RESEARCH ARTICLE

Survival Analysis of Lung Cancer patients in Brunei Darussalam

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Abstract

   Background: Cancer has been the most common cause of deaths in Brunei Darussalam including lung cancer as one of the top killers. This study presents the survival analysis of primary lung cancer patients in Brunei Darussalam. **Methods:** This is a retrospective cohort study of a 15-year period (2002-2016) involving 797 primary lung cancer cases. De-identified data extracted from Brunei Darussalam Cancer Registry was analyzed using Kaplan-Meier method and log-rank test. Bonferroni corrections were performed. **Results:** 6 months, 1-year, 3-year, 5-year survival rates of lung cancer patients were 62.2%, 51.0%, 38.0% and 34.7% respectively. The median survival time was 12.4 months (95% Cl: 9.2, 15.7). Patients diagnosed 2002-2006 had significant longer survival than patients diagnosed 2007-2011 (p=0.039) and those diagnosed 2011-2016 (p<0.001). Survival time of patients diagnosed 2007-2011 was significantly longer than patients diagnosed 2012-2016 (p=0.049). Patients with localised disease had significantly longer survival time than patients with regional involvement (p<0.001) and distal site involvement (p<0.001). Patients with distal disease had significantly poorer survival rate than patients with regional involvement (p<0.001). Patients aged 50 or above had significantly shorter survival time than patients diagnosed at age 40-49 (p=0.003). There was no significant difference between survival time of other demographic characteristics. **Conclusions:** The median survival time for lung cancer patients in this study was 12.4 months. Early diagnosis, early stage of cancer, and younger age were associated with longer survival time among lung cancer patients in Brunei Darussalam.

Keywords: Brunei Darussalam- population-based cancer registry- lung cancer- survival rate- risk factors

Introduction

   According to GLOBACAN 2020 (Ferlay et al., 2021), cancer death is currently the world's primary cause of death and it contributed to the deaths of estimated 10 million people in 2020 alone. A study conducted by Sung et al., (2020) reported that lung cancer remained as the leading cause of death for decades (with 1.8 million deaths) and was the second most commonly diagnosed cancer in 2020 worldwide. Following the rapid production of cigarette and heightened popularity of tobacco smoking in the 1930s, lung cancer became a worldwide epidemic and tobacco smoking contributed to approximately more than 80% of lung cancer cases in USA and France, 61% in Asian countries and 40% in Africa (Islami et al., 2015). It was also later demonstrated that exposure to radon, air pollution, arsenic, asbestos, and other hazardous chemicals poses as a potential factor for higher incidence rate of lung cancer (Ridge et al., 2013).

   In Brunei Darussalam, cancer deaths outbalance mortality attributable to cardiovascular diseases and diabetes mellitus and ascend to be the top killer of the population since 2009 (Ministry of Health Brunei Darussalam, 2012). In 2016, 353 deaths attributable to cancer accounted for 21.6% of all deaths and lung cancer alone resulted in 68 death cases or 19.3% of cancer mortality, representing the first leading cause of mortality in men and the second leading cause of mortality in women after breast cancer (Ministry of Health Brunei Darussalam, 2016). Leong et al., (2023) analysed database of the national cancer registry (Brunei Darussalam Cancer Registry) and reported that the age-standardised incidence rates (ASIR) per 100,000 persons for malignancy of lungs and bronchus in both males and females in Brunei Darussalam in 2020 were 24.2 and 17.8 respectively. This study aims to investigate the survival statistics of primary lung cancer in Brunei Darussalam corresponding to factors including stages of cancer, period of diagnosis and sociodemographic characteristics such as age groups, genders, ethnicities and place of living. This information could provide further insight on the factors associated with survival of lung cancer and in the planning and implementation of cancer control programme to improve lung cancer survival in Brunei Darussalam.

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Materials and Methods

Study Design, Population and Sample

This is a retrospective cohort study of primary lung cancers registered in a population-based cancer registry of 15-year study period from the year 2002 to 2016. The study population includes all primary malignant lung cancer cases registered (including citizens, permanent residents and foreigners) in the Brunei Darussalam Cancer Registry (BDCR) who were diagnosed during the study period. BDCR is a population-based cancer registry established in 2001, which manages national database of malignant cancers in Brunei. The BDCR recently published a comprehensive 20-years report (Ministry of Health Brunei Darussalam, 2022). To enhance data completeness, the registry routinely sources cancer listings from the pathology department, national death registry and medical records from the health services (Leong et al., 2023). Since the establishment of electronic medical records, Brunei Healthcare Information Management System (BruHIMS) in 2013, data accuracy was enhanced with finer verification of information in the medical records (Leong et al., 2019). Multiple studies analysing BDCR's national database on different types of malignancy earned publications including survival prognosis of colorectal cancer (Lee et al., 2021), breast cancer (Leong et al., 2019), and childhood cancer (Leong et al., 2020), to name a few. Based on the above criteria, there were a total of 797 patients and all eligible patients were included without sampling.

Data collection

De-identified data based on above criteria were extracted from the database of BDCR in Excel format and included age, genders, date of birth, date of death, date of diagnosis, laterality of origin site, Surveillance, Epidemiology, and End Results (SEER) stages of cancer (Seiffert et al., 1993), district of residence, ethnicity and type of cancer by International Classification of Disease-10 (ICD-10) and ICD-0 coding (Fritz et al., 2013).

Statistical Analysis

Analysis of de-identified data was carried out using R version 4.2.1 for Windows and RStudio Desktop version 2022.07.1+554 statistical software. Specifically survival package was used for survival analyses. Before data analysis, data cleaning and verification of data discrepancy with BDCR were carried out. BDCR captures and records the deaths of patients through verification with both the national death registry which registers all deaths in Brunei, and also from the electronic medical health records. Survival times in months were calculated by date of death minus date of diagnosis for patients who passed away in the study period. There were three cases of data discrepancy in which the date of death indicated that the patient had already passed away during the study period but status data remained alive in the raw data. Further verification of the data with BDCR was carried out. Patients who were still alive or lost to follow-up at the end of the study period were right censored. Kaplan-Meier tests were performed to investigate the 6-months,

1-year, 3-year and 5-year overall survival rates as well as median survival time with 95% confidence intervals (CIs). Log-rank tests were also carried out to compare survival probabilities corresponding to stages of cancer, year of diagnosis and socioeconomic characteristics including age group, ethnicity, genders and district by address. All patients have been grouped into 3 categories determined by their SEER staging code on the extent of malignancy using the localised, regional and distal (LOC-REG-DIS) staging system (Seiffert et al., 1993). Bonferroni corrections were carried out to account for multiple pairwise testing. Statistically significant differences were determined by p<0.05 for all analyses.

Ethical Consideration

Full ethical approvals were granted by the Pengiran Anak Puteri Rashidah Sa'adatul Bolkiah Institute of Health Sciences Research Ethics Committee (PAPRSB IHSREC), and Medical and Health Research Ethics Committee (MHREC), and data collection was initiated following ethics clearance and upon permission from the Ministry of Health Brunei Darussalam. De-identified data with relevant variables, secured with passwords was provided by the Brunei Darussalam Cancer Register. Researcher for the study signed data protection declaration and agreed to safe handling of the file and data.

Results

Sociodemographic characteristics of the sample population

There were 797 patients diagnosed with primary malignant lung cancer from 2002 to 2016 and all of them were included in the study. Majority of the patients were 50 years old and above (86.3%), males (58.6%), Malay (77.3%), and living in Brunei-Muara district (62.4%). At least half of the population (57.5%) were diagnosed with SEER Stage 7 lung cancer. Socioeconomic characteristics of study sample are summarized in Table 1.

Survival rates and median survival time of lung cancer patients

Kaplan-Meier test showed that the 6-months survival, 1-year survival, 3-year survival and 5-year survival rates for malignant lung cancer patients in Brunei Darussalam were 62.2%, 51.0%, 38.0% and 34.7% respectively. The median survival time of lung cancer patients was 12.4 months (95% CI: 9.2, 15.7). Survival curves of sample study is shown in Figure 1.

Comparison of survival statistics between three 5-year periods

Comparison of survival probability between three 5-year periods was being carried out by categorizing into three groups which were from 2002 to 2006, 2007 to 2011 and 2012 to 2016. Log-rank test demonstrated significant differences in lung cancer patient's survival time between the three 5-year periods (p=0.001). Bonferroni test revealed that survival time of patients diagnosed with lung cancer from 2002 to 2006 was significant longer than patients diagnosed from 2007 to 2011 (p=0.039) and

Table 1 Sociodemographic Characteristics of Study Sample

Variable	n (%)
Age	
20-29	3 (0.4)
30-39	17 (2.1)
40-49	90 (11.3)
50 & above	687 (86.3)
Gender	
Male	467 (58.6)
Female	330 (41.4)
District	
Brunei-Muara	474 (62.4)
Tutong	129 (17.0)
Kuala Belait	120 (15.8)
Temburong	37 (4.9)
Race	
Malay	616 (77.3)
Chinese	130 (16.3)
Others	51 (6.4)
Diagnosis during 5-year period	
Group 1 (2002 to 2006)	245 (30.7)
Group 2 (2007 to 2011)	225 (28.2)
Group 3 (2012 to 2016)	327 (41.0)
SEER stages	
Localised	94 (13.0)
Regional	213 (29.5)
Distant	415 (57.5)

those diagnosed from 2011 to 2016 (p<0.001). Survival time of patients diagnosed from 2007 to 2011 was also significantly longer than patients diagnosed from 2012 to 2016 (p=0.049). Comparison and survival curves are presented in Table 2 and Figure 2 respectively.

Comparison of survival statistics corresponding to stage of cancer

Only 722 lung cancer patients were included as there were 75 cases with unknown stage (coded SEER Stage 9) (Seiffert et al., 1993). Log-rank test demonstrated significant differences in lung cancer patient's survival with different extent of malignancy according to LOC-REG-DIS staging system (p<0.001). Bonferroni test presented that the survival time of patients with localised disease was significantly longer than patients with regional disease (p<0.001) and distant site involvement (p<0.001). Patients with regional disease also had significantly better survival prognosis than patients with distant site involvement (p<0.001). Comparison is summarized in Table 2 and survival curves are shown in Figure 3.

Comparison of survival statistics corresponding to socioeconomic characteristics
Gender

Log-rank test demonstrated no significant differences in survival experience between two genders (p=0.413). Five-year survival rate of males and females were 33.0% and 37.3% respectively. Comparison is summarized in Table 2.

Age Group

Comparison of survival times by age was being carried out by dividing into three age groups which were 20-39, 40-49, and 50 and above. The minimum and maximum age of the study sample were 21 and 104 respectively. There were only two patients aged 20 to 29 so they were grouped with patients aged 30 to 39. Log-rank test demonstrated significant differences in lung cancer patient's survival in three different age groups (p=0.004). Bonferroni test showed that the survival time of patients aged 50 and above was significantly shorter than those aged 40 to 49 (p=0.003). There was no significant difference in survival times between patients with aged 20 to 39 with patients aged 40 to 49 (p=0.791) and 50 and above (p=0.094).
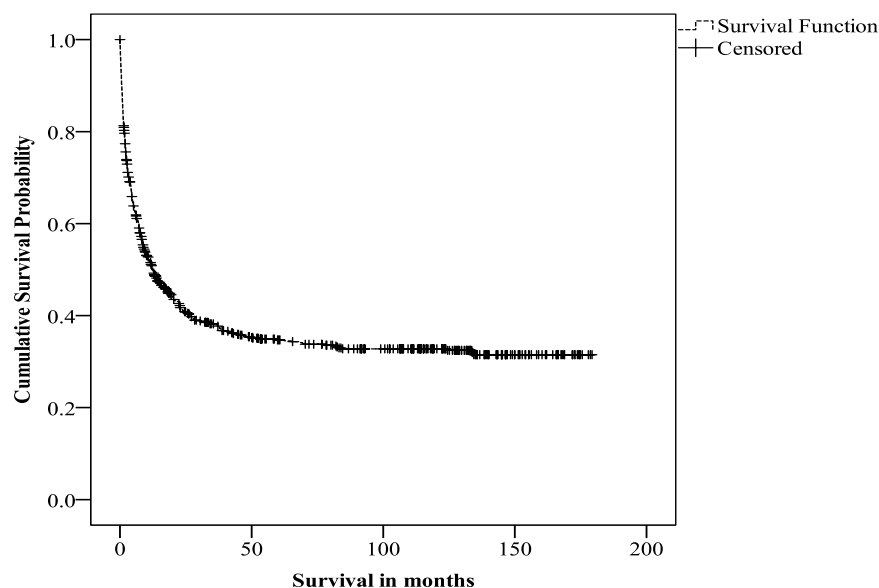

Figure 1. Survival Curve of Lung Cancer during Study Period (2002 to 2016) (n=797).
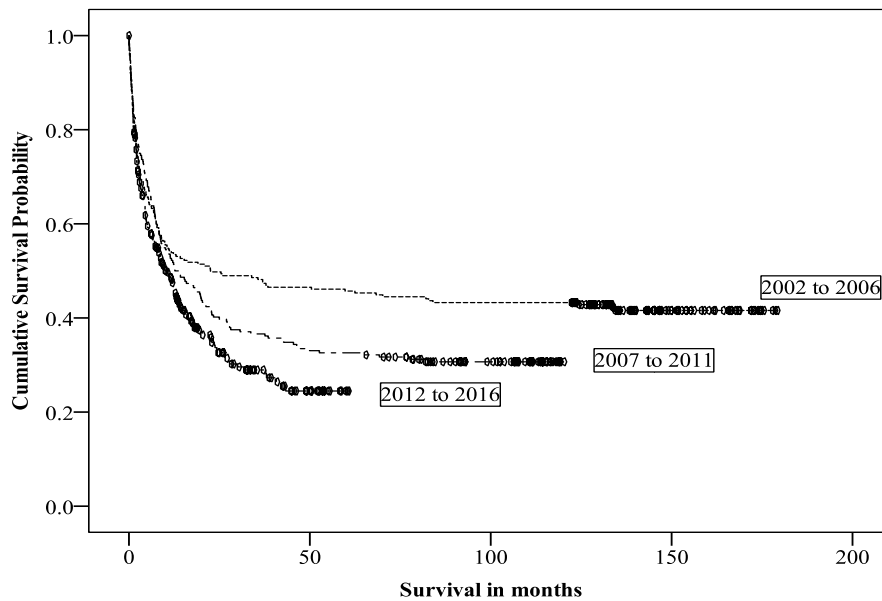
Figure 2. Survival Curves of Lung Cancer Patients with Different Periods of Diagnosis

Comparison and survival curves are presented in Table 2 and Figure 4 respectively.

District of living

Only 760 patients were included as there were missing data of geographical district in 37 patients. Log-rank test revealed that there were no significant differences in survival experiences of lung cancer patients living in different districts (p=0.291). Comparison is presented in Table 2.

Ethnicity

Log-rank test demonstrated no significant difference between survival probability of patients of various ethnic origin (p=0.522). Comparison is summarized in Table 2.

Discussion

The median survival time of lung cancer patients diagnosed from 2002 to 2016 was 12.4 months (95% CI: 9.2, 15.7) in comparison to 6.1 months for the 630 patients diagnosed with lung cancer between 1987 to 2012 in Brunei (Naing et al., 2017). Over the last decade, numerous smoking cessation programme were introduced and implemented nationally including the establishment of smoking cessation service in community health centers in 2005 and high inflation of tobacco tax to curtail local demand (Ong et al., 2017). According to Ministry of Health Brunei Darussalam (2021), all licensed cigarette business ceased to operate in Brunei Darussalam because of exorbitant excise taxes (almost 200%) and increased
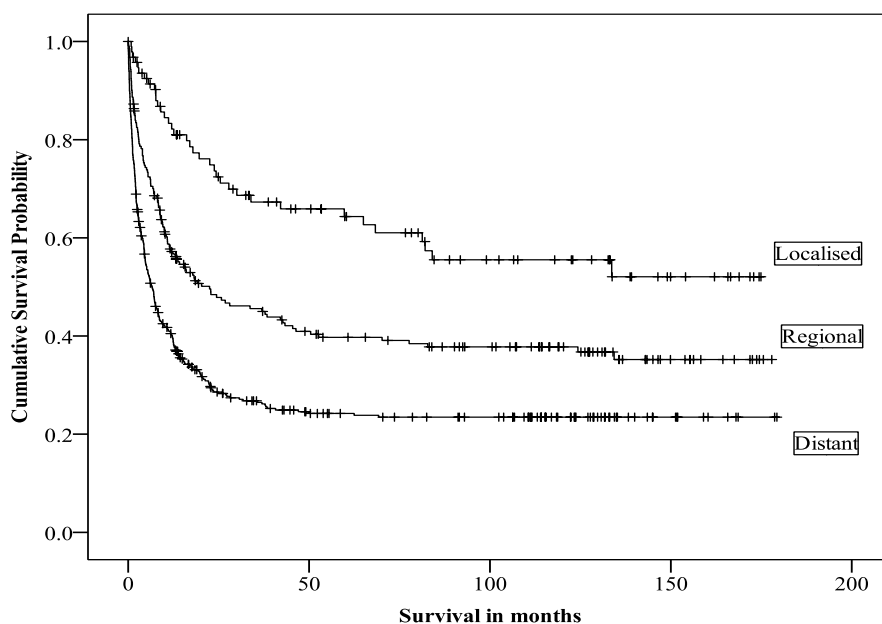

Figure 3. Survival Curves of Lung Cancer Patients with Different Stages at Diagnosis.

Table 2. Comparison of Survival Experience with Different Periods of Diagnosis, SEER Stages and Socioeconomical Characteristics

	n of deaths	Censored		Median survival time in months		3-year survival rate (%)	5-year survival rate (%)	X^2 (df)
		n	%	Estimate	(95% CI)			[p value]
Periods of diagnosis								
2002-2006	142	103	42.0	21	(0.0, 58.0)	48.2	45.7	Overall[1]: 14.67 (2) [0.001]; 2002-2006 vs 2012-2016 [<0.001]†; 2002-2006 vs 2007-2011 [0.039]†; 2007-2011 vs 2012-2016 [0.049]†
2007-2011	155	70	31.1	16	(6.3, 19.1)	36.6	32.6	
2012-2016	209	118	36.1	1	(7.6, 13.9)	28.9	24.5	
SEER stages								
Localised	36	58	61.7	-		67.3	64.3	Overall[1]: 60.11 (2) [<0.001]; Localised vs Regional [<0.001]†; Localised vs Distant [<0.001]† Distant vs Regional [<0.001]†
Regional	125	88	41.3	22.5	(6.9, 38.1)	45.6	39.7	
Distant	304	111	26.7	7	(4.9, 8.2)	26.5	23.8	
Gender								
Male	305	162	34.7	11	(8.5, 13.7)	36.2	33.0	Overall[1]:0.67 (1)[0.413]
Female	201	129	39.1	16	(9.5, 21.5)	39.9	37.3	
Age Group								
20-39	10	10	50.0	21	-	49.5	49.5	Overall[1]:11.02 (2) [0.004]; 40-49 vs 50&above:[0.003]†
40--49	45	45	50.0	16	(7.1, 68.6)	51.0	44.4	
50 & above	451	236	34.4	1	(8.5, 13.7)	36.1	33.0	
District of living								
Brunei-Muara	294	180	38.0	13	(8.9, 17.5)	38.1	35.2	Overall[1]:3.74 (3) [0.291]
Tutong	89	40	31.0	9	(4.6, 13.0)	32.8	28.5	
Kuala Belait	71	49	40.8	20	(9.2, 31.4)	44.6	41.2	
Temburong	26	11	29.7	6	(1.0, 11.1)	34.7	28.4	
Ethnic origin								
Malay	395	221	35.9	12	(9.1, 14.8)	36.3	34.0	Overall[1]:1.30 (2)[0.522]
Chinese	79	51	39.2	23	(5.2, 40.5)	44.4	38.2	
Other	32	19	37.3	8	(0.0, 30.1)	42.4	32.2	

[1], Overall log rank test; †, p-value is adjusted by Bonferroni method (Three multiple comparisons)

license fees. The finding suggests significantly more favorable survival time which could be due to overall advancement of treatment modalities for lung malignancy and possibly earlier diagnosis of cancer due to increased awareness about lung cancer and relation of tobacco exposure to development of tumor.

Our study found that patients diagnosed with lung cancers in the earlier years had a considerably longer survival probability than those diagnosed afterwards. In spite of recent introduction of local advanced treatments into Brunei Darussalam and implementation of strategies for strict tobacco control, the difference could be contributed to the refinement in the national cancer surveillance and reporting systems over the decade and the introduction of electronic medical records such as BruHIMS in 2013.

In previous decades, only conventional surgery and chemotherapy were available as local treatment options for cancer patients in Brunei Darussalam and those required radiation therapy had to travel frequently to overseas cancer centers for treatment. In view of the importance of providing patients treatment close to home, Brunei Darussalam established its own first national cancer treatment center, The Brunei Cancer Centre, in 2009. Reduced waiting time for more advanced treatment modalities over the decade brought conveniences and ease the burden of traveling among the lung cancer patients. However, our study found a reduction in the survival time in the later period of study. Our study has not analyzed data on cancer treatment, further studies to look into the differences in treatment modalities and its potential impact on survival should be considered.

More than half (57.5%) of patients with primary lung cancer was only diagnosed when lung cancer had metastasized to distant sites such as bone and brain. Wagland et al., (2017) debated that high frequency of late diagnosis is reported because early stage of lung cancer is often asymptomatic and specific features such
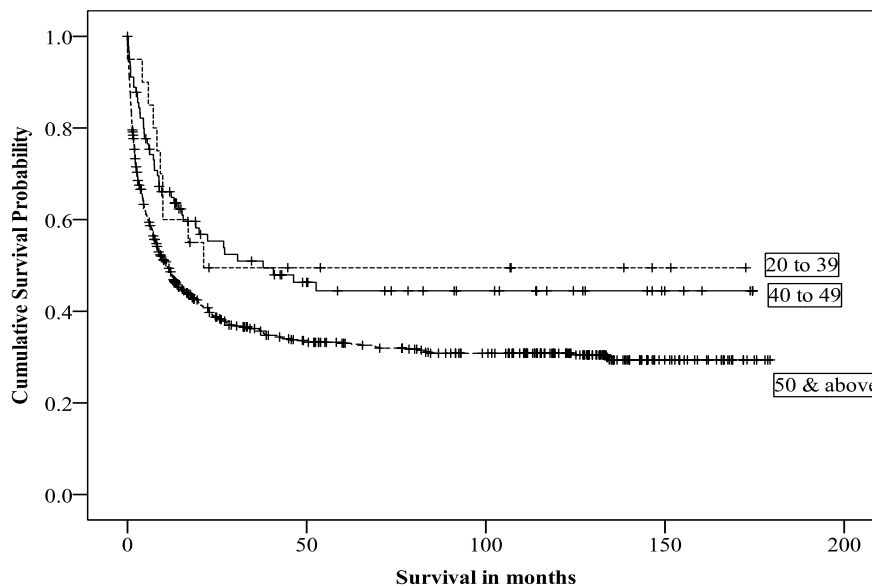
Figure 4. Survival Curves of Lung Cancer Patients in Different Age Groups.

as hemoptysis recurrent pneumonia, unexplained weight loss, chest pain, breathing difficulty only appear at later stages of lung cancer. In addition, other presenting symptoms such as breathing changes, fatigue and cough are "commonly presented" and luring both patients and physicians with thought that it was just a trivial condition (Wagland et al., 2017).

Our result also indicates that there was generally significantly longer survival time for patients diagnosed with early stage of lung cancer when the tumor was still localised and significantly shorter survival time for patients diagnosed with more advanced/metastatic stage of lung cancer. This pattern is consistent with findings from overseas studies (American Cancer Society, 2022; Lu et al., 2019). American Cancer Society (2022) analyzed that the 5-year relative survival rate decreased as patients are diagnosed with more advanced stage of primary lung cancer (both small cell lung cancer and non-small cell lung cancer) ranging from the earlier localised to regional followed by distal disease. In comparison to the survival rates in this study, Lu et al., (2019) established that lung cancer patients in their study had a lower 5-year survival time of 50.3%, 22.6% and 2.9% in localised, regional and distant disease respectively. A study was conducted by Chong et al., (2013) on the survival of non-small lung cancer patients in Brunei Darussalam on a study period of 2002 to 2009. They observed that 5-year survival rates for advanced stage were very low compared to other foreign reports as over 41% of the patients had refused treatment offered by their medical practitioners, possibly opted in traditional medicine such as herbal remedies (Chong et al., 2013).

About 86.2% of patients were older than the age of 50 when diagnosed with lung cancer. This is also evident in a study conducted by Lewandowska et al., (2022) in Poland demonstrating the interrelation of increasing age with the chance of lung cancer growth. Our result shows patients diagnosed with lung cancer at the age of 50

and above had significantly lower survival probability than those diagnosed from the age of 40-49. A study conducted by Tas et al., (2013) revealed that aging was one of the major factors that determined the survival prognosis of patient with lung cancer. Elderly patients, as a consequence of physiological aging process, carry a higher chance of acquiring comorbidities than young patients and they often present with geriatric syndromes such as osteoporosis, dementia, incontinence (Dagnault and Archambault, 2012). Evidently, outcomes of lung cancer patients with co-morbidities were associated with unproductive treatment and poor survival time. Secondly, toxicity due to chemotherapy is more frequent in elderly patients predominantly explained by deteriorating renal and hematopoietic physiological role (Tas et al., 2013). This may result in hindrance to accepting chemotherapy or withdrawal from it due to physical intolerance. Other than that, common cognitive impairment in elderly patients due to dementia and depression could pose disturbance in cancer treatments with issues such as non-compliance, refusal to accept treatment, inability to make decision on treatment options and missed identification of serious symptoms or even complications after operation (Extermann and Hurria, 2007). Also, age represents as a vital factor in making decision to undergo operation for the elderly. As reported by Sigel et al., (2009) on Stage 1 lung cancer, rate of lung resection surgery was 90% in patients aged <65 meanwhile there was only 79% in patients above the age of 80. As discussed, elderly lung cancer patients are prone to encounter side effects, co-morbidities and psychological issues, steering into limited treatment options and poorer survival patterns.

There were few limitations in this study. Firstly, the cancer surveillance system in Brunei Darussalam during early study period might not be as complete as the recent one, this could contribute to an underestimation of lung cancer death cases leading to overestimation of survival curve and survival time of patients diagnosed in the early

study period. Before the establishment of BruHIMS in 2013, the data was retrieved from paper-based medical case notes which might not be easily accessible when patient files had to be passed around different departments in the hospital. Also, there were missing details of stage of lung cancer at diagnosis in 75 patients and living district of 37 patients in this study. This could lead to potential bias in the overall survival analysis. Our study did not look into the impact on survival from different treatment modalities and contributory impact of risk factors such as smoking or comorbidities, further studies to study the impact from different treatment modalities and risk factors would provide a more comprehensive picture. Effective smoking cessation campaigns and strategies are also imperative in reducing incidence of lung cancer.

Overall, the median survival time of all primary lung cancer patients diagnosed in this study had at least doubled in comparison to the patients diagnosed from 1987 to 2012, which indicates overall advancement of patient care over the previous decades. Older age and advanced metastatic stage of lung malignancy were the significant contributors to poorer survival prognosis in primary lung cancer patients in Brunei Darussalam. In the effort to improve the survival prognosis of lung cancer patients, patients with heavy smoking history or presentation of symptoms should undergo recommended screening test to allow for early identification and treatment of malignancy.

Author Contribution Statement

Acknowledgements

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