A Review of Lung Cancer Research in Malaysia

Kan Chan Siang, MD[1], Chan Kok Meng John, FRCS CTh[1,2]

[1]Department of Cardiothoracic Surgery, Sarawak Heart Centre, 94300 Kota Samarahan, Kuching, Sarawak, Malaysia, [2]National Heart and Lung Institute, Imperial College London, U.K.

ABSTRACT

Lung cancer is a major cause of mortality and morbidity in Malaysia and worldwide. This paper reviews all research and publications on lung cancer in Malaysia published between 2000-2015. 89 papers were identified, of which 64 papers were selected and reviewed on the basis of their relevance to the review. The epidemiology, risk factors, cell types, clinical presentation, diagnosis, treatment, outcomes, prevention, and the social impact of lung cancer in the country are reviewed and summarized. The clinical relevance of the studies done in the country are discussed along with recommendations for future research.

KEY WORDS:
Lung cancer; lung carcinoma; lung neoplasm

INTRODUCTION

Lung cancer is the leading cause of cancer related deaths worldwide with 30-40% occurring in developing countries.[1] In 2012, there were more than 1.8 million lung cancer diagnoses worldwide causing 1.6 million deaths. The incidence of lung cancer and consequent death from this disease is anticipated to increase over the next decade due to the high rates of smoking.[2]

This review covers all studies on lung cancer done in Malaysia. A review of research done in the country on lung cancer is important as results reported worldwide, particularly in Western developed countries, may not necessarily be the same in a developing Asian country. A literature search of articles as detailed in the paper *"Bibliography of clinical research in Malaysia: methods and brief results"* covering the years 2000-2015 was undertaken. The PubMed search involved the medical subject heading (MeSH) "lung neoplasm". 89 papers were identified of which 64 were selected for their relevance.[3]

SECTION 1: REVIEW OF THE LITERATURE

EPIDEMIOLOGY

Incidence and prevalence

According to the 2014 World Health Organization report, lung cancer accounted for 19.1 deaths per 100,000 population in Malaysia or 4,088 deaths per year (3.22% of all deaths), the second most common cause of death due to cancer in the country after breast cancer, and the eighth most common cause of death from all causes. In 2014, cancer of the trachea, bronchus and lung accounted for 24.6% of all cancer mortality in males in the country, the most common cancer death, while in females, it accounted for 13% of all cancer deaths, the second most common cancer death after breast cancer. 4,403 lung cancers were diagnosed in the country in 2014, 3,240 in males (the most common cancer diagnosed), and 1,163 in females (the fourth most common cancer diagnosed).

Information on the epidemiology of lung cancer was also obtained from the National Cancer Registry (NCR). From its last published report in 2007, lung cancer was the third most common cancer in the country, the second most common cancer in males and the 4th most common in females.[4]

Age

The mean age at which lung cancer is diagnosed in Malaysia is about 60 years with a peak age of diagnosis in the 7th decade. The incidence of diagnosed lung cancer in Malaysian patients aged less than 40 years is relatively low at approximately 6.2%.[5] Younger patients were more likely than older patients to have adenocarcinoma with poorer World Health Organization (WHO) performance status.[6] Late stage presentation and therefore inoperability is very common in the younger age groups as they usually remain asymptomatic or ignore symptoms longer. In one study, all patients less than 40 years old with non small cell lung cancer (NSCLC) presented with either stage IIIb or metastatic disease, compared to 77% of older patients ($p<0.001$).[6]

Ethnicity

There was an over representation of Chinese among patients with lung cancer. The ethnic distribution was similar for the younger and older groups of lung cancer patients. (Chinese 71%, Malay 19%, Indian 9%, others 1%, $p<0.001$).[5,6] The age-standardized incidence of lung cancer amongst the Chinese is two-fold that of non-Chinese. The precise reason for this observation is uncertain but smoking volume and a genetic predisposition to cancer may be partly responsible.[7]

Primary lung cancer

Historically, squamous cell carcinoma was the commonest lung cancer cell type. However, over the years, adenocarcinoma has now replaced squamous cell carcinoma as the commonest lung cancer cell type (Table I). The reason for this shift of cell type is unknown. Possible reasons include diagnostic advances, switch of smoking from high-tar to low-tar filtered cigarettes and changes in smoking patterns.[5]

An eight-year retrospective study done at University of Malaya Medical Center revealed adenocarcinoma subtype as the most common cell type in all age groups with a

Corresponding Author: KMJohnChan@yahoo.com

Table I: Histological Subtypes of lung cancer in different institution in Malaysia

Author (ref)	Institutions	Sample Size (n)	Adenocarcinoma (%)	Squamous Cell (%)	Large Cell (%)	Poor or no Differentiation (%)	Small Cell (%)	Other (%)
C-K Liam *et al*	UMMC (1991-1999)	580	252 (43.4)	165 (28.4)	19 (3.3)	70 (12.1)	69 (11.9)	5 (0.9)
S.H How *et al*	UMMC (Sept 1994 – Aug 2002)	503	206 (40.9)	153 (30.4)	14 (2.8)	65 (12.9)	65 (12.9)	-
A R M Fauzi *et al*	Hospital Sultanah Aminah (Jan 1997 – Dec 1999)	236	66 (28.0)	73 (30.9)	19 (8.1)	28 (11.9)	45 (19.0)	5 (2.1)
Catherine MM *et al*	UMMC (Mac 1998 – Oct 1999)	50	19 (38.0)	17 (34.0)	-	-	5 (10.0)	7 (14.0)
L-C Koh *et al*	Seremban Hospital & Nilai Cancer Institute (Jan 1996 – Apr 2004)	119	35 (29.4)	55 (46.2)	8 (6.7)	-	-	21 (17.6)
S.H How *et al*	UMMC (May 2001 – Jan 2002)	24	15 (62.5)	4 (16.7)	3 (12.5)		2 (8.3)	-
T.H. Ng *et al*	HTAA§ (Nov 2007 – Nov 2009)	95	88 (92.6)				4 (4.2)	3 (3.2)
S H How *et al*	HTAA (Aug 2007 – Aug 2010)	149	78 (52.3)	28 (18.8)	1 (0.7)	21 (14.1)	6 (4.0)	6 (4.0)
C-K Liam *et al*	UMMC & HTAA (Aug 2010 – Dec 2011)	151	131 (86.8)	11 (7.3)	1 (0.7)	-	-	1 (0.7)
N.S.Y Tiffany *et al*	Sime Darby Medical Center (Jan 2011 – Apr 2012)	484	467 (96.5)	12 (2.5)	3 (0.6)	-	-	2 (0.4)

§ Hospital TengkuAmpuanAfzan, Kuantan, Pahang

Table II: Stage at presentation of lung cancer in different institutions in Malaysia

Author (ref)	Institutions	Sample Size (n)	Stage Ia (%)	Stage Ib (%)	Stage IIa (%)	Stage IIb (%)	Stage IIIa (%)	Stage IIIb (%)	Stage IV (%)
C-K Liam *et al*	UMMC (1991-1999)	510	16 (31.3)	35 (68.6)	2 (0.4)	15 (2.9)	41 (8.0)	186 (36.5)	215 (42.2)
L.N Hooi *et al*	Penang GH (1995 – 2001)	67	35 (52.2)		16 (23.9)		16 (23.9)		-
L-C Koh *et al*	Seremban Hospital & Nilai Cancer Institute (Jan 1996 – Apr 2004)	119	8 (6.7)				111 (93.3)		-
Bassam Abd Rasool Hassan *et al*	Penang General Hospital (2003 – 2009)	118	11 (6.9)		25 (21.2)		47 (39.8)		29 (24.6)
T.H. Ng *et al*	HTAA (Nov 2007 – Nov 2009)	95	-	-	-	-	3 (3.2)	50 (51.6)	43 (45.2)
S H How *et al*	HTAA (Aug 2007 – Aug 2010)	149	-	-	-	-	5 (3.4)	76 (51%)	68 (45.6)
C-K Liam *et al*	UMMC & HTAA (Aug 2010 – Dec 2011)	151	4 (2.6)	4 (2.6)	2 (1.3)	2 (1.3)	7 (4.6)	9 (6.0)	123 (81.5)

comparatively higher incidence in the younger patient less than 40 years old 24/36 (77.7%) vs 228/544 (41.9%); p<0.001; younger patients were less likely to develop squamous cell carcinoma (p = 0.047).[6] Another study done by the same group revealed that the percentage of patients diagnosed with adenocarcinoma increased from 25% during the period 1967–1976 to 43% during the period 1991–1999 with a corresponding drop in the incidence of large cell carcinoma from 12% to 3%. There was no significant shift in the incidence of squamous cell carcinoma.[5] Small cell lung cancer (SCLC) accounted for about 12% of all lung cancer cases. In recent years, the incidence of SCLC seems to be on the decline. Two-thirds of cases of SCLC are diagnosed with advanced stage disease.[5]

Several rare lung tumours were reported in Malaysia. Clear cell tumours of the lung are rare type of primary lung neoplasm. Shiran and colleague reported a case of clear cell "sugar" tumour of the lung. Although the majority of clear cell tumours follow a benign course, there are reported cases of malignant features such as lymphovascular invasion, necrosis and pleomorphism.[8] Primitive Neuroectodermal Tumours (PNETs), a type of aggressive tumour arising from mutation of the pluripotent neural crest cells, typically occur in the bone and soft tissues and rarely present as an organ-based neoplasm. Primary lung PNETs may rarely occur but involvement of the heart as the site of metastasis is even rarer. Harris, *et al* reported a rare case of pulmonary PNETs with pericardial involvement.[9]

Multiple primary malignancies involving the lung are extremely rare. Iqbal, et al published a case report describing a patient with three simultaneous primary cancers: in the larynx (well differentiated squamous cell carcinoma), lung (non-small cell carcinoma) and thyroid (sclerosing papillary carcinoma).[10]

Secondary lung cancer

The common primary sites of metastasis to the lung are from the colon, breast and bone. In one study, the median survival for patients with lung metastasis from primary breast cancer was found to be 24 months.[11] A retrospective review of medical records in 31 patients diagnosed with giant cell tumour of the bone in University Malaya reported that 4 patients developed pulmonary metastasis.[12] A similar study conducted by Faisham, et al revealed that 6 out of 24 patients with giant cell tumour of the bone had pulmonary metastasis. 2 patients with resectable disease were treated with surgical resection, 2 were treated with chemotherapy and the disease remained non progressive, while the remaining 2 patients refused chemotherapy (in which one of them succumbed to the disease due to massive hemoptysis). The study concluded that aggressive treatment of pulmonary metastases in patients with aggressive giant cell tumour of the bone is mandatory for overall prognosis.[13]

Tumour size reflects tumour burden and/or the extent of disease. A retrospective data review conducted at Universiti Sains Malaysia studied the association between tumour volume and the occurrence of lung metastasis in patients with osteosarcoma. 47% of the 70 patients with osteosarcoma studied had evidence of lung metastasis. Tumour volume was directly associated with occurrence of lung metastasis (p=0.048). The proportion having lung metastasis when the primary tumour volume exceeded 371 cm^2 was 69% compared to 34% in smaller tumours. An increase in tumour volume represented an increase in the probability of lung metastasis with a positive predictive value of 69%.[14]

PUBLIC KNOWLEDGE AND AWARENESS

A cross-sectional study on lung cancer awareness was conducted by Al-Naggar, *et al* in 2012, involving 150 secondary school teachers randomly chosen from three different secondary schools in the Kudat district, Sabah. The overall knowledge on lung cancer was found to be low.[51] More than half the secondary school male teachers (57%) thought that only males are affected by lung cancer, and 71% thought that lung cancer can be transmitted from person to person.[51] Knowledge on the risk factor for lung cancer was better with 91% of participants aware that cigarette smoking is the main risk factors for lung cancer.[51] Similar results were observed in another similar study involving 213 university students, which revealed that 100% of the participants were aware that smoking is the main risk factor for lung cancer, and 90% were aware of passive smoking as a risk factor.[52]

PREVENTION

According to the National Health and Morbidity Survey (III) conducted in 2006, the prevalence of smokers in Malaysia was 27%. However, it is noteworthy that a significant proportion of people who develop lung cancer in Malaysia are life-long non-smokers.[48] The percentage of male patients with lung cancer who were smokers increased significantly from 86% in 1967–1976 to 92% in 1991-1999.[5] The percentage of people with lung cancer who had never smoked was higher among the younger patients (58% vs 19%, p<0.001).[6] This is in contrary to the Western populations, in which younger lung cancer patients are more likely to have been smokers. However, data regarding the intensity of smoking was not available in 17% of the patients studied.[6] Another single institution prospective study done by Catherine *et al*, support the fact that smoking was more common in older patients (60 years and above) (p=0.002) and there were significantly more smokers in the older patients who had carcinoma. The subanalysis of the same study also revealed that the older age group smokers averaged 67.7 (range 20–120) pack-years, while the younger smokers averaged 29.3 (range 10–92) pack-years.[15] Adenocarcinoma and squamous cell carcinoma were both significantly less strongly associated with cigarette smoking in the younger than in the older patients. (p<0.001 and p=0.027 respectively). A high percentage of non-smoking female patients with adenocarcinoma and a younger age of diagnosis of adenocarcinoma suggest that risk factors other than active smoking may be involved in carcinogenesis in these patients.[49]

CLINICAL PRESENTATION

Clinical symptoms suggestive of lung cancer include cough, hemoptysis, weight loss and chest pain. A cohort study of 160 patients done at a University Hospital showed that the main cause of haemoptysis in older patients (60 years old and above) was bronchogenic carcinoma (49%).[15] The majority of bronchogenic carcinoma in this study was located in the proximal airways.[15]

Pleural effusions were found to be a common sign of lung cancer. In a retrospective study of 189 patients with mean age 51.2 years, malignancy ranked as the second most common cause of exudative pleural effusions (30%) after tuberculosis. 95% of malignant pleural effusions were due to primary lung cancer.[16] Another prospective study done in the same institution 3 years later by How, *et al,* revealed that neoplastic pleural effusions was more common than that due to tuberculosis (34% versus 23%).[17] The histological diagnosis of malignant pleural effusion was made by bronchoscopic biopsy in 66% of cases, by pleural fluid cytology in 59%, and by pleural biopsy in 50%. The combination of these three procedures significantly increased the diagnostic yield to 96%.[17] Malignant effusions were found to be more frequent among patients older than 50 years (75%) and were likely to be large at presentation.[16]

Clinical symptoms and signs due to Cushing's disease may be associated with pulmonary carcinoid tumour with ectopic ACTH production and its precursors. Wong, *et al* reported a rare case of ectopic ACTH-producing atypical carcinoid associated with a non-functioning pituitary macroadenoma, which is strongly associated with multiple endocrine neoplasia (MEN) type 1.[18] In a rare condition known as Masquerade Syndrome, there is a presence of an ocular

involvement of lung cancer. Pathology involves exudative type retinal detachment which is manifested as sudden and progressive loss of visual field and reduction in visual acuity. Kalthum, *et al* reported a rare case of Masquerade Syndrome secondary to poorly differentiated adenocarcinoma of the lung in a 37 year-old gentleman.[19]

MANAGEMENT

Diagnosis

In Malaysia, most lung cancer cases are diagnosed late with either locally advanced disease or distant metastasis (Table II). 75-88% of lung cancer cases are diagnosed in stage III or IV; these patients can only be offered palliative therapy.[5] Only about 12% of cases present early enough to be offered curative surgical resection.[4]

Loh, *et al,* studied the time to diagnosis of lung cancer from clinical presentation. Significant delay is present in the diagnosis of lung cancer with the median patient-delay being 60 days (range 30–150 days) and the median doctor-delay being 33 days (range 18–72 days).20 Reasons for the delay in diagnosis of lung cancer include the failure to recognize symptoms and patient beliefs in traditional complementary medicine.[20]

Following an abnormal CXR, bronchoscopy was diagnostic of lung cancer in 54% of older patients versus 33% in younger patients (p=0.005). Bronchoscopy alone or combined with CT of the thorax achieved the highest yield of diagnosis regardless of the age group and was significantly more diagnostic in older patients (60 years and above).[15] Liam, *et al* carried out a retrospective analysis on 503 patients with confirmed lung cancer to determine if the diagnostic yield of flexible bronchoscopy was dependent on tumour location. Bronchoscopy sampling procedures involved several techniques including bronchial washing (BW), bronchial brushing (BB), broncho-alveolar lavage (BAL), transbronchial biopsy (TBB) and endobronchial biopsy (EBB). BW followed by EBB and then BB were performed sequentially for patients with bronchoscopically visible tumours. For patients with tumours which were not visible by bronchoscopy, BAL was performed first, then BB, followed by TBB. EBB was reported to be less likely to be diagnostic in patients with tumours in the middle or lingular lobe bronchi. The diagnostic yield of all the other sampling techniques were not influenced by the location of the tumours or tumour visibility by bronchoscopy.[21] Overall, the diagnostic yield of bronchoscopy sampling in this study was 71%.[21] Lung cancer lesions were most frequently located in the upper lobe (47.5%). Lesions in the upper lobes are often technically difficult to access because of the acute angulation of the bronchoscope needed to reach them. Squamous cell carcinoma and small cell lung carcinoma were more commonly associated with bronchoscopically visible tumours compared to the other cell types.[21] In another retrospective study of all bronchoscopy records for investigation of lung cancer at Hospital Sultanah Aminah, Johor Bahru, the addition of cytological specimens from BB and BW to EBB significantly increased the diagnostic yield by 17% (22/59 to 32/59) when no mass lesion was visible bronchoscopically. When endobrochial lesions were visible, the addition of cytology specimens to endobronchial biopsy produced only a small insignificant increase in the positive result for cancer and was not cost effective.[22] The authors concluded that routine cytological specimen collection by BB and BW in cases of visible endobronchial lesions during bronchoscopy had low additional value and should be discouraged.

Transbronchial needle aspiration (TNBA) is another valuable tool to diagnose lesions in the mediastinum and lung without subjecting the patient to surgical biopsy.[21] This technique is used to sample either suspected lesions or enlarged paratracheal and subcarinal lymph nodes identified by CT scanning. A retrospective review of patients undergoing TNBA at Hospital Tengku Ampuan Afzan reported a success rate of 60% in yielding histological diagnosis.[23] TBNA is particularly useful in establishing histological diagnosis in patients with peripheral lung lesions, mediastinal lymphadenopathy (for staging or diagnosis), and drainage of mediastinal cyst or abscess.[23] However, the technique is operator-dependent, and also dependent on other factors to achieve high yield, including type of needle used, technique, CT evaluation, tissue preparation and interpretation, as well as nodal site and size.[23] Conventional TNBA is gradually being superseded by endobrochial or endoscopic ultrasound guided TNBA, which was reported to give a diagnostic yield as high as 90%, and has been shown to reduce the need for surgical staging.[24]

A case study done by Gita, *et al*, reported a successful diagnosis of a colloid carcinoma or mucinous carcinoma of the lung (a subtype of peripheral lung adenocarcinoma) with CT-guided transthoracic-FNA. Cytological diagnosis of colloid carcinoma is extremely difficult owing to the paucity of tumour cells relative to the amount of mucin present.[25]

Sanchithanandan, *et al* reported a rare case of two synchronous primary non-small cell lung cancers (NSCLC) diagnosed post-operatively following pathological examination of the resected lobe using immunohistochemistry markers (IHC); TTF-1 and the epithelial marker CK-7 are highly sensitive and specific for a primary NSCLC and non-reactive for metastatic lung adenocarcinomas.[26]

Biomarkers

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein encoded by a gene located at the short arm of chromosome 7; it functions to stimulate a wide range of cellular functions such as cell proliferation, differentiation, migration and survival. Specific mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) are associated with improved responses in NSCLC patients receiving EGFR-targeting tyrosine kinase inhibitors (TKIs).

In Malaysian patients with NSCLC, the EGFR mutation rate was found to be similar to that in other Asian populations but higher compared to Western populations.[27] In a study conducted by Tiffany, *et al,* all of the EGFR mutations were found in adenocarcinoma tumours except one that was in squamous cell carcinoma. The mutation rate was 46% (221/484) and was more frequent in women (61%, p<0.001).[28]

Similar results were observed in a retrospective study done on patients from 44 private and public hospitals between 2009 and 2011 where 40% of tumours from 812 patients with advanced adenocarcinoma were EGFR mutation positive.[29] In a study by Liam, *et al,* EGFR mutations were significantly more frequent among females (53% vs 28%, p<0.001) and in non-smokers (55% vs 21%, p<0.001). Non-smoking status was the only independent predictor of EGFR mutation positivity (OR: 3.82, p=0.002). These observations may suggest some association with preferential occurrence of EGFR mutations in non-smoking women.29 Most EFGR mutations involved deletions in exon 19 and 21 (24% and 19% respectively) and were significantly more common in females (p<0.001). Exon 19 deletions in tumours tended to occur in younger patients (mean age 57.4 years) compared to exon 21 deletions (mean age 65.1 years), a mean difference of 7.8 years.[27] Complex mutations were also observed, where 8 tumours carried 2 mutations and 1 tumour carried 3 mutations.

Direct sequencing is considered the "gold standard" in nucleic acids studies, but its use was limited due to low sensitivity, high cost and long turnaround time. High resolution melting (HRM) and Scorpion amplification refractory mutation system (ARMS) are emerging techniques for rapid detection of DNA sequence variation. Both methods were found to be useful for detection of EGFR mutations; all mutations identified by ARMS in one study were correctly matched in HRM analysis.[28] The detection of EGFR mutation-positive tumours by Scorpion ARMS was comparable to that by direct sequencing in one study (170 of 396 tumours or 42.9% compared to 151 of 416 tumours or 36.3%).[29]

TREATMENT AND OUTCOMES

Surgical resection

The most effective option for treatment of lung cancer is surgical resection, when feasible. However, most patients with lung cancer do not undergo surgical resection; in a single institution study, only 8% of patients with NSCLC underwent surgical resection. The main reason for the low operative rate was the high proportion of patients who presented with advanced inoperable disease.[31] Following surgical resection, the 5-year survival was 29% and the median survival was 27 months (Table III).[31] Completeness of resection was the main determinant of survival outcomes. Complete resection had significantly better median survival than those in whom the tumour could not be totally removed (31 months vs 10 months). The overall five-year survival rate was 34% in the group with complete resection, whereas there was no patient with incomplete resection who survived to 5 years in this study.[31]

Chemotherapy and Radiotherapy

The majority of patients are diagnosed at an advanced or metastatic stage of disease in which case chemotherapy and/or concurrent administration of chemotherapy and radiation is the most beneficial form of treatment. Current chemotherapeutic drugs kill cancer cells mainly by inducing apoptosis. In a retrospective observational study on 814 cases of lung cancer between 2003 and 2009, treatment response (reduction in the size of the primary lesion) to chemotherapy was observed after the 3rd cycle of treatment with gemcitabine plus cisplatin, and the 4th or 5th cycle for etoposide plus cisplatin. Reduction in number of metastasis and/or disappearance of cancer invasion was noticeable after the 5th cycle of treatment with gemcitabine plus cisplatin and the 6th cycle of treatment with etoposide plus cisplatin.[32] In another study on 33 patients done by Leow, *et al,* at the same institution, patients who received gemcitabine-carboplatin combination chemotherapy over a 2.5 years period had a 27% overall response rate. The median survival rate among patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 was 11 months, as compared to 4 months in patients with ECOG performance status of 2, with the difference being statistically significant.[33] The results of this study also suggests that three cycles of cytotoxic chemotherapy may suffice as only 14% of all patients (2/14) undergoing the full course of six cycles showed further tumour regression. However, the number of patients in this study was very small and may not represent the actual response rate. Future studies involving larger numbers of patients should compare the efficacy of three-cycle and six-cycle regimens of carboplatin-gemtacibine combination chemotherapy.[33]

In another study, data from two local institutions, Seremban General Hospital and Nilai Cancer Institute, were collected. The median survival of NSCLC patients who accepted cancer-specific therapy i.e. surgery, chemotherapy or radiotherapy, was significantly longer compared to those who opted out of cancer-specific treatment (8.6 months versus 2.2 months, p<0.001). However, despite the small significant survival benefit in accepting cancer-specific treatment, the overall prognosis for patients with NSCLC remains poor.[34] How, *et al* reported an overall median survival of 18 weeks in 149 patients with histologically confirmed lung cancer in their study. This study was conducted in a single referral hospital of the state of Pahang from 2007 to 2010. They also revealed that among NSCLC patients on treatment, 1- and 2-year survival rates were only 27% and 15% respectively. The median survival of patients who received treatment was 35 weeks as compared to 16 weeks for those who did not (p<0.001).[35]

Hypercalcemia can occur in cancer patients with and without bone metastasis. Chemotherapy lowered serum calcium levels significantly in lung cancer patients who were initially hypercalcemic at diagnosis, in particular with chemotherapy regimen: Gemcitabine + Cisplatin (after the 3rd cycle of treatment) in lung cancer, probably by reducing parathyroid hormone-related protein (p=0.003). [32]

Biologically Targeted Therapy

Recently, oncogenic driver mutations have been detected in NSCLC and tumours with mutations in oncogenes such as epidermal growth factor receptor (EGFR), ALK, ROS1 and others can be treated with appropriate oncogene-driven targeted therapy with improved outcomes. Tumours with EGFR deletions in exons 19 and 21 have improved response to treatment with EGFR-targeted tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib.

EFGR-TKIs have been approved as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. Studies have shown that when given alone, oral gefitinib showed significant durable anti-tumour activity in a significant proportion of Malaysian patients with locally advanced and metastatic primary adenocarcinoma of the lung.[36] The relatively high prevalence of epidermal growth factor receptor (EGFR) mutations predicting altered biology and more favourable response to EGFR tyrosine kinase inhibitors may explain the better survival rate of lung cancer patients in Asians compared to Caucasians.[29]

A retrospective study done by the Liam and colleagues involving a total of 23 patients receiving gefitinib monotherapy reported disease control in 14 patients (61%); of these, 11 patients (48%) showed at least 30% reduction in tumour size of the primary and/or metastatic tumours (partial response), while 3 patients (13%) had stable disease (absence of either response or progressive disease for a minimum of 8 weeks). The response rate was significantly higher in those who had never smoked (10 of 15 or 67%) compared with that of smokers (1 of 8 or 13%) (p=0.027). The median time to symptom improvement was 1.5 weeks (range 0.5–6). [37] Adverse effects associated with gefitinib treatment were generally mild and consisted of grade 1 or 2 skin toxicity, which included dry skin, acne, pruritic rash, loss of finger nails and toe nails.[36] Another study done by the same authors several years later on advanced lung adenocarcinoma patients with unknown EGFR mutation status also similarly reported that the response rate to gefitinib was higher in women and never-smokers compared to men and ever-smokers.[37] They also reported that patients with good WHO performance status 1 or 2 had a response rate of 61%, whereas none of the patients with WHO performance status 3 or 4 responded to treatment given.[30]

The phase III, randomized, open-label ENSURE study evaluated first-line erlotinib versus gemcitabine/cisplatin in patients from China, Malaysia and the Philippines with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). In this study, it was reported that the median progression-free survival was 11 months in the erlotinib group versus 5.5 months in the gemcitabine/cisplatin group, regardless of EGFR tumour mutation type (HR 0.34, 95% CI 0.22-0.51, p<0.0001), and objective response rate was 62.7% for erlotinib and 33.6% for gemcitabine/cisplatin.[39] Treatment-related serious adverse events occurred in 2.7% patients receiving first-line erlotinib compared to 10.6% of patients with cytotoxic chemotherapy (gemcitabine/cisplatin).[38]

The use of EGFR-TKIs is associated with unique dermatologic side effects. Ong, *et al,* reported two cases of NSCLC developing atypical (papulo-pustular) eruptions shortly after initiation of EGFR-TKIs. Both patients received oral erlotinib and gefitinib following radiotherapy/chemotherapy. They developed acneiform over the face and upper trunk (after 10 days and 2 weeks commencement of erlotinib and gefitinib respectively). The cutaneous side effects of both patients resolved with oral doxycycline and topical benzoyl peroxide.[39]

Lung carcinoma in pregnancy is rare especially in never smokers. Treatment of advanced lung cancer in pregnancy is challenging because one has to weigh the benefits and risks of treatment, both to the mother and the fetus. Compared to cytotoxic chemotherapy, EFGR tyrosine kinase inhibitors treatment is more effective, targeted and associated with fewer side effects. Lee, *et al*, reported a successful pregnancy in a patient diagnosed with stage IV lung adenocarcinoma with multiple lung secondaries and lymphangitis carcinomatosis, who showed both clinical and radiological responses to oral EGFR-tyrosine kinase inhibitor (Erlotinib and Gefitinib).[40]

Traditional & Complementary Medicine

A study conducted by Lee, *et al*, showed the cytotoxic potential of the Phyllanthus plant in inhibiting A549 (lung carcinoma) and MCF-7 (breast carcinoma) cell growth by effectively reducing invasion, migration, and adhesion of the cells in a time- and dose-dependent manner (p<0.05). The extract of this plant had lower toxicity in normal cells with the cell viability percentage remaining above 50%. The authors concluded that the extract of various species of *Phyllanthus* was shown to be capable of inducing apoptosis in conjunction with its anti-metastatic action due to the presence of polyphenol compounds in the plant. However, the exact bioactive compounds in *Phyllanthus* exerting the anti-metastasis have not yet been identified.[41]

Distant metastases

The skeletal system is the most commonly affected organ in lung metastasis. A study done at University Malaya showed that 21% of primary lung cancer result in bone metastasis with male predominance observed (n=21, 65.6%). The survival of patients with metastatic disease is generally dependent on the type of primary tumour. Patients with primary lung cancer with bone metastases had the shortest mean survival time (16.0 ±1.7 months) as compared to other primary cancer. This study also showed a marginally higher incidence of long bone metastasis than axial skeleton metastasis.[42] The treatment of bone metastasis is usually palliative and aims to adequately control pain, and to anticipate or stabilize pathological fracture.[43]

It is sometimes challenging to distinguish spinal tuberculosis from metastatic lung adenocarcinoma. Zamzuri, *et al* reported a rare case of metastatic adenocarcinoma of the lung to the spine with T7 vertebra body collapse which was thought to be spinal tuberculosis due to a positive Mantoux test and elevated erythrocyte sedimentation rate (ESR). However, the patient did not respond to anti-tuberculosis drugs. CT thorax subsequently revealed a peripherally located right lower lobe lesion which was an adenocarcinoma in histopathological examination.[44]

Primary lung cancers also have tendencies to metastasize to the brain with an estimated incidence of around 20–40%. Patients with brain metastases from an underlying lung primary seem to fare less well in terms of overall survival compared with other primary tumour sites such as breast or colorectal cancer. A retrospective study by Tang, et al on 125 patients with confirmed non-small cell lung carcinoma and brain metastases reported the overall median survival of 3.4 months (95% CI: 1.7–5.1).[45] Median survival of patients with

multiple metastases receiving whole brain radiotherapy (WBRT) was 1.5 months, 1-3 metastases receiving WBRT was 3.6 months and 1-3 metastases receiving surgery or stereostatic radiosurgery/stereostatic radiotherapy was prolonged to 8.9 months (2.5 fold increase for those received on WBRT).[45] ECOG score, presence of seizure, treatment modalities (receiving either SRS/SRT±WBRT or WBRT alone) as well as receiving post-therapy systemic treatment were significant factors affecting prognosis on both univariate and multivariate analysis.[45]

A case report revealed a rare complication of metastatic lung cancer leading to intussusception of the bowel. The patient presented with upper gastrointestinal bleeding suggestive of duodenal ulcer; subsequent CT thorax/abdomen showed a mass at the head of pancreas and lesion at the left lung. The histopathological examination of both lesions showed similar histology, findings were suggestive of small cell carcinoma of the lung with metastasis to the small bowel and pancreas, with an incidental finding of intussusception at the jejunum intra-operatively.[46]

Catherine, *et al* published a case report describing two patients with metastatic lung cancer diagnosed during pregnancy. Both ladies were diagnosed to have lung carcinoma (squamous cell carcinoma and adenocarcinoma) at 31 and 35 weeks respectively. They managed to deliver healthy babies with adequate birth weight prematurely. However, due to the advanced stage of the disease, both of them did not survive. In both cases, palliative chemotherapy was declined because of the mothers' concern for their fetus. There is no published data on optimal chemotherapy and radiotherapy strategies for lung cancer patients who are pregnant.[47]

PATIENT COMPLIANCE

Patients who fail to attend follow-up may after initial investigations result in delays in the appropriate treatment which affect outcomes. A prospective study was done by Ng, *et al* involving 95 patients aimed at determining the prevalence, patient characteristics and reasons for defaulting follow-up and treatment among patients with lung cancer. The prevalence of patients defaulting treatment and follow-up was 21% (20/95), two thirds of them were persistent defaulters (defined as defaulting two consecutive appointments), while the other one third were intermittent defaulters (defined as defaulting at least one follow-up or planned treatment at a given appointment date).[53] Most of the defaulters gave the reason of being "too ill" to come (39%) and logistic difficulties. There was no correlation between patient education, income, Eastern Cooperation Oncology Group (ECOG) performance status, stage of the disease, race or gender. However, education level of their children was found to be significantly associated with defaulter rate.[53] In another study, Hooi, *et al,* reported 16% of patients were lost to follow-up even with concerted efforts to locate them. Patients commonly requested for discharge from hospital once they are terminally ill and did not return for follow-up.[31]

SOCIAL IMPACT

Debilitating impact and traumatic effect of the diagnosis of cancer on the quality of life (QOL) of the afflicted individuals, their spouses and their families is inevitable. A cross-sectional study was performed recruiting 95 adolescent children from 50 families aged 13–18 years to parents who were suffering from colorectal, breast or lung cancer (the three most common cancers in Malaysia). Adolescents with parental cancer had significantly lower scores in emotional functioning ($p<0.05$). Male adolescents had significantly higher quality of life overall and in physical functioning compared to female adolescents. Furthermore, monthly household incomes (household incomes of less vs more than RM 5,000) had significant differences in emotional QOL and school QOL.[54]

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

This review of the research studies done in Malaysia contributes towards our overall knowledge, understanding and management of patients with lung cancer in the country. Lung cancer has been identified as an important cause of mortality and morbidity in the country;[3,7] adequate resources must be allocated towards better primary prevention, earlier and more effective diagnosis, better treatment and palliation, and better support for patients and their families.

Smoking has been shown to be the main risk factor for lung cancer.[5,6,48] Knowledge of this amongst the general public is good but there are still significant numbers of smokers in the country. Efforts are needed to discourage smoking amongst the population through both financial disincentives and restrictions on smoking in public places. Greater efforts must be made to increase the numbers and availability of smoking cessation clinics in the country, and every encouragement and incentive must be given to smokers to attend these clinics.

Public awareness of the symptoms, signs and nature of lung cancer was found to be poor.[52,53] This has been identified as a cause of late presentation of the disease at an inoperable stage in many patients, and also a delay in diagnosis.[6] Greater efforts must be made towards educating the public on the symptoms and signs of lung cancer and the need to seek early medical attention at a stage when the disease is still curable. In addition, protocols must be in place for general practitioners and physicians for early referral for imaging and other diagnostic procedures in patients with symptoms and signs suggestive of lung cancer.

Studies using bronchoscopy to obtain tissue diagnosis reported good diagnostic yields using bronchial washing (BW), bronchial brushing (BB), broncho-alveolar lavage (BAL), transbronchial biopsy (TBB) and endobronchial biopsy (EBB).[21,22] Chest physicians must become familiar with these techniques with or without endobronchial ultrasound (EBUS) guidance and make this the standard of care.

Adenocarcinoma has been identified as the most common subtype of lung cancer in Malaysia (Table I).[5,6] Studies have

identified a large proportion of adenocarcinoma patients in Malaysia with mutations in the epidermal growth factor receptors (EGFR), similar to other Asian countries but much higher rates compared to Western countries.[28,29] These patients demonstrate increased responsiveness to treatment with EGFR-targeted tyrosine kinase inhibitors, with improved survival being reported.[36,38] Testing for EGFR mutations in lung adenocarcinoma patients is therefore mandatory and all histopathology laboratories in the country receiving lung tumour biopsies and specimens must make this their routine practice and be adequately trained and equipped for this. In addition, EGFR-targeted tyrosine kinase inhibitor therapy must be readily available to chest physicians and oncologists.

Several small studies using chemo and radiotherapy in advanced lung cancer were reported.[32,33] Insights were offered into the optimal choice, regime and duration of chemotherapy agents. However, these observations need to be confirmed in larger studies.

A study on the social impact of lung cancer on the patient's family and carers reminds us that support for the patient and family is needed beyond the medical treatment given.[54] This is too often forgotten and adequate training and provision of these services are needed in the country.

SECTION 3: FUTURE RESEARCH DIRECTION

An important observation of this review is that survival rates from lung cancer is poor mainly due to the advanced stage at which the disease is diagnosed in most patients precluding curative surgical resection (Tables I and III).[4,5] Greater efforts must therefore be put towards earlier detection of the diseases. In addition to better education of the public on the symptoms and signs of lung cancer, screening of at risk individuals for lung cancer must be considered. The benefits of screening for lung cancer in at risk individuals, i.e. current or ex-smokers, has been demonstrated in a large randomized controlled trial in the United States, the National Lung Cancer Trial, where a 20% survival advantage was reported in the individuals screened by low dose CT scan.[55] However, it is unclear if such a screening programme is feasible in Malaysia where most CT scan departments are already working to capacity with existing clinical demand. Moreover, the incidence of false positive nodule detection in this country may be significantly higher given the higher incidence of tuberculosis in this country.[16,17] A pilot feasibility study on lung cancer screening in this country is therefore necessary before we embark on a nationwide lung cancer screening programme. It is now possible to detect tumour DNA in circulating blood. Research is needed to determine if it may be possible to use this as as a screening tool for lung cancer.

There is also an absence of comprehensive nationwide data on lung cancer diagnosis by disease stage, the treatments given, and the long term outcomes. The studies reported in this review in most cases covered individual centers. The National Cancer Registry has unfortunately not reported in recent years and also does not have comprehensive data on long term survival according to treatment modalities. There is a need for a comprehensive national database on lung cancer to better understand the true burden of disease, appropriateness of management and treatment of the condition, and the long term outcomes. To this end, the recent launch of the National Thoracic and Cardiovascular Surgical Database (NCTSD) Registry is timely.

The high prevalence of exon 19 and 21 EGFR mutations in lung adenocarcinoma tumours amongst Malaysian patients is promising due to its improved responsiveness to EGFR inhibitors. However, acquired resistance to EGFR inhibitors develops after a period of treatment and research is needed to better understand and overcome this.

More recent developments in lung cancer therapy include the use of immunotherapy in advanced disease with the potential for improved survival. Genomic profiling and biomarker analysis is likely to identify tumours which would respond to immunotherapy. Studies on this are needed in the country as our population may differ from that in western countries where most of these research is currently being done.

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