Five year survival of non-small cell lung cancer patients in Brunei Darussalam

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ABSTRACT

Introduction: Lung cancer has been the leading cause of cancer deaths in Brunei Darussalam for the past five years. This study is the first to supply data for the 5-year survival of patients diagnosed with non-small cell lung cancer (NSCLC) in Brunei Darussalam. **Materials and Methods:** From 2002 to 2009, 302 patients diagnosed with NSCLC were identified from the National Cancer Registry of Brunei Darussalam. Demographic and clinical data were retrospectively retrieved from the clinical notes. All deaths and dates of death were obtained and crosschecked with the National Birth and Death Registry at the Immigration Department. Data were analysed using SPSS statistical software and 5-year Kaplan -Meier survival curves were derived and analysed using Log Rank test. Predictors of 5-year survival were analysed using Cox regression analysis. **Results:** Mean age of the 302 patients was 64.9 ± 12.8 (27.4–90.6 years) with male to female ratio of 194:108. Racial distribution consisted of 84.4% (n=255) Malay, 12.5% (n=38) Chinese and 3.1% of other racial origin (indigenous and foreign nationals). Histological types of NSCLC consisted of 67.9% (n=205) adenocarcinoma, 16.2% (n=49) squamous cell carcinoma, 6.3% (n=19) large cell carcinoma, 5.3% (n=16) bronchioalveolar carcinoma and 4.3% of other origin. Only 13.9% of patients underwent surgical resection. At completion of follow-up, only 47 (15.5%) patients were still alive. There were 255 deaths. Overall 5-year survival for the whole group was 3.6% with a median survival time of 6.5 ± 0.9 months (95% CI: 4.7-8.4 months) but according to stage of disease was 60.9% for Stage IA, 29.9% for Stage IB, 10.0% for Stage IIB, 7% for Stage IIIB and 3% for Stage IV. Significant prognostic factors were younger age at diagnosis, surgical resection, tumour types and tumour stages. **Conclusion:** Overall 5-year survival of patients diagnosed with NSCLC in Brunei Darussalam is still generally poor but comparable to previously reported data. Significant prognostic factors were younger age at diagnosis, surgical resection, tumour types and tumour stages.

Keywords: Carcinoma, non-small-cell lung cancer, survival analysis, thoracic surgery, cancer staging

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INTRODUCTION

Lung cancer is a major global health issue with an annual worldwide incidence of over

1.6 million (Age standardised rate of 22.9/ 100,000 population) and an annual worldwide mortality of over 1.3 million lives lost (Age standardised rate of 19.3/100,000 population), as reported by the World Health Organisation GLOBOCAN Country Fast Statistics for 2008. [1] It is a problem of epidemic proportion, with an increase of over 300,000 reported cases from 2002 to 2008, and as the world population ages, these numbers are expected to increase. [2]

In Brunei Darussalam, cancer mortality has ranked as the number one cause of death for the past 5 years. Estimated incidence rate (per 100,000) for all cancers in Brunei Darussalam for the year 2008 was reported to be about 112.5, which was sixth among all the ASEAN countries with Singapore having the highest. [3] Among all the different cancers, lung cancer claims the highest mortality rate with over 24.9% of all cancer deaths in 2008 in Brunei Darussalam. [4] This high mortality rate is thought to be due to the advanced stage of the disease by the time of diagnosis with less than a quarter of cases amenable to surgical excision. [5]

The reported 5-year survival rate for non-small cell lung cancer (NSCLC) varies from 60%-80% for early Stage I to under 10% for advanced Stage IV disease. [6–8] However, 5-year survival data is lacking for patients diagnosed with NSCLC in Brunei Darussalam. This study is the first to report on the 5-year survival rate of patients diagnosed with NSCLC in Brunei Darussalam.

MATERIALS AND METHODS

Patients: Patients diagnosed with NSCLC in Brunei Darussalam were identified from the National Cancer Registry from 1st January 2002 to 31st December 2009. Only patients with a diagnosis of NSCLC, between the age of 18-80 years were included in the study. Patients diagnosed with small-cell lung cancer (SCLC) or who were diagnosed or had received surgery abroad or had other malignancies with pulmonary metastases were excluded from the study. Ethical approval to retrieve the above data was obtained from the Medical Health Research and Ethics Committee (MHREC) at RIPAS hospital.

Data Collection: Patients' medical notes were retrieved and demographic as well as clinical data were collected. Data on the types of surgical resection, chemotherapy and radiotherapy treatments given to patients were retrieved from operative notes kept at the Department of Surgery Operation Note database and patients' medical records kept at the National Cancer Centre. Tumour stages and other histopathology data of the resected specimens or fine needle aspiration cytology (FNAC) were obtained from the Department of Histopathology at Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital and Cancer Registry.

Patients' statuses on the 31st December 2009 were obtained from clinic follow-up notes at the Surgical Outpatient Department at RIPAS Hospital, and at the National Cancer Centre outpatient Department at Jerudong Park Medical Centre. These data were further cross-referenced with dates and causes of death retrieved from death certificates kept at the National Birth and Death Registry in the Immigration Department, Ministry of Home Affairs.

Statistical analysis: All categorical data we-

re compared using the Chi squared test. Survival time was defined as follows: Patients' deaths were considered as events and survival time is the time to event from date of histological confirmation of diagnosis. Patients who are alive were censored as of the last known follow-up on the 31st December 2009. Survival time was analysed using SPSS 15 (SPSS, Inc., Chicago, IL, USA) statistical software to derive the 5-year Kaplan-Meier overall survival curve as well as survival curves for each disease stage. Survival between the stages was compared using the log-rank test. Predictors of 5-year survival were determined by Cox regression analysis. Statistical significance was assumed when the *p* value was < 0.05.

RESULTS

A total of 302 patients were diagnosed with NSCLC during the study period with a mean age of 64.9 ± 12.8 years and a male predominance. The racial distribution was consistent with the national breakdown with a majority of Malays (84.4%), followed by the Chinese (12.5%). Patients' demographics are shown in Table 1.

Among the types of cancer, adenocarcinoma was the most common NSCLC types (67.9%) followed by squamous cell carcinoma (SCC) (16.2%) (Table 1).

There were no gender differences in tumour types except for bronchioalveolar, which was significantly more common in female patients (Table 2). The majority of patients (80.8%) presented in advanced Stage III (32.8%) and IV (48.0%) disease, while 17.2% presented in early Stage I (13.6%) and Stage II (3.6%). In 2.0% of cases, the stage of the disease was not recorded. There were also no gender differences in terms of stage of the disease at presentation (Table 2).

Table 1: Demographic, clinical symptoms, tumour types and staging.

Variables	Sample Size (%) (N=302)
Gender (M:F)	194:108
Mean Age (years) ± SD (Range)	64.9 ± 12.8 (27.4 to 90.6)
Race	
Malay	255 (84.4)
Chinese	38 (12.5)
Others (indigenous and foreign nationals)	9 (3.1)
Symptoms and Co-morbidities	
Cough	104 (34.4)
Haemoptysis	66 (21.9)
Shortness of breath	69 (22.8)
Anorexia	62 (20.5)
Weight loss	111 (36.8)
Smoking history	204 (67.5)
Diabetes mellitus	43 (14.2)
Chronic obstructive pulmonary disease	28 (9.2)
Pulmonary tuberculosis	25 (8.3)
Histopathology	
Adenocarcinoma	205 (67.9)
Squamous Cell Carcinoma	49 (16.2)
Large cell Carcinoma	19 (6.3)
Bronchioalveolar	16 (5.3)
Others (Papillary carcinoma, adenosquamous, mucoepidermoid and unknown)	13 (4.3)
Pathological Stage	
Stage I *(Surgical/Medical)*	41 (13.6) *(25/16)*
Stage II *(Surgical/Medical)*	11 (3.6) *(5/6)*
Stage III	99 (32.8)
Stage IV	145 (48.0)
Unknown or unrecorded	6 (2.0)
Primary treatment	
Surgery	42 (13.9)
Medical	260 (86.1)
Primary chemotherapy	128 (49.2)
Radiotherapy	56 (21.5)
Refused/Unfit	94 (28.5)

Only 42 (13.6%) patients underwent surgical resection. Eighty-eight (32.6%) were given chemotherapy alone, 19 (7%) patients were treated with radiotherapy alone, 28 (10.4%) patients had chemo-radiation therapy and 94 (34.8%) were either unfit or treated palliatively. Eleven (4.1%) patients were

given neoadjuvant chemotherapy prior to surgery. Seventy-seven (28.4%) patients developed recurrence or metastases during the follow up period.

At completion of follow-up, only 47 patients were still alive. There were 255 deaths. Overall 5-year survival of the whole group was 3.6% with a median overall survival of about 6.5 ± 0.9 months (95% CI: 4.7 - 8.4 months; Figure 1) but according to stage of disease was 60.9% for Stage IA, 29.9% for Stage IB, 10.0% for Stage IIB, 7% for Stage IIIB and 3% for Stage IV (Table 3). The 1-year, 2-year and 3-year survival rates according to stages of disease is shown in Table 3 which is comparable to reported series.

Younger age at diagnosis, surgical resection as primary treatment, tumour types and tumour stage were significant prognostic factors using Cox regression analysis (Table 4; Figures 2, 3 and 4).

DISCUSSION

Cancer mortality ranked as the number one cause of death worldwide, as well as in Brunei Darussalam for the past five years, with lung cancer at the top, claiming over 17.5% of all cancer deaths each year, to as high as 24.9% in 2008. [4] This study is the first cancer study to date to be conducted in Brunei Darussalam looking at the 5-year survival outcomes. The epidemiological data generated will provide useful data for subsequent studies on lung cancers.

As with many other studies reported worldwide, the mean age of patients diagnosed with NSCLC in Brunei Darussalam is about 65 years with men twice as likely affected by the disease than women. [5, 6, 8, 9] The racial distribution of NSCLC generally reflects the racial distribution of the population of Brunei Darussalam, with over 66% of the population consisting of Malay origin and just under 11% of Chinese origin. [4]

Among the subtypes of NSCLC, adenocarcinoma represents the most common histological subtypes making up over 68% of NSCLC encountered in Brunei Darussalam. This is comparable to other Asian countries

Table 2: Distribution of tumour stage and histological types of NSCLC according to gender.

	Gender		
	Male (%) N=194	**Female (%) N=108**	***p***
Stage of NSCLC			
Stage I	25 (12.9)	16 (14.8)	*NS*
Stage II	8 (4.1)	3 (2.8)	*NS*
Stage III	68 (35.0)	31 (28.7)	*NS*
Stage IV	89 (45.9)	56 (51.8)	*NS*
Unknown or not recorded	4 (2.1)	2 (1.9)	*NS*
Histological types of NSCLC			
Adenocarcinoma	132 (68.1)	73 (67.6)	*NS*
Squamous Cell Carcinoma	34 (17.5)	15 (13.9)	*NS*
Large Cell Carcinoma	14 (7.2)	6 (5.5)	*NS*
Bronchioalveolar	8 (4.1)	12 (11.1)	0.02
Others (Papillary carcinoma, adenosquamous, mucoepidermoid and unknown)	6 (3.1)	2 (1.9)	*NS*

NS; non-significant

Table 3: Survival rates at 1-year, 2-year, 3-year and 5-year of the different tumour stages.

Stage	1 Year	2 Years	3 Years	5 Years
IA	95.8	87.1	78.0	60.9
IB	74.7	74.7	52.3	29.9
IIB	60.0	50.0	30.0	10.0
IIIA	72.7	36.4	21.8	0.0
IIIB	36.8	20.3	9.3	7.4
IV	24.4	9.4	6.2	2.8
Overall	34.4	15.9	8.3	3.6

Figures presented as percentage (%)

Table 4: Cox regression analysis of prognostic factors in patients diagnosed with NSCLC.

Variables in equation	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Medical vs. Surgical	0.828	0.308	7.217	1	*0.007* *	2.289	1.251-4.189
Age	-1.407	0.453	9.662	1	*0.002* *	0.245	0.101-0.595
Gender	0.005	0.141	0.004	1	0.974	1.005	0.761-1.326
Race	-0.726	0.438	2.747	1	0.097	0.484	0.205-0.1142
Pulmonary TB	0.472	0.261	3.282	1	0.7	1.604	0.962-2.674
COPD	-0.002	0.235	0	1	0.994	0.998	0.630-1.581
Diabetes mellitus	-0.222	0.191	1.36	1	0.244	0.801	0.551-1.163
Tumour types	-1.179	0.495	5.663	1	*0.017* *	0.308	0.116-0.812
Tumour stage	1.332	0.524	6.467	1	*0.011* *	3.788	1.357-10.576

* Indicate significant prognostic factors for 5-year survival rates in patients with NSCLC
COPD; chronic obstructive pulmonary disease

with a similar proportion reported in Japan. [2] Geographical differences in the incidences of NSCLC types have previously been reported with adenocarcinoma being more frequent in Asia, and SCC predominating in Europe. [10]

Our incidence of the SCC subtype was surprisingly low at 16%, compared to the Japanese group who reported a rate of 25%. [2] This low incidence also cannot be explained by any possible decreasing trend of smoking since over two thirds of our study population gave a history of smoking. There may be other explanations for this observation, which may need further evaluative studies.

The majority of our patients (80.8%) presented rather late at advanced stage III

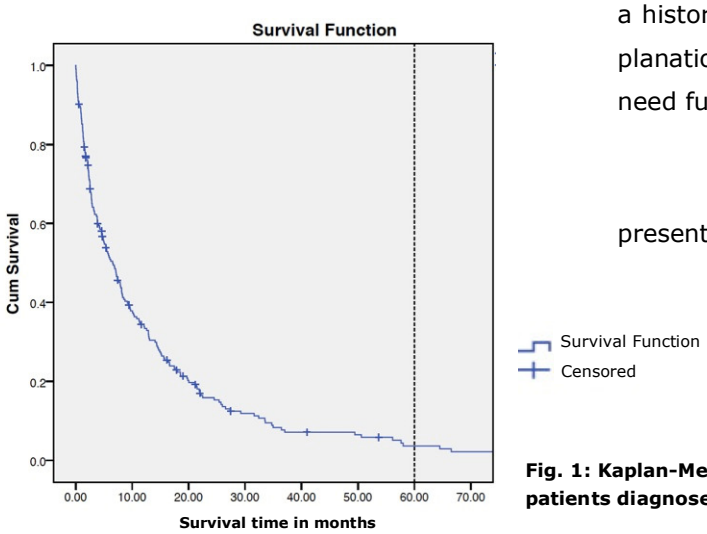

Fig. 1: Kaplan-Meier 5-year overall survival curve of patients diagnosed with NSCLC.

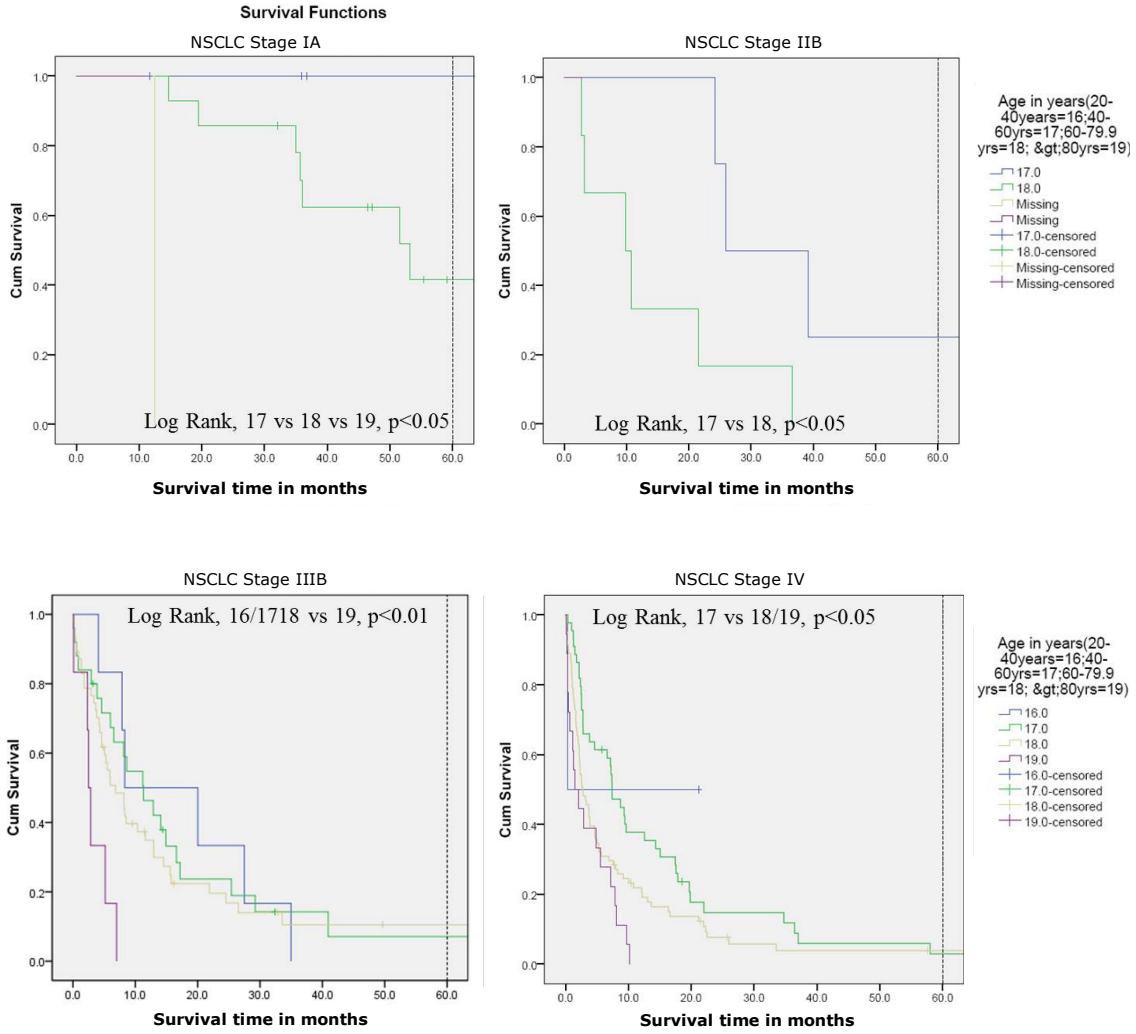

Fig. 2: 5-year survival curves comparing Age as prognostic factor at various stratum of Tumour Stage showing only significant differences for Stage IA, IIB, IIIB and IV.

and IV, which is no longer curable. Only 17.2% of our patients presented in early stage I and II at time of diagnosis and only 14% of patients underwent surgical resection for their cancers, in comparison with the Japanese, who reported over 28% of their patients presenting in early stages I and II. [2] The same Japanese group also reported that 43% of their patients underwent surgical resection of their lung cancer as their initial therapy, which is amazingly high in comparison with most reported series. The high proportion of patients presenting with advanced stage NSCLC in Brunei Darussalam is also alarmingly high compared to Pakistan (62.3%) and Japan (59%), which most likely reflects the delay in presentation of the disease to medical attention. Westeel *et al*. reported on the negative impact of rurality of patients domicle on lung cancer survival in a population based study, suggesting that patients living in very rural areas away from lung cancer specialist treatment centres plays a significant factor in the poor long-term out-

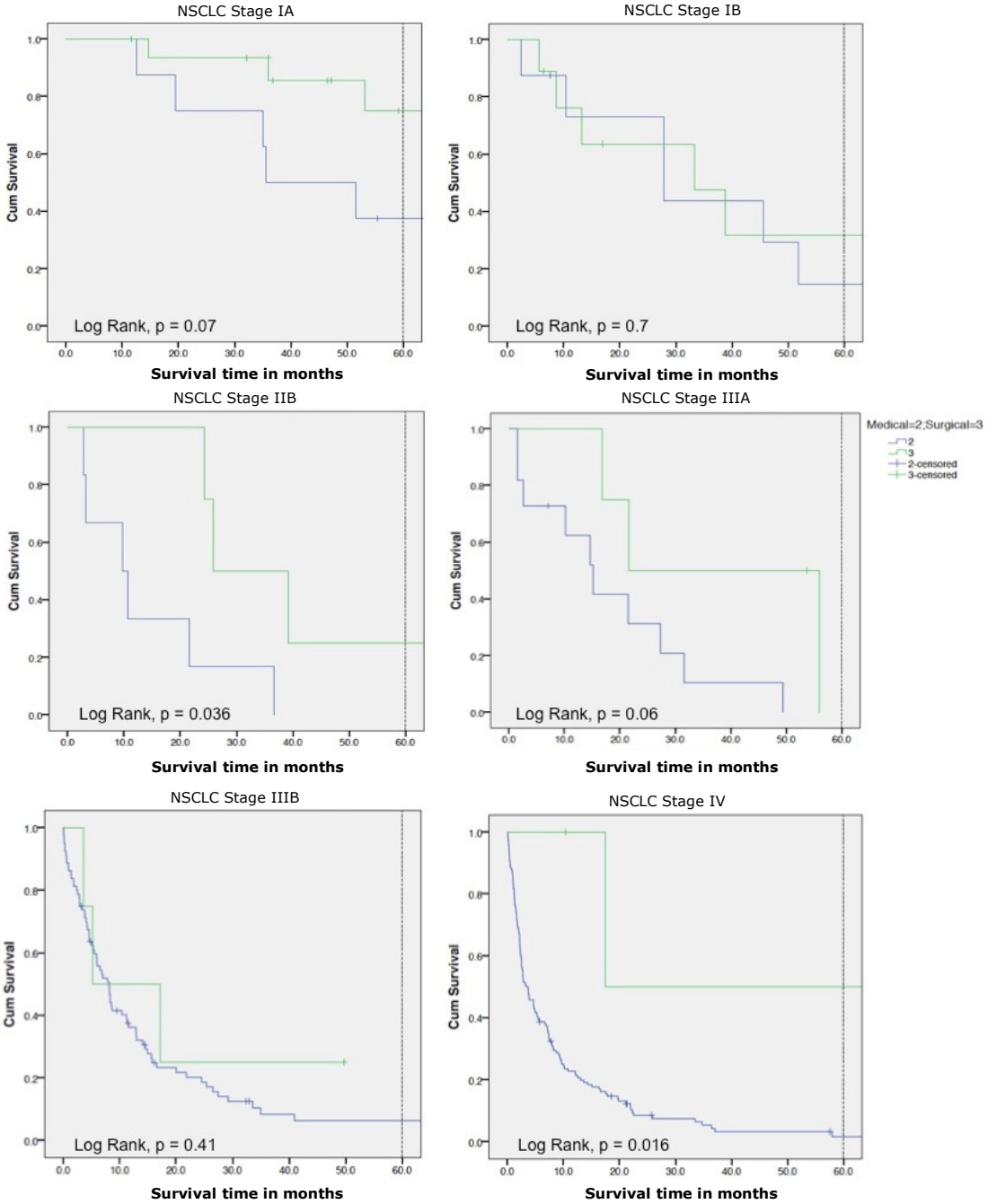

Fig. 3: Survival curves between surgical resection and medical therapy (chemotherapy, radiotherapy, chemo-radiotherapy and palliative) between the different stages of tumors.

land suggested that the differences between urban and rural locality of patients is based on socioeconomic status and deprivation. If the socioeconomic deprivation was taken into account, the differences in incidence and survival of lung cancer in urban and rural areas were abolished. [12] In Brunei Darussalam, 71% of the population reside in the Brunei-Muara district where the main tertiary referral centre for lung cancer specialist treatment is located. Twenty-nine percent of the remaining population are found in the three other di-

stricts, where referral and journey times may add to the delay in making an early diagnosis. Whether living far from the main treatment centres in Brunei Darussalam has any impact on survival will need to be studied in the future.

The 5-year survival of patients presenting with Stage I NSCLC in our study population, is lower than other reported series. [13] The Japanese groups are generally known to be very aggressive in their surgical intervention and their pathological stages are generally reflective of the true stage of the disease, hence they consistently reported superior results. [13] In comparison with our local data, our early stages I and II groups consisted of over 40% who were unfit or refused any surgical intervention and of these 15 out of 22 refused any medical intervention and were treated with symptomatic palliative care. Similarly our 5-year survival rates for advanced stage III and IV was extremely low compared to other reported series, again because a large proportion of over 41% of patients with Stage III and IV in our study completely refused any form of chemotherapy or radiotherapy for their lung cancer, in comparison to the Japanese group who reported only 12% who were treated with best supportive therapy. [2, 13] One of the reasons for this high proportion of patients initially refusing any form of medical or surgical treatment is possibly their belief in traditional "kampong" or "village" remedies. The treatment is passed down from generation to generation using untested herbal concoction, which are taken for up to several months, before patients agree to try conventional Western treatments. Usually by then, their disease is at a stage when it is no longer curable or resectable.

Our study has shown that age at diagnosis, surgical resection, tumour types and tumour stages are significant prognostic factors for 5-year survival in our patient population. Young age at diagnosis was associated with significantly better 5-year survival than older age groups (Figure 2). Surgical resection of NSCLC in our study is associated with significant survival benefits across all tumour stages except for stage IB and IIA which may be accounted for by the small number of cases in these latter two groups (Figure 3). Even in stage IV NSCLC, 5-year survival was significantly better in surgical patients than in medically treated patients but only in selected patients. One of our patients in stage IV, pre–

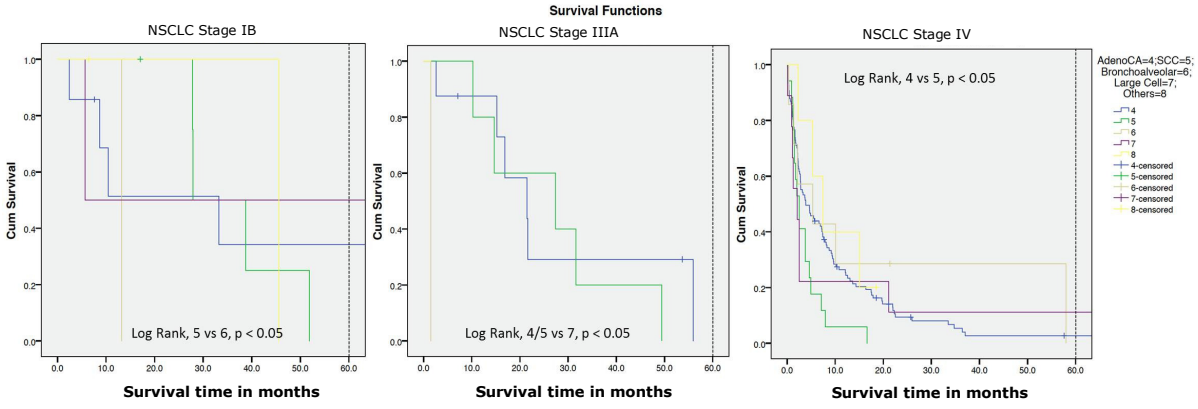

Fig. 4: 5-year survival curves comparing tumour types as prognostic factor at various stratum of tumour stage showing only significant differences for Stages IB, IIIA and IV.

sented with severe frontal headache and was found to have a frontal lobe brain tumour for which she underwent resection. Histology later confirmed an adenocarcinoma metastasis possibly of lung origin. A computed tomography scan of the chest with FNAC confirmed a central right lower lobe adenocarcinoma of the lung. This was successfully resected with a right pneumonectomy and the patient is still alive after eight years of follow up.

In our study population, adenocarcinoma tended to have better prognosis than SCC, which is better than bronchoalveolar or large cell carcinoma (Figure 4). Patients with other histological subtypes tended to do badly in terms of prognosis. Clinic-pathological factors such as younger age at diagnosis, gender, histological cell types, tumour differentiation, tumour stage and smoking status have continued to be proven as robust prognostic implications for survival after diagnosis. [14, 15]

This is the first study to look at the 5-year survival of patients diagnosed with NSCLC in Brunei Darussalam. However, there are several limitation. First, it was a retrospective study and is inherently associated with problems in that of missing or incomplete data i.e. a small proportion of the patients had to be excluded from the current analysis. Another limitation was the lack of a single repository for records on all deaths in Brunei Darussalam and hence patient mortality had to be cross-referenced by several sources. Lastly, medical notes of patients who passed away were difficult to track down and the only source was our cancer registry, which was then cross-referenced with the records kept at the National Birth and Death Registries at the Immigration Department.

In conclusion, the overall 5-year survival rate of patients diagnosed with NSCLC in Brunei Darussalam is generally still poor due to the large proportion of patients presenting with advanced stage of the disease. There may be other factors, which may also contribute to this poor outcome, which will need further study in the future. However, the 5-year survival rate for early stage NSCLC is comparable to current reports from other countries. Younger age, surgical resection as primary treatment, tumour histology and stage are significant prognostic factors or 5-year survival. Data on survival rates will provide clinicians the armamentarium to address prognostic and treatment issues when communicating with their patients.

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