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Adenocarcinoma of the lung in Chinese patients: a revisit and some perspectives from the literature

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Abstract

Aim—To establish an updated clinical profile of adenocarcinoma of the lung.

Design—Retrospective review of clinical charts, chest radiography, and computed tomography of consecutive patients who attended Queen Mary Hospital in Hong Kong between June 1995 and December 1997.

Results—In the 115 patients studied, 13% were <40 years of age (33.3% ever smokers). Haemoptysis is more common among patients with early disease, while finger clubbing was detected more commonly among smokers and ex-smokers. Most (98.3%) patients had abnormal chest radiology including presence of mass lesion, pleural effusion, collapse/consolidation, and effusion. Patients with adenocarcinoma were significantly more likely to be younger, female, in advanced disease (stage IIIB and IV), non-smoker, and symptomatic on presentation ($p<0.05$) than those with squamous cell lung cancer ($n=128$).

Conclusion—The clinical profile of Chinese adenocarcinoma patients should help clinicians in the diagnosis and management of these patients.

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Keywords: lung cancer; adenocarcinoma; clinical profiles

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this disease with particular emphasis on presentation, symptomatology, and clinical staging, and compare these characteristics with patients with squamous cell lung carcinoma. Our experience with this series of patients should help clinicians have further insights into the clinical characteristics of those with adenocarcinoma of the lung.

Methods

SUBJECTS

The clinical charts, chest radiographs, and (whenever available) thoracic computed tomography of all patients with a final diagnosis of adenocarcinoma of the lung admitted to the Department of Medicine of the University of Hong Kong, between June 1995 and December 1997, were reviewed. Our institution is the largest teaching hospital in Hong Kong SAR and is a tertiary referral centre for all respiratory diseases including lung cancer. Inclusion criteria included histological or cytological evidence of adenocarcinoma of the lung and fulfilment of other diagnostic criteria.⁴ These included the presence of the following: compatible plain chest radiograph and/or thoracic computed tomography; clinical features of bronchial carcinoma including appropriate symptoms and signs; compatible clinical or radiological metastatic lesions with or without cytological or histological evidence; and absence of other known malignancies or diseases that would otherwise explain the overall clinical picture. The presence of a possible non-pulmonary primary adenocarcinoma was excluded in each case by detailed symptomatic inquiry, full physical examination (including breast examination for women, testicular examination for men, and rectal examination), and appropriate investigations in the presence of appropriate systemic symptoms (including gastroscopy, colonoscopy, abdominal and pelvic ultrasound or computed tomography, and thyroid isotope scan).

CLINICAL FEATURES

Relevant clinical data were extracted from the charts of eligible patients. These included smoking history, presenting symptoms; presence or otherwise of constitutional symptoms (weight loss, lethargy, and malaise), respiratory symptoms including persistent cough (defined as daily coughing for more than week weeks), sputum production, haemoptysis, dyspnoea, chest pain, recurrent or unresolved pneumonia, hoarseness of voice, neck masses, bone pain, or other systemic symptoms. The abnormal signs found on initial physical examination of the respiratory and other systems were also recorded.

Lung cancer is the commonest lethal malignant disease worldwide and many cases are already at advanced stage on presentation.^{1 2} Despite considerable medical advances, the five year survival for patients with lung cancer is merely 14%.² In Hong Kong, lung cancer accounts for more than 40% of all cancer deaths, and is the commonest lethal cancer in both genders. Adenocarcinoma has surpassed squamous cell carcinoma as the commonest histological type of lung cancer in many localities including Hong Kong.³⁻⁶ Since the establishment of the Hong Kong Cancer Registry in 1990, adenocarcinoma has been consistently found to be the commonest histological lung cancer type, and has accounted for 30% of newly diagnosed lung cancer from 1990 to 1996. Although there have been some published series on the clinical profiles of patients with lung cancer over the last three decades,⁷⁻⁹ few recent studies had addressed this increasingly important and common type of lung cancer in a systematic manner. We have, therefore, performed this review on Chinese patients with adenocarcinoma of the lung in Hong Kong. We aimed to establish an updated clinical profile of

RADIOLOGICAL FEATURES

The presenting chest radiographs and thoracic computed tomography were reviewed by one specialist thoracic radiologist (GCO) and the abnormalities were specified as follows: normal, mass lesion, collapse and/or consolidation, pleural effusion, pneumothorax, lymph nodes, and intrapulmonary or bone metastasis.

OTHER ASSESSMENTS

Since April 1978 flexible fiberoptic bronchoscopy had been a routine diagnostic procedure for suspected cases of lung cancer in our institution. The tumour was classified according to whether or not it was macroscopically visible at bronchoscopy. One specialist pathologist (MPW), according to standard World Health Organisation classification,⁴ reviewed all histological and cytological specimens. The TNM (tumour, node, and metastasis) staging of the lung cancer was determined by the combined information obtained through detailed clinical examination, skeletal imaging, ultrasound scanning, lymph node or other tissue biopsy, and contrast computed tomography using standard criteria.¹¹

DATA ANALYSIS

Summary statistics of the presenting clinical and radiographic features were obtained by cross tabulations. Ex-smokers were reclassified as smokers. Patients were arbitrarily classified as "young" if their age at presentation was 40 years or less, and as "early" presenters if the TMN staging was II or less. Comparison of data between groups of patients was by χ^2 tests, Fisher's exact tests, and Mann-Whitney U test where appropriate. Where appropriate statistical analysis was performed to determine if "early" presenters of the disease would be identified on the basis of information obtained at presentation. A p value of <0.05 was taken as indicative of statistical significance. The analysis was performed using the Statistical Analysis System package.

Results

SUBJECTS WITH ADENOCARCINOMA

From June 1995 to December 1997, a total of 354 consecutive new cases of primary cancer of the lung were diagnosed in our centre. Of these, 115, 128, 12, 74, and 25 patients were histologically classified as adenocarcinoma, squamous cell, large cell, non-small cell, and small cell lung cancer. Among the patients with adenocarcinoma of the lung, there were 40 women and the median (range) age of the cohort was 58 (22–87) years. A previous or current history of cigarette smoking was present in 64 (55.7%) patients of whom eight were women and 34 were current smokers. Fifteen (13.0%) patients were aged 40 years or less at the time of presentation. Based on the TNM classification, there were one (0.9%), five (4.3%), five (4.3%), 31 (27.0%), and 73 (63.5%) patients who had stage I, II, IIIA, IIIB, and IV disease at diagnosis respectively. There were therefore only six (5.2%) patients who presented with "early" disease, namely TMN stage II or less. The youngest patient was a

women who had never smoked, who was 22 years of age on presentation with stage IV disease.

PRESENTING FEATURES OF ADENOCARCINOMA

The presenting features of these patients are summarised in table 1. Five patients were entirely asymptomatic at time of presentation and were found to have abnormal lesions on incidental chest radiographs. All these five patients had unresectable (TNM stages IIIB or IV) disease. Thirty seven, 47, and 25 patients had one, two, and three or more symptoms at presentation respectively. The commonest presenting symptoms were persistent cough, haemoptysis, malaise, and weight loss. Weight loss was a common presenting feature (28.7%) but it occurred largely in association with other symptoms and was, therefore, not a specific indicator of disease. Persistent cough and haemoptysis were the sole presenting symptoms in 10 (8.7%) and seven (6.1%) cases. Together, these symptoms were present in 74 (64.3%) of cases. The mean duration of symptoms before presentation was 80 (range 1–730) days. Haemoptysis occurred significantly more commonly in those who were considered as "early" presenters (TMN stage II or lower) than the "late" presenters ($p < 0.001$). There was no significant difference in the other presenting features or findings between those who were "early" and "late" presenters.

The physical findings on initial presentation are summarised in table 1. Twenty five (21.7%) cases did not have abnormal physical signs at the time of presentation. Of these, 89.3% of cases had advanced (TNM stage IIIB or IV) diseases. Among those in whom physical signs were found, pleural effusion, cervical lymph nodes, finger clubbing, and pulmonary collapse/consolidation were among the most common. Pleural effusion and cervical lymphadenopathy were the sole presenting findings in 17 (14.8%) and six (5.2%) cases respectively. Finger clubbing was more

Table 1 Clinical symptoms at presentation in patients with adenocarcinoma of the lung

Presenting features	No (%) patients	Mean duration (days)
Symptoms		
Asymptomatic	5 (4.3)	—
Persistent cough	56 (48.7)	66.6
Haemoptysis	35 (30.4)	106.0
Malaise and weight loss	33 (28.7)	58.2
Dyspnoea	29 (25.2)	42.3
Chest pain	21 (18.3)	74.9
Neurological	9 (7.8)	47.2
Bone pain	8 (7.0)	38.5
Hoarseness	7 (6.1)	25.9
Neck mass	5 (4.3)	82.2
Unresolved pneumonia	2 (1.7)	2.0
Miscellaneous	8 (7.0)	49.0
Signs		
Normal	25 (21.7)	—
Pleural effusion	37 (32.2)	—
Cervical lymph node	30 (26.1)	—
Clubbing/HPO	20 (17.4)	—
Collapse/consolidation	17 (14.8)	—
Hepatomegaly	8 (7.0)	—
Neurological	7 (6.1)	—
Superior vena cava obstruction	5 (4.3)	—
Others	6 (5.2)	—

HPO = hypertrophic pulmonary osteoarthropathy.

Table 2 Comparison of clinical features between adenocarcinoma and squamous cell lung cancer

	Adenocarcinoma			Squamous cell		
	All (n=115)	Never smoker (n=51)	Ever smoker (n=64)	All (n=128)	Never smoker (n=19)	Ever smoker (n=109)
Median age (range) in years	58 (22–87)*	54 (22–87)	60 (37–84)	69 (42–88)	67 (42–81)	69 (42–88)
No of patients (% of patients)						
Female	40 (34.8)*	34 (66.7)†	6 (9.4)	23 (18.0)	9 (47.3)†	14 (12.8)
Stage IIB/IV disease	105 (91.3)*	47 (92.1)	58 (90.6)	96 (75)	16 (84.2)	80 (73.4)
No of patients with symptoms (% of patients)						
Asymptomatic	5 (4.3)*	1 (0.02)*	4 (6.3)*	22 (17.2)	4 (21.1)	18 (16.5)
Persistent cough	56 (48.7)	27 (25.9)	29 (45.3)	66 (51.6)	8 (42.1)	58 (53.2)
Haemoptysis	34 (29.6)	14 (27.4)	20 (31.3)	30 (23.4)	3 (15.8)	27 (24.8)
Malaise and weight loss	33 (28.7)	17 (33.3)	16 (25)	26 (20.3)	5 (26.3)	21 (16.4)
Dyspnoea	29 (25.2)	15 (29.4)	14 (21.9)	40 (31.3)	4 (21.1)	36 (33.0)
Chest pain	21 (18.3)	11 (21.6)	10 (15.6)	23 (18.0)	3 (15.8)	20 (18.3)
Hoarseness	7 (6.1)	1 (2.0)	6 (9.4)	6 (4.7)	1 (5.3)	5 (4.6)
Pleural involvement	37 (32.2)	21 (41.2)	16 (25)	29 (22.7)	6 (31.6)	23 (21.1)

*Indicates $p < 0.001$ when compared data from corresponding patient group or subgroup with squamous cell lung cancer.

†Indicates $p < 0.001$ when compared with smokers who had the same histological type of lung cancer.

commonly found among previous or current smokers than those who had never smoked ($p < 0.005$). Taken together, other than haemoptysis, there was no particular pattern of presenting symptoms, physical signs, and imaging findings that would distinguish between the “early” from the “late” presenters. There was no significant difference in the presenting symptoms between adenocarcinoma patients who were never or ever smokers ($p > 0.05$, table 2).

OTHER INVESTIGATIONS IN ADENOCARCINOMA

Chest radiographs and computed tomography were available for review in 113 and 73 patients respectively (table 3). The commonest abnormality at presentation was a mass lesion, followed by pleural effusion. Computed tomography had positively identified a greater percentage of lesions compared with the chest radiographs (table 3). Diagnostic bronchoscopy was performed on 69 patients in whom 54 (78.3%) showed centrally located, that is, macroscopically visible, tumours. Concomitant presence of pleural effusion and abnormal cervical lymph nodes occurred in 58 (50.4%) cases.

Discussion

In this study, 13% of our adenocarcinoma patients were younger than 40 years of age on presentation and only 33.3% of these had ever smoked. Most of the female patients (80%) had never smoked. The presence of persistent cough and haemoptysis occurred in 64.3% of patients. Most patients had mass lesion or pleural effusion on the presenting chest radiograph. There were significantly more patients presenting with haemoptysis in early disease (TNM less than II) compared with more

advanced TNM staging ($p < 0.001$). Finger clubbing was found significantly more commonly among patients who had been smokers ($p < 0.005$). However, there was no significant difference in the presenting features, physical or imaging findings between those who were 40 years or younger and those who were over 40. Unfortunately, all the patients who had adenocarcinoma diagnosed from incidental chest radiographs had advanced diseases as had the majority (89.3%) of cases who had a normal physical examination.

Most Western studies have consistently showed a low incidence of lung cancer in non-smokers and young subjects less than 40–50 years of age.^{12–14} However, our results show a preponderance of young female adenocarcinoma patients who have never smoked (table 2). This directly contrasts the results reported by the Edinburgh Lung Cancer Group, which reported that only 2% of 3070 patients had never smoked.¹⁴ The Edinburgh study also reported that non-smoking patients with lung cancers (predominantly adenocarcinoma) were significantly older than their counterparts (75.4 v 68.0 years),¹⁴ although there was no such significant age difference in our adenocarcinoma patients (54 v 60 years; table 2). In fact, our patients with adenocarcinoma were significantly younger than their counterparts who had squamous cell lung cancer (58 v 69 years; table 2). There are also another nine studies, conducted in the 1960s and 1970s, on non-smoking Caucasian patients who had lung cancer.^{14–22} These showed that adenocarcinoma, squamous cell and small cell lung cancers accounted for 31%–69%, 6%–32%, 7%–42% of all lung cancer types respectively. The characteristics of patients in the aforementioned studies do not correspond with those of the Chinese patients. A recent pathological survey in Hong Kong, which was not accompanied with analysis on clinical and radiological features, showed that adenocarcinoma accounted for 37.3% of all lung cancers and 50% of these cases were under 40 years of age.⁶

Although the association between smoking and lung cancer has been well established,²³ a higher proportion of the patients with bronchial adenocarcinoma are non-smokers.^{14–22} The smoking rates for the general population in

Table 3 Imaging findings in 115 patients with adenocarcinoma of the lung

Finding	No (%) having chest radiography (n=113)	No (%) having computed tomography (n=73)	No of findings detected only by computed tomography
Normal	2 (1.7)	0	0
Mass	81 (71.9)	55 (75.3)	11
Pleural effusion	45 (39.1)	28 (38.4)	7
Collapse/consolidation	18 (15.6)	18 (24.7)	11
Metastases	9 (7.8)	35 (47.9)	29
Mediastinal lymph node	7 (6.1)	39 (53.4)	34
Pneumothorax	2 (1.7)	3 (4.1)	2

Hong Kong were recently reported to be 2.9% for women and 27.1% for men respectively.²⁴ In this study, 43.9% of the adenocarcinoma patients had never smoked and there were significantly more women than men who had never smoked (81.0% *v* 12.8%), although there appears to be more female smokers in our cohort than in the general population. The high incidence of adenocarcinoma of the lung among non-smoking young Chinese women in Hong Kong also sharply contrasts that reported from Europe and North America.¹⁴⁻²² The aetiological factors for the high incidence of bronchial adenocarcinoma in women in Hong Kong, who are largely non-smokers, remain obscure.²⁵⁻²⁶ Studies of passive smoking in Hong Kong have given inconsistent results,²⁷⁻²⁸ and studies on other environmental inhaled agents such as fumes from kerosene stoves and incense burners have also been negative.²⁹ Similarly, HLA antigen analysis and genetic studies to date have not been able to define the aetiological factors.³⁰⁻³⁶

The long duration of symptoms before diagnosis reflects a possible low index of suspicion of lung cancer among doctors and also the non-specific nature of many of the presenting symptoms. This was probably also perpetuated by the traditional clinical teaching of a remote probability of lung cancer among non-smokers. Although emergence of symptoms is usually indicative of advanced disease status and poor prognosis, carcinoma of the major bronchi might present early. Abnormalities were found in the presenting chest radiographs in 98.3% of the patients. This suggests that, although not being cost effective as a screening tool, chest radiography is a sensitive and cost effective initial investigation for patients with suspected disease. Our results therefore suggest that Chinese patients, particularly women, irrespective of their risk factor profiles, should undergo intensive investigations to exclude lung cancer in the presence of mass lesion, pleural effusion, or collapse/consolidation seen on chest radiography (table 2).

We have also compared the clinical profiles of our patients with a concurrent cohort of patients with squamous cell lung cancer (n=128; 23 women; stages I, II, IIIA, IIIB, and IV were 1.6%, 3.1%, 20.3%, 39.1%, and 35.9% respectively). Patients with adenocarcinoma were significantly more likely to be younger ($p<0.0001$), of female gender ($p=0.03$), never smokers ($p<0.001$), in advanced disease, that is stage IIIB and IV ($p=0.001$), but less likely to be asymptomatic ($p=0.001$) when compared with their counterparts with squamous cell lung cancer (table 2). There were, otherwise, no significant difference in the presenting features for patients with adenocarcinoma and squamous cell lung cancer ($p>0.05$). A previous history of smoking was not associated with any significant difference in the staging of lung cancer on presentation in both histological types of lung cancer ($p>0.05$, table 2). Smokers with squamous cell lung cancer were significantly more likely to be

asymptomatic at presentation than their counterparts with adenocarcinoma ($p=0.003$, table 2), although there is no obvious explanation.

Adenocarcinoma of the lung is an increasingly more prevalent lung malignancy and our experience shows that it predominantly affects women who have never smoked and are symptomatic on presentation with advanced disease. Our explanation on this series of patients should help clinicians in the evaluation of patients, particularly Chinese females, with lung cancer.

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Medical Anniversary

Sir William James Erasmus Wilson, 25 November 1809

Sir William James Erasmus Wilson (1809–84) was born in Marylebone High Street, London, the son of an Aberdeen naval surgeon who settled as a surgeon in Dartford, Kent. He was educated at Epsom College and St Bartholomew's (1831), became a lecturer in anatomy and physiology at the Middlesex Hospital, assistant editor of the *Lancet* (1840), surgeon to St Pancras Infirmary, FRS (1845), President of the Medical Society of London (1878), President of the Royal College of Surgeons (1881), and was knighted in 1881.

He had a successful consulting practice as a dermatologist; it was said that when he entered a room those present would start scratching themselves. His numerous benefactions included restoring Swanscombe church, rebuilding the headmaster's house at Epsom College, founding a scholarship at the Royal College of Music, and endowing a chair of dermatology at the Royal College of Surgeons. He paid £10 000 to transport Cleopatra's Needle from Alexandria to the Victoria Embankment, London and £30 000 for a new wing and chapel to the Margate Seabathing Infirmary.



He died at his home in Westgate on 7 August 1884 leaving £200 000 to the Royal College of Surgeons.—D G James