechanisms have been implemented in the planning of this analysis to produce meaningful outcomes. This chapter outlines the approaches used to accomplish the goals of this report. Research methodology refers to research definition, data collection processes, sampling method and analytic models for data processing. In order to meet the study goals, these approach components must be correctly chosen to reflect a consistent outcome.

2.1 Research Design

Research design can be described as a strategy for the collection and use of data such that the desired knowledge is appropriately gathered, or a theory can be correctly tested.

This study will be a retrospective cohort study that involves all patients who attend HUSM and meet all criteria of inclusion and exclusion. It consists of data from a target population to be obtained at a given time.

2.2 Sampling Design

2.2.1 Study Area

Hospital Universiti Sains Malaysia (HUSM), Kubang kerian, Kelantan.

2.2.2 Study Population

The *reference population* for this study is prostate cancer patients in Kelantan. The *source population* for this study is the prostate cancer patients attended HUSM in between 2009 until 2014 who fulfil the inclusion and exclusion criteria.

2.2.3 Study Duration

The study duration will be between January 2020 until Jun 2020.

2.2.4 Subject Criteria

2.2.4.1 Inclusion criteria:

- i. Patients with traceable records.
- ii. Patients with follow up of at least 5 years with HUSM.
- iii. Patient diagnosed with prostate cancer with histopathological confirmation.

2.2.4.2 Exclusion criteria:

- i. Patient with concurrent pathology
- ii. Incomplete data record

2.2.5 Sampling Technique

This study will apply a non-probability sampling technique.

2.2.6 Sample Size Calculation

The sample size determination for this study was obtained using Power and Sample Size Calculation (PS) Software. The significant level was set at (α) 0.05 and the power study (1- β) was 80%. The sample size estimation will be based on survival analysis.

The ratio of control to cases (M) and median survival time on control (M1) was obtained from literatures.

The accrual time (A) for this study will be five years (60 months) and the accrual time for follow up till end of recruitment will be about 60 months (F).

The detectable hazard ratio of the control relative to experimental group (R) is determined by researcher and expert opinion.

Additional 20% sample size (n) required for considering estimated 20% missing data or loss to follow up.

Summarize information for sample size calculation using Power and Sample Size (PS) software;

(α) : Significant level = 0.05

 $(1 - \beta)$: Power = 0.8

(R) : Hazard ratio (relative risk) of the control treatment relative to experimental treatment was determine by clinical expert = 2

(m1) : Medium retention time on control treatment was obtained from literature = 45.6(22).

(m) : Ratio of control to experimental patients = 0.6(23)

(A) : The accrual time during which subject were recruited = 60 months

(F) : Additional follow-up after end of recruitment = 60 months

(n) : Sample size determination by PS Software (Considering estimated 20% for missing data/loss to follow up (additional 20% was added))

Based on result of sample size calculation from Power and Sample Size Calculation (PS) Software, the required sample size will be 150 cases after adding 20% possible missing data or loss to follow up.

2.3. Data Collection

The cases of prostate cancer will be collected from the HUSM's Record Unit. These records were then checked by the lead researcher and the details required to be collected for the compilation of data using a proforma including variables such as demographic patients, diagnostic age, ASA classification, ECOG ratings, prostate family history, PSA base level and after 5 years, stage on diagnosis and 5 years on, treatment options given, histopathological documentation of specimens taken, serum blood, compliance and mortality.

2.4 Operational Definition

2.4.1 Prostate Cancer Patient

A patient clinically diagnosed through a Digital Rectal test.

2.4.2 Gleason Score.

A scoring method uses to assess the pathologic classification of the tumour, which represents the sum of main and secondary development patterns and is obtained by tumor biopsy.

2.4.3 Cancer Metastatic

Existence of cancer metastases was confirmed by bone scan and ultrasound.

2.4.4 Duration of Survival

Duration of survival was described as time between diagnosis and death, the last visit reported or until the end of follow up at December 2014.

2.4.5 Censored cases

Censored cases were described as patients that were alive, untraceable and who died from causes other than prostate cancer.

2.4.6 Events

Events were patients who at the end of the follow-up phase died of prostate cancer.

2.4.7 Cause of death

The cause of death due to prostate cancer was established by the medical report of the patient.

2.5 Statistical Data Analysis

Data will be analyzed using R Language (version 4.0.3) and RStudio (version 1.3.1093). Continuous variables will be presented in the form of mean (2), median, and range, while categorical variables will be presented in proportions. Kaplan-Meier (K-M) survival curves were designed to approximate median survival times. The Univariate Cox proportional hazard model will be used to classify possible prognostic factors. A p-value two-tailed under 0.05 was statistically significant.

2.6 Ethical Consideration

2.6.1 Subject vulnerability

No subject vulnerability will be involved as this study will be using a secondary data collected from record unit's HUSM.

2.6.2 Declaration of absence of conflict of interest

There is no conflict of interest.

2.6.3 Privacy and confidentiality

All forms are anonymous and will be encrypted into Microsoft Excel. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually.

2.6.4 Community sensitivities and benefits

No community sensitive will be involved in this study. The study will benefits the community in empowering management of prostate cancer patients and enhancing clinicians and community understanding of the disease.

2.6.5 Honorarium and incentives

There will be no honorarium or incentives will be given to the participants.

2.7 Study Flow Chart



2.8 Gantt Chart

Research activity	20	19						202	0					
	Ν	D	J	F	Μ	Α	М	J	J	Α	S	0	Ν	D
Dissertation topic discussion at department														
and ethics approval						F								
Subjects recruitment and data collection														
Data analysis and interpretation														
Presentation and submission reports											_			
Report writing														
Submission of dissertation reports														

2.9 References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5):E359-86.

2. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA oncology. 2017;3(4):524-48.

3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.

4. Ito K. Prostate cancer in Asian men. Nature Reviews Urology. 2014;11(4):197-212.

5. Pu YS, Chiang HS, Lin CC, Huang CY, Huang KH, Chen J. Changing trends of prostate cancer in Asia. The Aging Male. 2004;7(2):120-32.

6. MOH. Malaysian Study on Cancer Survival (MySCan). Putrajaya: National Cancer Institute, Ministry of Health Malaysia; 2018.

7. A.A. Manan, N.S.T. Ibrahim, N.H. Abdullah. Malaysian National Cancer Registry Report 2007-2011. Putrajaya: National Cancer Institue, Ministry of Health Malaysia; 2016.

8. Baade PD, Youlden DR, Cramb SM, Dunn J, Gardiner RA. Epidemiology of prostate cancer in the Asia-Pacific region. Prostate International. 2013;1(2):47-58.

9. Center for Cancer Control and Information Services. Cancer Statistics in Japan Tokyo: Center for Cancer Control and Information Services; 2010 [Available from: http://ganjoho.jp/pro/statistics/en/table_download.html.

10. Wong C, Chow K, Lim G, Bhalla V, Lee H, Chia K. Cancer survival in Singapore, 1968-2002. Singapore Cancer Registry. 2008.

11. Liu Y, Xia Q, Xia J, Zhu H, Jiang H, Chen X, et al. The impact of marriage on the overall survival of prostate cancer patients: A Surveillance, Epidemiology, and End Results (SEER) analysis. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2019;13(5):E135-e9.

12. Abdollah F, Sun M, Thuret R, Abdo A, Morgan M, Jeldres C, et al. The effect of marital status on stage and survival of prostate cancer patients treated with radical prostatectomy: a population-based study. Cancer causes & control : CCC. 2011;22(8):1085-95.

13. Baldwin LM, Andrilla CH, Porter MP, Rosenblatt RA, Patel S, Doescher MP. Treatment of early-stage prostate cancer among rural and urban patients. Cancer. 2013;119(16):3067-75.

14. DeRouen MC, Schupp CW, Yang J, Koo J, Hertz A, Shariff-Marco S, et al. Impact of individual and neighborhood factors on socioeconomic disparities in localized and advanced prostate cancer risk. Cancer causes & control : CCC. 2018;29(10):951-66.

15. Namiki M, Akaza H, Lee SE, Song J-M, Umbas R, Zhou L, et al. Prostate Cancer Working Group Report. Japanese Journal of Clinical Oncology. 2010;40(suppl_1):i70-i5.

16. Cotter MP, Gern RW, Ho GY, Chang RY, Burk RD. Role of family history and ethnicity on the mode and age of prostate cancer presentation. The Prostate. 2002;50(4):216-21.

17. Saidi H, Karuri D, Nyaim E. Correlation of clinical data, anatomical site and disease stage in colorectal cancer. East African medical journal. 2008;85(6):259-62.

18. Liu D, Kuai Y, Zhu R, Zhou C, Tao Y, Han W, et al. Prognosis of prostate cancer and bone metastasis pattern of patients: a SEER-based study and a local hospital based study from China. Scientific Reports. 2020;10(1):9104.

19. Cui P-F, Cong X-F, Gao F, Yin J-X, Niu Z-R, Zhao S-C, et al. Prognostic factors for overall survival in prostate cancer patients with different site-specific visceral metastases: A study of 1358 patients. World J Clin Cases. 2020;8(1):54-67.

20. Yahaya JJ, Okecha T, Odida M, Wabinga H. Prognostic Factors for Overall Survival of Patients with Prostate Cancer in Kyadondo County, Uganda. Prostate Cancer. 2020;2020:8517130.

21. Beksisa J, Getinet T, Tanie S, Diribi J, Hassen HY. Survival and prognostic determinants of prostate cancer patients in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A retrospective cohort study. PLoS One. 2020;15(1):e0229854-e.

22. Law WL, Choi HK, Lee YM, Ho JW. The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer. Annals of surgical oncology. 2007;14(9):2559-66.

23. Ghazali AK, Musa KI, Naing NN, Mahmood Z. Prognostic factors in patients with colorectal cancer at Hospital Universiti Sains Malaysia. Asian Journal of Surgery. 2010;33(1):127-33.

3.0 Appendix

Proforma (Data Collection Form)

Number :

Ethnics : Malay / Chinese / Indian / others :

Age at diagnosis :

ASA classification :

1	Normal healthy fit person
2	Patient with mild systemic disease
3	Patient with severe systemic disease
4	Patient with severe systemic disease that is constant threat to life
5	Moribund patient

ECOG score :

0	Fully active					
1	Symptomatic but ambulating. Restricted in physical strenuous activity					
2	In bed <50%. Ambulating and capable of all self care					
3	In bed >50%. Capable but only limited self care					
4	100% bedridden					

Family history of prostate cancer :

Yes	First degree
	Second degree
	Unknown
No	

PSA level :

Baseline : elevated (>4.0ng/ml) / not elevated (<4.0ng/ml) 5 years : elevated (>4.0ng/ml) / not elevated (<4.0ng/ml)

Hemoglobin Level

Baseline: normal (>11.0g/dL) / anemia (<11.0g/dL) 5 years : normal (>11.0g/dL) / anemia (<11.0g/dL)

LDH Level

Baseline: (<200 U/L) / (>200 U/L) 5 years : (<200 U/L) / (>200 U/L)

ALP Level

Baseline : (<140 U/L) / (>120U/L) 5 years : (<140 U/L) / (>120U/L)

TNM / staging :			
Upon diagnosis	T :	N :	M :
5 years after diagnosis	T :	N :	M :

Gleason Score: (less than 6) / (more than 6)

Differentiation :

Well
Moderate
Poor
Not specified

Modalities of Treatment:

Radical Prostatectomy/ Radiotherapy / Watchful Waiting / Medical Castration / Surgical Castration

Type of Medical Castration

Anti Androgen / Androgen deprivation therapy

Follow up at least for 2 years : Yes / No

If yes, compliance to treatment regime : Yes / No

Mortality (within 5 years)

Yes	Disease related
	Not disease related
No	
Unknown	

If yes : (month/year) : _____

Period since diagnosis(months) : _____



29th November 2020

Dr. Ahmad Firdaus Ahmad Lutfi Department of Surgery School of Medical Sciences Universiti Sains Malaysia 16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/20090495

Protocol Title : Retrospective Study on Survival Analysis and Its Prognostic Factors of Prostate

Cancer Patients in Hospital USM.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code USM/JEPeM/20090495, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from 29th November 2020 until 28th November 2021.

Study Site: Hospital Universiti Sains Malaysia.

The following researchers are also involved in this study:

- 1. Assoc. Prof. Dr. Andee Dzulkarnaen Zakaria
- 2. Dr. Mohamed Ashraf Mohamed Daud
- 3. Dr. Nik Mohd Nurhafizi Nik Anuar

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the above mentioned document, the following technical documents were included in the review on which this approval was based:

1. Data Collection Form

While the study is in progress, we request you to submit to us the following documents:

- 1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of JEPeM-USM FORM 3(B) 2019: Continuing Review **Application Form.**
- 2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.
- 3. Revisions in the informed consent form using the JEPeM-USM FORM 3(A) 2019: Study **Protocol Amendment Submission Form.**
- 4. Reports of adverse events including from other study sites (national, international) using the JEPeM-USM FORM 3(G) 2019: Adverse Events Report.
- 5. Notice of early termination of the study and reasons for such using JEPeM-USM FORM 3(E) 2019.
- 6. Any event which may have ethical significance.



16150 Kubang Kerian, Kelantan. Malaysia. Tel. : +609 - 767 3000/2354/2362

www.usm.mv

Universiti Sains Malaysia

Fax. : + 609 - 767 2351

Email: jepem@usm.my Laman Web : www.jepem.kk.usm.mv

Kampus Kesihatan

Human Research Ethics Committee USM (HREC)

- 7. Any information which is needed by the JEPeM-USM to do ongoing review.
- 8. Notice of time of completion of the study using JEPeM-USM FORM 3(C) 2019: Final Report Form.

Please note that forms may be downloaded from the JEPeM-USM website: www.jepem.kk.usm.my

JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

Sincerely,

A M

PROF. DR. HANS AMIN VAN ROSTENBERGHE Chairperson Jawatankuasa Etika Penyelidikan (Manusia) JEPeM Universiti Sains Malaysia

<Approval><Dr. Ahmad Firdaus><USM/JEPeM/20090495

Page 2 of 2

CHAPTER 3.0 MANUSCRIPT

3.1 Title Page

A RETROSPECTIVE STUDY ON SURVIVAL ANALYSIS AND ITS PROGNOSTIC FACTORS OF PROSTATE CANCER PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

Running Title

Survival Analysis and Prognostic Factor of Prostate Cancer Patients in HUSM

Authors & Affiliation

- Dr Ahmad Firdaus Bin Ahmad Lutfi Department of Surgery, School of Medical Sciences, Hospital Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan.
- Associate Professor Dr Andee Dzulkarnaen Bin Zakaria
 Department of Surgery, School of Medical Sciences, Hospital Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan.
- Dr. Mohamed Ashraf bin Mohamed Daud Department of Surgery, School of Medical Sciences, Hospital Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan.
- Dr Nik Mohd Nurhafizi Bin Nik Anuar
 Department of Surgery, School of Medical Sciences, Hospital Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan.

Corresponding Author

1. Associate Professor Dr Andee Dzulkarnaen Bin Zakaria

Department of Surgery,

School of Medical Sciences, Hospital Universiti Sains Malaysia,

16150 Kota Bharu, Kelantan.

Email : andee@usm.my

Tel : 09-7673000 ext: 6774, 6776