Survival of Patients Surgically Treated for Lung Cancer

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Summary

A study was done on survival of patients surgically treated for lung cancer from 1995-2001. The average operative rate for 852 patients was 4.8%. In 67 surgically treated patients (54M, 13F), the commonest histological type was squamous cell carcinoma (52.2%) followed by adenocarcinoma (26.9%). The surgical-pathological stage was stage I in 52.2%. Postoperatively, five-year survival was 29%, with a median survival of 27 months. Completeness of resection was the foremost determinant of survival outcome and stage higher than stage I was an adverse prognostic factor. These results indicate that the current outlook for lung cancer patients remains poor.

Key Words: Lung cancer, Surgery, Survival, Malaysia

Introduction

Accurate epidemiological data on lung cancer in Malaysia is not available, however, there is evidence that it is the leading cause of cancer death and one of the most common cancers in this country[1-3]. Surgical resection offers the only realistic chance of cure for lung cancer patients with non-small cell carcinoma, and prognosis and outcome are currently dependent on surgical resectability[4]. There had been no studies in Malaysia on outcome of lung cancer patients who had undergone surgery, and this study was done to ascertain the resection rate and outcome of patients with lung cancer operated upon with a view to curative resection.

Materials and Methods

A retrospective study was done on patients with lung cancer seen by the respiratory medical unit, who underwent surgery with a view to curative resection, between 1995 and 2001. New cases of lung cancer diagnosed during this period were identified from the unit's registration book for new cases, from cancer notification records and from the cancer register. The lung cancer patients who had surgery were ascertained from information in cancer notification forms and the unit's cancer register as well as records in the Department of Cardiothoracic Surgery. Those who already had surgery before referral to the respiratory medical unit were excluded from further analysis. Patients' records were traced and information was obtained

on demographic data, surgical procedure, operative findings, stage and histological type of cancer. Outcome data was obtained from follow-up records in Penang Hospital and hospitals in other states where patients were followed-up and in some cases, by telephone calls to patients and their relatives.

Statistical analyses were performed using a statistical software package (Version 11.0, SPSS for Windows; Chicago, Illinois, USA). Descriptive statistics were used to describe patient characteristics. Continuous variables were expressed as mean ± SD and categorical data were expressed as counts and proportions. Differences between any two groups were analysed by Chi-square test for categorical variables. Kaplan-Meier analysis was applied to study survival of patients and the log rank test was used to compare cumulative survival between groups. A Cox regression model was used to test for significance between groups with different stage of disease and completeness of resection after adjusting for age, sex, ethnic group and histological cell type. A P value of less than 0.05 was considered statistically significant.

Results

Between 1995 and 2001, out of 1,187 new lung cancer patients seen by the unit, 80 had surgery with a view to curative resection. Thirteen of these 80 patients (including 9 local patients) already had surgery before referral to the respiratory medical unit, and were excluded from further analysis. Hence, the average operative rate for patients evaluated by the respiratory medical unit was 67/1174 (5.7%). Nearly two-thirds of the 67 patients included in the study (61.2 %) were local residents whereas the remainder were from two neighbouring states. If only local residents were considered the operative rate fell to 41/852 (4.8%). Altogether 54 male and 13 female patients had surgery, giving a male: female ratio of 4.2:1. Chinese accounted for 74.6% of patients, 13.4% were Malay, 10.5% Indian and 1.5% Eurasian.

Figure 1 shows the age distribution; the mean age at the time of surgery was 55.5 ± 12.1 years (range 21 - 76 years) and 82.1% of patients were aged between 41 - 70 years. All the patients had non-small cell carcinoma. The commonest cell type was squamous cell carcinoma (52.2%), 26.9% had adenocarcinoma, 6.0% each had large cell/undifferentiated carcinoma and adenosquamous carcinoma and 8.9% had other cell types. These other cell types included carcinoid tumour in 3 patients, mucoepidermoid carcinoma in 2 patients, and leiomyosarcoma in 1 patient. With respect to smoking history, 46 patients were smokers (68.7%), including one who was an ex-smoker. The proportion of smokers was much lower in women than in men (7.7% vs. 83.3%, p < 0.05). Adenocarcinoma was the commonest cell type in females (38.5%) and in non-smokers of both sexes (52.4%), whereas squamous cell carcinoma was the commonest cell type in males (59.3%) and smokers (65.2%). The proportion of patients with adenocarcinoma was significantly higher in non-smokers than in smokers (52.4% vs. 15.2%, p < 0.05), conversely, the proportion of patients with squamous cell carcinoma was higher in smokers than in non-smokers (65.2% vs. 23.8%, p < 0.05). There were six patients aged under 40 years (4 female and 2 male); only 1 of whom was a smoker. The cell type was carcinoid tumour in 3, and mucoepidermoid carcinoma, adenocarcinoma and leiomyosarcoma in 1 each.

The preoperative diagnosis was established by fine needle aspiration biopsy in 44.8% of cases, bronchoscopic biopsy in 35.8%, and by sputum cytology, video-assisted thoracoscopic biopsy and open lung biopsy in 1.5% each; in the remaining 10 patients (14.9%), no definitive histopathological diagnosis was ascertained prior to surgery. Pneumonectomy was performed in 17 cases, lobectomy or bilobectomy in 42 cases, wedge resection and completion pneumonectomy in 1 case each, and exploratory thoracotomy in the remaining 6 cases (Table I). The wedge resection was carried out for a patient with squamous cell carcinoma who had been successfully treated with

radiotherapy and combination chemotherapy for small cell carcinoma causing superior vena cava obstruction five years previously. The patient who had completion pneumonectomy had a metachronous adenocarcinoma three years following upper lobectomy. In the 6 patients who had "open and close" thoracotomy, resection was abandoned because the tumour could not be mobilised from adjacent structures in 5 patients and in 1 case (with a stage I squamous cell carcinoma) the lung could not be mobilised because of extensive scarring/adhesions from old pulmonary tuberculosis. Complete resection could not be achieved in another four patients; three had tumour adherent to the parietal pleura/chest wall and one had microscopically proven tumour at the resection margin. The side of the surgery was on the right in 65.7% and on the left in 34.3%. With respect to surgical-pathological staging[5], 52.2% of patients had stage I disease, 17 (23.9%) had stage II and15 (23.9%) had stage III disease.

Patients were assessed up until August 2002. Eleven patients were lost to follow-up; of these, 4 were local residents, 4 were from a neighbouring state, and another 3 had shifted out of state without leaving a forwarding address. Thirty-eight patients had died: 34 of lung cancer, 3 of other causes and the cause of death for 1 patient could not be ascertained because his death in the community was not medically certified (Table II). In the 34 patients whose cause of death was lung cancer, 16 had developed distant metastases, the commonest sites being brain, bone and contralateral lung. One death was related to pneumonectomy; the patient succumbed to complications after an attempt to close a bronchopleural fistula more than two years after initial surgery for removal of a mucoepidermoid carcinoma. The other two deaths were from unrelated causes; one patient with squamous cell carcinoma of the lung died of a second primary,

adenocarcinoma of pancreas, and a schizophrenic man died of acute pulmonary oedema secondary to uncontrolled hypertension. Just over half of those who died did so during the first year after surgery; however, two patients died of their cancer more than 4 years after surgical resection. One patient with bronchioloalveolar carcinoma had resection of solitary cerebral metastases on two occasions before she died 57 months after lobectomy, and another patient died 54 months after pneumonectomy for squamous cell carcinoma from recurrence in the contralateral lung. Eighteen patients were still alive after a median duration of follow-up of 45.5 months; 16 were disease free whereas 2 had evidence of metastatic disease.

The survival curve of the entire group is presented in Figure 2. The overall five-year survival was 29%, with a median survival of 27 months after surgery. Cox regression showed that patients who had complete resection had better survival than those in whom the tumour could not be totally removed and those with surgical-pathological stage I disease had significantly better long-term survival than those with higher stage of disease. Figure 3a shows the adjusted survival curve in relation to completeness of tumour resection (log rank p = 0.0001) and Figure 3b shows the adjusted survival curve constructed by a Cox regression model in relation to stage (log rank p = 0.0136). Median survival was significantly better in patients who had complete resection compared to those in whom the tumour could not be totally removed (31 months vs. 10 months) and in patients with stage I disease compared to those with higher stage (52 months vs. 18 months). In this study, no patient with incomplete resection survived to 5 years and the majority of patients who survived for 5 years or more had stage I disease (87.5%). The overall five-year survival was 34% in the group with complete resection and it was 42% in those with surgical-pathological stage I lung cancer.

Table I: Type of Operation

Year	Lobectomy	Bilobectomy	Pneumo-nectomy	Wedge resection	Completion pneumonectomy	"Open and close" thoracotomy
1995	3	4	4			
1996	1	1	4			2
1997	3	1	3			1
1998	10	2	1	1	1	
1999	6	1	3			
2000	5	2	1			2
2001	3	1				1
Total	31	11	17	1	1	6

Table II: Timing and Cause of Death in 38 Patients Who Died Following Surgery for Lung Cancer

Duration after surgery/months	Died of lung cancer	Cause of death related to pneumonectomy	Died of unrelated causes	Cause of death unknown
0 - 6	7			
6 - 12	12		1	
12 - 18	4		1	
18 - 24	3			
24 - 30	3	1		
30 - 36	2			1
36 - 42	1			
42 - 48	-	-		-
48 - 54	1			
54 - 60	1			
Total	34	1	2	1

Fig. 1 Age distribution

Age group/years
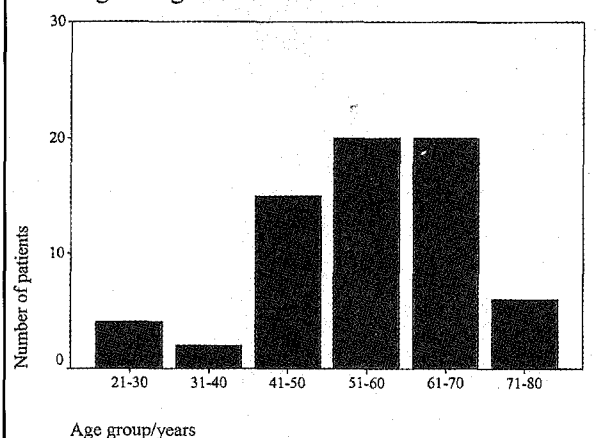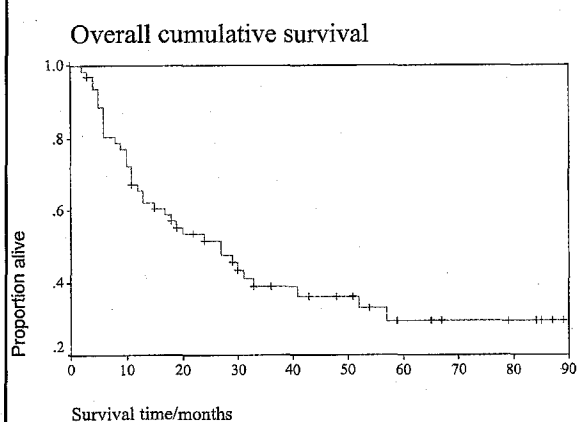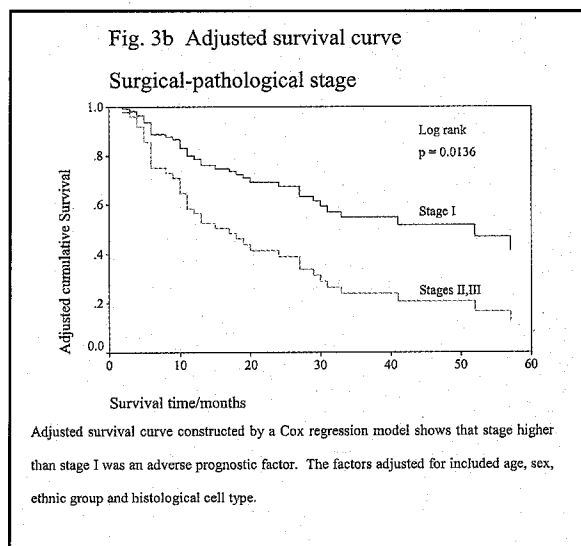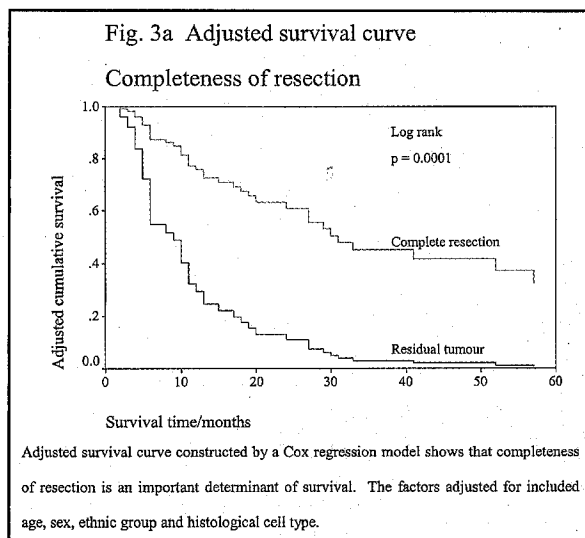
Fig. 2 Kaplan-Meier survival plot

Overall cumulative survival

Survival time/months

Proportional survival in 67 patients with lung cancer who had surgery with a view to curative resection. Median survival after surgery was 27 months and overall five-year survival was 29%.

Fig. 3a Adjusted survival curve

Completeness of resection

Adjusted survival curve constructed by a Cox regression model shows that completeness of resection is an important determinant of survival. The factors adjusted for included age, sex, ethnic group and histological cell type.

Fig. 3b Adjusted survival curve

Surgical-pathological stage

Adjusted survival curve constructed by a Cox regression model shows that stage higher than stage I was an adverse prognostic factor. The factors adjusted for included age, sex, ethnic group and histological cell type.

Discussion

There is no doubt that lung cancer imposes a heavy burden on health care in Malaysia, particularly on inpatient services. The Ministry of Health lists cancer of the trachea, bronchus and lung as the commonest malignancy based on government hospital discharges[3,6]. A study done in 1995 on cancer admissions to a large regional hospital[7] concurred that the commonest primary site among inpatients was lung (193/1335, 14.5% of cases).

With reference to incidence figures, a pilot survey carried out to determine cancer incidence in six districts in Malaysia in 1997[8] showed that lung cancer accounted for 11.2% of cancers, with a site-specific incidence of 10.1 per 100 000 population. It ranked as the commonest cancer in males with a gender-specific incidence of 14.1 per 100 000 males, and was fourth in females with a gender-specific incidence of 5.9 per 100,000 females. The Penang Cancer Registry, regional population based registry, reported in 1996 that the commonest primary site was lung, accounting for 13.8% of cancer cases[9]. Lung cancer was the leading cancer in males of all races and was ranked third in female patients. The gender-specific

incidences were 20.5 per 100,000 males and 7.0 per 100,000 females. From the data in this study, 861 local residents were seen during the seven years between 1995 and 2001 with newly diagnosed lung cancer, giving an average site specific incidence of at least 10.0 per 100,000 population for the state (based on an estimated population for 1998 of 1,234,400). It must be borne in mind that this figure includes only patients seen by the respiratory medical unit in our hospital, and does not include those patients treated by other centres.

Patients operated before assessment by our unit were excluded because most were referred for further treatment after incomplete resection or management of tumour recurrence; therefore, these patients were a selected group likely to have unfavourable outcome. Some patients from other states were referred specifically for surgery because the hospital is a regional referral centre for thoracic surgical services. Thus, the average operative rate calculated for all newly diagnosed lung cancer patients was 5.7%, but when only local residents were considered, so as to avoid overestimation of the operative rate from patients referred from other states solely for surgery, the rate was only 4.8%. The reasons for the low

operative rate were the high proportion of patients who presented with advanced inoperable disease or poor general condition precluding surgery; furthermore, a small number of potentially resectable patients were not operated because they refused surgery.

Data on the operative rate in Malaysia can be gleaned from various studies that have been reported over the years. The first large series of lung cancer patients in Malaysia was reported by University Hospital in 1979[10]. At that time the University Hospital was one of two major centres offering thoracic surgical services in Malaysia. About 12% of the 388 patients seen between 1967 and 1976 were considered operable but of these, more than half (53%) refused operation. Another large series from the Klang Valley reporting on 589 lung cancer patients seen between 1978 and 1986 at the National Tuberculosis Centre, Kuala Lumpur[11], found that the initial treatment was surgery in only 27 patients (4.6%) and of these 4 were found to be unresectable and had thoracotomy only. In the study on cancer admissions to Penang Hospital done in 1995[7], the initial treatment was surgery in 19 out of 193 patients studied (9.8%); two of these patients had only partial resection of the tumour. Data on 61 lung cancer patients obtained during the survey to determine cancer incidence in two districts in Penang in 1997[8], showed that thoracotomy with a view to curative resection was carried out in 7 patients (11.5%), and the tumour was found to be unresectable in one patient. Since this last study was carried out in the community and was not hospital based, it included those treated initially by private hospitals. It is no coincidence that the operative rate was higher than in other series because the patients included had access to thoracic surgical services in both the government-run state hospital as well as in the private sector. All these figures indicate that the resection rate in this country is low (certainly below 10%, and with the true overall figure perhaps even below 5%) and much lower than the resection rates of up to 25% quoted by studies from some European countries and the United States of America[12-14].

In this, as in other studies of lung cancer in Malaysia, the majority of patients had the main risk factor for lung cancer, cigarette smoking. With reference to the histological cell type, this study and earlier local lung cancer series[10,11,15] have shown that the smoking rate is lower in females than in males and the commonest histological type in females, particularly in non-smokers, is adenocarcinoma. Most Western series show that the majority of female lung cancer patients are smokers whereas the opposite is true in Asian populations[16]. There is no data to address this problem in Malaysia although much work has been carried out in other Asian countries, where investigations into non-smoking risk factors such as the use of kerosene stoves, exposure to cooking oil vapours and other factors have so far failed to conclusively identify the aetiological agent[17-19]. More studies will be needed to determine the factors, genetic or environmental, contributing to the development of lung cancer in non-smokers, particularly women, before this mystery can be solved.

It is known that lung cancer survivors have a continued risk of subsequent primary tumours[20], and that surgical treatment of second primary pulmonary neoplasms can be performed in selected patients with acceptable long-term survival[21,22]. In this study, two patients were operated upon for metachronous tumours; one had a second lung cancer after previous surgical treatment for primary pulmonary carcinoma and another had a new non-small cell carcinoma after successful treatment for small cell lung cancer. The first patient had completion pneumonectomy, which offers a second chance for cure to patients with lung cancer[23]. The patient who had previous small cell carcinoma developed an asymptomatic peripheral lesion in the contralateral lung five years after initial presentation. Since there was no preoperative diagnosis he was subjected to wedge resection, which is a useful option in patients with small stage I tumours, although there is a higher recurrence rate than with lobectomy[24,25]. It is accepted that the overall prognosis for patients with small cell carcinoma is poor although survival

may be usefully prolonged with combination chemotherapy, with survival beyond five years occurring in only 3 - 8% of patients[26]. Therefore, it is remarkable that this patient remains well four years after surgery.

There was no operative mortality in this group of patients although lung cancer surgery, particularly pneumonectomy, is known to carry a definite risk for operative mortality and cardiopulmonary complications[24,27]. The lack of operative mortality reflects careful patient selection and surgical management and the relatively high lobectomy rate (62.7%). The only death caused by surgery was related to bronchopleural fistula, a known complication of pneumonectomy with a significant mortality risk[28,29].

As in other studies, the majority of deaths were caused by recurrent disease; concomitant diseases and malignant tumours in other organs are also recognised causes of death in patients followed-up after lung cancer surgery[30]. Although most disease recurrence occurs within the first 3 years, a small proportion may appear late, and in this study, one patient died of her disease 57 months after lobectomy, having had cerebral metastases resected on two occasions. It has been known since the 1920s that lung cancer is the most common primary tumour resulting in brain metastases and resection of solitary brain metastasis can result in long-term survival[31,32]. For survivors of lung cancer surgery, long-term follow-up beyond five years is recommended because the risk of late disease recurrence and second primary malignancies may persist up to 10 years or more[33].

Survival data on lung cancer patients in Malaysia has been difficult to obtain because patients diagnosed and/or treated at referral centres are often referred back to their own states for follow-up in peripheral hospitals. In addition, patients commonly request for discharge from hospital once they are terminally ill, and others do not return for follow-up of their own accord. In this study, 16.4% of patients were lost to follow-up even with concerted efforts to locate them using the network of government Chest Clinics in the states involved. The number of patients involved in this study is small and a proportion had not been followed-up until five years after surgery. Hence, although this study gives estimated figures for survival, accurate data on the outcome of patients surgically treated for lung cancer can only be obtained if a larger study is undertaken over a longer time frame. After surgical resection, long-term survival in patients with non-small cell carcinoma can be up to 70% depending on stage. Encouraging five-year survival rates of up to 67% for stage I disease and up to 55% for stage II disease are reported[5]. In this study, the overall five-year survival figure of 29% closely resembles that found in earlier published studies on survival rates in patients resected for lung cancer[34]. It is well accepted that stage of disease is an important predictor of survival. The five-year survival for patients with stage I disease of 42% is somewhat lower than the figure quoted for other studies[35,36], and it was not possible to discriminate differences in survival in patients with higher stages.

It can be inferred from the low resection rate and survival results in this study that in general, lung cancer patients in Malaysia have a poor outlook for long-term survival. It is likely that fewer than 5% are alive five years after diagnosis since treatment modalities other than surgery provide only a limited chance of cure. This estimate compares poorly with five-year survival rates of up to 14% reported by some European countries[37]. If the survival rate is to improve, efforts must be made to ensure that a higher proportion of lung cancer patients are diagnosed at an early stage and that patients with operable tumours have ready access to potentially curative surgery.

Conclusion

Between 1995 and 2001, out of 852 new lung cancer cases diagnosed among local residents only 4.8% underwent surgery with a view to curative resection. The overall five-year survival for 67 patients operated during this period was 29%;

completeness of resection was an important determinant of survival outcome and stage higher than stage I was an adverse prognostic factor. Given these results, it can be concluded that the current outlook for lung cancer patients remains poor and the major emphasis must clearly be on prevention by means of an aggressive anti-smoking campaign.

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