Common Beliefs and Referral Patterns among Physicians in the Therapeutic Approach to Non-small Cell Lung Cancer

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Research Question: What are the beliefs and referral patterns among physicians in the therapeutic approach to Non-small cell Lung Cancer (NSCLC)?
Background: Lung cancer is the leading cause of cancer death in men and women combined. Survival benefit seen with chemotherapy and other multimodality therapy, be it curative or palliative.
Study Design: cross-sectional analytical survey
Study Setting: The questionnaire was distributed to physicians in the different private and government tertiary hospitals in the National Capital Region, namely, St Luke's Medical Center (SLMC), University of the East-Ramon Magsaysay Memorial Medical Center (UERMMMC), Philippine Heart Center (PHC), Manila Doctors' Hospital (MDH), and University of the Philippines-Philippine General Hospital (UP-PGH).
Study population: The study participants were physicians practicing adult patient care with high concentration of lung cancer patients within their practice. Specialties include Family Medicine, General Internal Medicine, Pulmonology, and Thoraco-Cardiovascular Surgery (TCVS).
Statistical Analysis: Likelihood ratios with a 95% confidence interval
Results: Out of the 319 questionnaires given, 216 were returned with a response rate of 68%. Majority of the physicians believed that screening for lung cancer is mandated in high risk patients. For treatment beliefs, respondents' perception were categorized according to stage of lung cancer, whether it is early, unresectable, or metastatic NSCLC. For early stage (Stage I to IIIA) NSCLC, majority of physicians tend to believe that adjuvant chemotherapy would prolong survival. For unresectable locally advanced (Stage IIIA-IIIB) NSCLC, 62% agreed with combined modality treatment (chemotherapy and radiotherapy) as more effective in improving survival than radiotherapy alone or chemotherapy alone. For metastatic (Stage IV) NSCLC, responses were varied across specialties regarding survival benefit with chemotherapy. Majority of the physicians believed that chemotherapy and radiotherapy plays a significant role in palliation. Referral patterns were categorized by stage of the disease. For stage IIII, physicians' responses were varied across designation, completion of training, and specialty. Referral to Medical Oncology experts was the referral trend for Stage III locally advanced NSCLC patients. Hospice was the least referral path. In Stage IV NSCLC patients, the trend was referral to Medical Oncologist and Hospice care specialist
Conclusion: Physicians, both within and between specialties, have varied opinions regarding screening, referral patterns, and therapeutic approach to non-small cell lung cancer. With the growing number of therapeutic options available, referring physicians should be more vigilant, not be influenced by biases and restricted access to patient care, and give patients the opportunity to consider all of their treatment options. In this way, optimum patient care and prolonged survival outcome is achieved. *Phil Journal of Chest Disease. Vol. 13 No. 1 pp: 1-9*

Keywords: Lung cancer, Therapy, referral system

Introduction

Lung cancer represents one of the most common causes of morbidity and mortality worldwide. It resulted to more than 1 million deaths worldwide,[1] and is the leading cause of cancer-related mortality in both men and women (31% and 27%, respectively) in the United States.[2] In the Philippines, lung cancer comprises 16.1% and is the leading cancer site for both sexes combined.[3] Due to the high disease burden, it has received much attention as a target for therapy, with trials focusing

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on management with surgery, radiation, and chemotherapy. In recent years, clinical trials in the management of non-small cell lung cancer (NSCLC) have shown survival benefit with the use of chemotherapy and other multimodality treatment, be it curative or palliative. However, physicians' beliefs about the effectiveness of therapy varied widely. The nihilistic attitudes of doctors toward the prognosis and treatment of NSCLC may be a contributory factor to the high rates of no treatment. An Australian study has shown that 26% of those not receiving treatment were of good performance status.[5] It was also observed that 36% of patients not receiving treatment did not see a specialist.[6] If this was not due to patients' choice not to seek a specialist opinion, then it could be due to the clinicians' decision. Thus, the contribution of physician referral to this practice variation needs to be explored. All of these factors in the management of NSCLC should be considered and optimized to improve patient care and outcome.

This study therefore aims to describe beliefs and referral patterns among physicians in the therapeutic approach to Non-small cell Lung Cancer (NSCLC).

Methodology

Study Design. Cross-sectional analytical survey

*Study Setting***.** The questionnaire was distributed to physicians in the different private and government tertiary hospitals in the National Capital Region, namely, St. Luke's Medical Center (SLMC), University of the East Ramon Magsaysay Memorial Medical Center (UERMMMC), Philippine Heart Center (PHC), Manila Doctors' Hospital (MDH), and the University of the Philippines-Philippine General Hospital (UP-PGH).

Study Population. The study participants were all physicians practicing adult patient care with high concentration of lung cancer patients within their practice. Specialties include Family Medicine, General Internal Medicine, Pulmonology, and Thoraco-Cardiovascular Surgery (TCVS).

Sample Size and Design. A total of 33 clusters derived from a list of hospitals accredited by their respective specialty societies were chosen randomly. Each cluster was estimated to have 55 respondents practicing any of the specialties mentioned above. The sample size used to determine the number of clusters (n) was calculated using the following formula:[7]

$$n = \frac{N\sigma_c^2}{ND + \sigma_c^2}$$

where n=number of clusters
N=total population size (1815)
σ_c^2 =variance of the proportion in the population based on the study of Earle et al[6] which was 70%

$$D = \frac{B^2 M^2}{4}$$

where B= bound for error set at 0.01
M= average number of respondents per cluster

From this formula, the number of sample clusters needed for the study was 5. Sampled hospitals were SLMC, UE-RMMC, PHC, MDH, and UP-PGH. All family physicians, internists, pulmonologists, and thoracic surgeons in these clusters were given the questionnaires.

Maneuvers. *Data collection tool.* A 13-item questionnaire was used to describe the beliefs and referral patterns of the physicians aforementioned in the treatment of non-small cell lung cancer. The questionnaire, modified from that prepared by Schroen et a1[8] was developed and used for this study. Other than the respondent demographics, the questionnaire consisted of perceptions about screening, treatment efficacy, and patterns of referral for early, locally advanced/unresectab1e, and metastatic NSCLC. Respondents were asked to answer close-ended questions by checking pertinent answers. For screening and treatment benefits, respondents were required to choose only one option. For referral pattern preferences, respondents were allowed to check one or more answers. The modified questionnaire was piloted and pre-tested on a small sample of physicians, who were representative of the total target population. This was then revised further before the final implementation.

Modes of administering the questionnaire were mostly self-administered, and a few by direct person to person interview. Non-respondents were identified after three attempts have been made to obtain the questionnaire or if the physician refused outright to answer the questionnaire. They were followed up within two weeks from the time the questionnaires were distributed.

Table I General Demographic Characteristics

Characteristics	Frequency (n)	Percent (%)
Age		
25-30	97	44
31-35	51	24
36-40	38	18
41-50	24	11
>50	6	3
Gender		
Male	111	52
Female	103	48
Current designation		
Residents	90	42
Fellows-in-training	36	16
Consultants	90	42
Completion of medical training		
Prior to 1990	35	16
1991-1995	32	15
1996-2004	33	15
Still in training	116	54
Major field of practice		
Internal Medicine	98	45
Pulmonary medicine	48	22
TCVS	17	8
Family Medicine	53	25
Annual case load of NSCLC		
0-1	21	10
2-5	64	29
6-10	44	20
10-20	47	22
>25	40	19

*Statistical Analysis***.** Data analysis was performed using the computer software *Stata* (version 6.0).

Descriptive statistics were used and analysis was done. Analysis of data involving comparisons between beliefs in therapy and physician characteristics and referral patterns was performed using likelihood ratios (LR) with a 95% confidence interval (CI).

Results

Out of the 319 questionnaires given, 216 were returned with a response rate of 68%. It took the respondents approximately 5 minutes to answer. Non-respondents included 7 family physicians, 14 TCVS, 20 pulmonologists, 62 internists. The main reason for non-response was "too busy" or "forgot to answer." Others lacked interest and others felt that they were not knowledgeable enough to answer the questions.

The respondent characteristics were summarized in *Table 1*. Most of the respondents' age ranged from 25-30 years old. Males and females were almost equally

Table II Do you believe in SCREENING for lung cancer patients perceived to be at high risk for lung cancer?

Respondent characteristic	Response Options (%)		LR (95% CI)
	No	Yes	
Current designation			
Residents	10	90	0.56 (0.31-1.00)
Fellows- in-training	25	75	1.67 (0.86-3.24)
Consultants	20	80	1.25 (0.86-1.81)
Completion of medical training			
Prior to 1990	29	71	2.00 (1.05-3.80)
1991-1995	12	78	1.40 (0.66-2.99)
1996-2004	10	90	0.22 (0.07-0.67)
Still in training	14	86	0.80 (0.54-1.18)
Major field of practice			
Internal Medicine	10	90	0.57 (0.33-0.98)
Pulmonary Medicine	31	69	2.27 (1.39-3.73)
TCVS	18	82	0.80 (0.24-2.65)
Family Medicine	15	85	0.89 (0.46-1.72)
Annual case load of NSCLCA			
0-1	19	81	1.18 (0.42-3.29)
2-5	20	80	1.27 (0.78-2.09)
6-10	5	95	0.15 (0.04-0.57)
11-20	19	81	1.03 (0.55-1.93)
>25	20	80	1.08 (0.54-2.15)

Table III For EARLY STAGE (Stage I to IIIA) NSCLC patients do you believe survival is prolonged with chemotherapy vs. others?

Respondent Characteristics	Response Options (%)				LR (95% CI)
	Chemo*	Others**			
		RT**	Chemo-RT***	Not sure	
Current designation					
Residents	47	28	23	2	1.07 (0.78-1.47)
Fellows-in-training	69	8	15	8	2.79 (1.45-5.38)
Consultants	33	23	24	20	0.61 (0.43-0.87)
Completion of medical training					
Prior to 1990	40	8	28	24	0.82 (0.44-1.52)
1991-1995	34	25	22	19	0.64 (0.33-1.27)
1996-2004	33	37	21	9	0.33 (0.17-0.65)
Still in training	53	22	21	4	1.36 (1.06-1.74)
Major field of practice					
Internal Medicine	50	28	18	4	1.23 (0.92-1.64)
Pulmonary Medicine	52	17	15	16	1.33 (0.81-2.20)
TCVS	53	18	24	5	0.93 (0.37-2.32)
Family Medicine	26	21	36	17	0.44 (0.25-0.76)
Annual case load of NSCLC					
0-1	24	43	29	4	0.38 (0.15-1.01)
2-5	41	11	28	20	0.84 (0.55-1.28)
6-10	45	23	25	7	0.67 (0.39-1.13)
11-20	57	25	12	6	1.63 (0.98-2.71)
>25	48	27	20	5	1.09 (0.62-1.91)

* chemo = chemotherapy after complete resection
** RT = radiotherapy after complete resection
***Chemo-RT = combined chemotherapy & radiotherapy after complete resection

Table IV. For UNRESECTABLE LOCALLY ADVANCED (Stage IIIA to IIIB) NSCLC, do you believe survival is prolonged with chemo-RT vs. others?

Respondent Characteristics	Response Options (%)				LR (95% CI)
	Chemo*	Others**			
		RT**	Chemo-RT***	Not sure	
Current designation					
Residents	64	21	7	8	1.11 (0.78-1.55)
Fellows-in-training	77	11	6	6	2.14 (1.03-4.47)
Consultants	53	20	11	16	0.70 (0.51-0.95)
Completion of medical training					
Prior to 1990	46	26	3	25	0.52 (0.28-0.94)
1991-1995	44	22	22	2	0.48 (0.25-0.90)
1996-2004	82	9	6	3	1.44 (0.62-3.35)
Still in training	66	19	7	8	1.21 (0.92-1.58)
Major field of practice					
Internal Medicine	66	17	8	9	1.15 (0.84-1.57)
Pulmonary Medicine	65	29	6	0	1.12 (0.66-1.88)
TCVS	65	29	0	6	0.78 (0.30-2.03)
Family Medicine	53	9	13	25	0.69 (0.43-1.1)
Annual case load of NSCLC					
0-1	43	29	14	14	0.46 (0.20-1.04)
2-5	64	9	3	24	1.09 (0.71-1.68)
6-10	70	20	7	3	0.85 (0.48-1.54)
11-20	57	24	13	6	0.95 (0.57-1.58)
>25	65	23	10	2	1.30 (0.72-2.35)

* chemo = chemotherapy after complete resection
** RT = radiotherapy after complete resection .
***Chemo-RT = combined chemotherapy & radiotherapy after complete resection

distributed, as well as, the residents and consultants. A little more than half of the physicians included in the study were still in training. Internists topped the recruited list according to specialty, followed by family physicians, pulmonologist and TCVS. Twenty nine percent of the study population claimed to have seen approximately 2-5 cases of lung cancer in a year.

By proportion, majority of physicians believed that screening be done for patients perceived to be at high risk for lung cancer. When asked if the physicians believed screening for lung cancer patients perceived to be at high risk, the following results were noted: (*Table II*)

1. Regardless of current designation, physicians were more likely to say "Yes." (LR's crosses 1.0)
2. Physicians were less likely to say 'No' if they
   a. completed medical training in 1996-2004 (LR=0.22, 0.07-0.67)
   b. have Internal Medicine as specialty (LR=0.57, 0.33-0.98)

Table V In METASTATIC NSCLC (Stage IV), do you believe there is "palliative" vs. "survival" benefit with chemotherapy?

Respondent Characteristics	Treatment benefit with chemotherapy		LR (95% CI)
	Palliative	Survival	
Current designation			
Residents	38	62	1.01 (0.73-1.40)
Fellows-in-training	55	45	2.08 (1.15-3.78)
Consultants	30	70	0.71 (0.50-1.02)
Completion of medical training			
Prior to 1990	26	74	0.58 (0.28-1.17)
1991-1995	47	53	1.47 (0.78-2.78)
1996-2004	27	73	0.31 (0.15-0.63)
Still in training	41	59	1.18 (0.92-1.50)
Major field of practice			
Internal Medicine	43	57	1.25 (0.93-1.67)
Pulmonary Medicine	44	56	1.30 (0.79-2.14)
TCVS	23	77	0.37 (0.12-1.08)
Family Medicine	26	74	0.60 (0.35-1.03)
Annual case load of NSCLC			
0-1	10	90	0.18 (0.04-0.73)
2-5	36	64	0.94 (0.61-1.44)
6-10	36	64	0.62 (0.36-1.07)
11-20	38	62	1.07 (0.63-1.80)
>25	55	45	2.10 (1.20-3.70)

Table VI In METASTATIC NSCLC (Stage IV), do you believe there is "palliative" vs. "survival" benefit with radiotherapy?

Respondent Characteristics	Treatment benefit with chemotherapy		LR (95% CI)
	Palliative	Survival	
Current designation			
Residents	43	57	0.92 (0.67-1.28)
Fellows-in-training	75	25	3.62 (1.78-7.36)
Consultants	44	56	0.83 (0.60-1.15)
Completion of medical training			
Prior to 1990	46	54	0.87 (0.48-1.61)
1991-1995	67	33	2.28 (1.13-4.59)
1996-2004	30	70	0.21 (0.11-0.43)
Still in training	50	50	1.04 (0.81-1.33)
Major field of practice			
Internal Medicine	47	53	0.92 (0.17-1.03)
Pulmonary Medicine	56	44	1.33 (0.81-2.21)
TCVS	82	18	3.35 (0.99-11.31)
Family Medicine	36	64	0.58 (0.35-0.95)
Annual case load of NSCLC			
0-1	29	71	0.42 (0.17-1.03)
2-5	45	55	0.86 (0.57-1.30)
6-10	36	64	0.42 (0.24-0.73)
11-20	62	38	1.85 (1.10-3.13)
>25	65	35	2.14 (1.18-3.89)

   c. have 6-10 NSCLC cases per year (LR=0.15, 0.04-0.57)

Table VII To which of the following would you refer a patient with STAGE I/II NSCLC?

Respondent Characteristics	Response Options (%)*					LR (95% CI)
	Definitive Rx		General therapy			
	TCVS	MO	RO	PULMO	HOSP	
Current designation						
Residents	67	80	34	67	9	1.13 (0.83-1.56)
Fellows-in-training	80	58	11	53	3	0.93 (0.51-1.69)
Consultants	70	67	34	54	17	0.91 (0.66-1.25)
Completion of medical training						
Prior to 1990	57	69	25	51	9	0.48 (0.25-0.92)
1991-1995	84	56	41	47	13	1.18 (0.62-2.23)
1996-2004	73	76	33	67	30	0.68 (0.36-1.28)
Still in training	70	74	28	63	6	1.07 (0.84-1.38)
Major field of practice						
Internal Medicine	65	78	35	69	7	1.08 (0.81-1.45)
Pulmonary Medicine	88	54	10	40	4	1.03 (0.63-1.71)
TCVS	88	47	6	47	12	0.54 (0.21-1.37)
Family Medicine	58	81	47	62	25	0.92 (0.58-1.48)

* Values given as percentage responding 'Yes' to referral use. Each respondent could select one or more of the referral options and, therefore, they do not add up to 100%.
MO - Medical Oncologist, RO - Radiation Oncologist, PULMO - Pulmonologist
HOSP - Hospice care specialist

Table VIII To which of the following would you refer patients with STAGE III locally advanced NSCLC?

Respondent characteristics	Response Options (%)*					LR (95% CI)
	Oncology			Non-Oncology		
	MO	RO	HOSP	TCVS	PULMO	
Current Designation						
Residents	87	53	24	44	63	1.24 (0.82-1.86)
Fellows-in-training	92	56	8	44	50	0.61 (0.20-1.86)
Consultants	79	68	21	44	44	0.93 (0.57-1.53)
Completion of medical training						
Prior to 1990	88	63	17	46	31	0.63 (0.21-1.92)
1991-1995	66	75	22	34	38	0.45 (0.11-1.77)
1996-2004	85	64	30	55	67	1.15 (0.60-2.22)
Still training	88	53	18	44	60	0.92 (0.62-1.37)
Major field of practice						
Internal Medicine	88	56	17	41	67	0.94 (0.59-1.48)
Pulmonary Medicine	83	63	4	56	38	0.29 (0.08-1.14)
TCVS	94	59	6	76	35	0.33 (0.05-2.39)
Family Medicine	75	64	45	30	47	2.18 (1.35-3.54)

* Values given as percentage responding 'Yes' to referral use. Each respondent could select one or more of the referral options and, therefore, they do not add up to 100%.
MO - Medical Oncologist, RO - Radiation Oncologist, PULMO - Pulmonologist
HOSP - Hospice care specialist

3. Physicians were more likely to say 'No' if they
   a. completed medical training prior to 1990 (LR=2.00, 1.05-3.80)
   b. have pulmonary medicine as specialty (LR=2.27, 1.39-3.73)

Among Stage I-IIIA NSCLC patients, majority of physicians tend to believe that adjuvant chemotherapy would prolong survival, except the consultants, family medicine specialty, and those who completed training in 1996-2004.

In *Table III*, if adjuvant chemotherapy is believed to be the "best" answer in prolonging survival among Stage I-IIIA NSCLC patients, then:

1. according to current designation,
   a. residents were undecided. (LR crosses 1.0)
   b. fellows-in-training were more likely to believe chemotherapy. (LR=2.79, 1.45-5.38)
   c. consultants were least likely to believe chemotherapy. (LR=0.61, 0.43-0.87) t
2. Those trained in 1996-2004 were less likely to believe chemotherapy (LR=0.33, 0.17-0.65), while those still in training were more likely to believe chemotherapy (LR=1.36, 1.06-1.74)
3. Internists, pulmonologists, and thoracic surgeons similarly were undecided (LR's crosses 1.0). However, family medicine physicians were less likely to believe chemotherapy. (LR=0.44, 0.25-0.76)
4. Annual case load of NSCLC was not a determinant of the likelihood of believing this "best" answer. (LR's crosses 1.0)

Majority of physicians believed that combined chemotherapy and radiotherapy would prolong survival in Stage IIIA and IIIB NSCLC patients.

In *Table IV*, if combined chemotherapy and radiotherapy is believed to be the "best" answer in prolonging survival in unresectable locally advanced Stage IIIA and IIIB NSCLC patients, then:

1. according to current designation,
   a. residents were undecided. (LR crosses 1.0)
   b. fellows-in-training were more likely to believe in chemo-RT. (LR=2.14, 1.03-4.47)

Table IX To which of the followin2 would you refer a patient with STAGE IV NSCLC?

Respondent characteristics	Response Options (%)*					LR (95% CI)
	Oncology			Non-Oncology		
	MO	RO	HOSP	TCVS	PULMO	
Current Designation						
Residents	78	44	78	21	53	1.20 (0.86-1.67)
Fellows-in-training	81	53	56	14	56	1.23 (0.65-2.33)
Consultants	81	46	58	17	39	0.75 (0.50-1.12)
Completion of medical training						
Prior to 1990	86	49	43	3	29	0.70 (0.32-1.51)
1991-1995	75	34	56	13	34	0.09 (0.01-0.64)
1996-2004	85	55	76	36	48	1.13 (0.61-2.08)
Still training	78	47	72	19	57	1.16 (0.89-1.50)
Major field of practice						
Internal Medicine	76	43	69	23	55	0.86 (0.60-1.20)
Pulmonary Medicine	88	40	56	15	42	0.93 (0.52-1.66)
TCVS	82	41	76	18	41	1.17 (0.45-3.01)
Family Medicine	79	60	64	11	42	1.20 (0.73-2.00)

* Values given as percentage responding 'Yes' to referral use. Each respondent could select one or more of the referral options and, therefore, they do not add up to 100%.
MO - Medical Oncologist, RO - Radiation Oncologist, PULMO - Pulmonologist
HOSP - Hospice care specialist

c. consultants were least likely to believe in chemo-RT. (LR=0.70, 0.51-0.95)

2. those who completed medical training prior to 1990 and in 1991-1995 were less likely to believe in chemo-RT.(LR=0.52, 0.28-0.94; LR=0.48, 0.25-0.90 respectively)
3. major field of practice and annual caseload of NSCLC were not a determinant of the likelihood of believing this "best" answer. (LR's crosses 1.0)

Among metastatic Stage IV NSCLC patients, majority of physicians tend to believe in "survival" benefit with chemotherapy, except those with >25 case load of NSCLC per year or being fellows-in-training.

In *Table V*, among Stage IV NSCLC patients, if "palliative" vs. "survival" benefit with chemotherapy is believed to be the "best" answer, then:

1. Being with the fellows-in-training designation (LR=2.08, 1.15-3.78), and with the annual case load of > 25 (LR=2.10, 1.20-3.70) were determinants in likely believing in "palliative" benefit.
2. Having medical training completion in 1996-2004 (LR=0.31, 0.15-0.63), and annual caseload of 0-1 (LR=0.18, 0.04-0.73) were determinants in not likely believing in "palliative" benefit.
3. Major field of practice was not a determinant of the likelihood of believing the "best answer". (LR's crosses 1.0)

There was variability among physicians in the belief, whether "palliative" vs. "survival" benefit can occur from radiotherapy for Stage IV NSCLC patients.

In *Table VI*, if "palliative" vs. "survival" benefit with radiotherapy in Stage IV NSCLC is believed to be the "best" answer, then:

1. Being with fellows-in-training designation (LR=3.62, 1.78-7.36), 1991-1995 medical training (LR=2.28, 1.13-4.59), and annual case load of 11 to >25 NSCLC (LR> 1, > 1 to >3) were determinants in likely believing in "palliative" benefit with radiotherapy.
2. 1996-2004 medical training (LR=0.21, 0.11-0.43), family medicine as major practice (LR=0.58, 0.35-0.95), and 6-10 annual case load (LR=0.42, 0.24-0.73) were least likely to believe a "palliative" benefit with radiotherapy.

There was variability in the referral opinion among physicians for Stage I-II NSCLC patients, except for referral to hospice care where there is a trend towards not referring it to them.

In *Table VII*, if referral to TCVS/Medical Oncologist for definitive specific treatment vs. referral to Radiation Oncologist/Pulmonologist for non-specific general treatment is the "better" response option for patients with Stage I-II NSCLC, then completion of medical training prior to 1990 was a significant determinant in likely NOT referring to TCVS/MO (LR=0.48, 0.25-0.92). The other respondent characteristics did not come out as significant determinants for or against TCVS/MO referral.

Referral to Medical Oncology experts more than the radiation oncologist, pulmonologist, and TCVS experts was the referral trend for Stage III locally advanced NSCLC patients. Hospice was the least referral path.

In *Table VIII*, if referral to "Oncology" *(MO/RO/HOSP)* care vs. "Non-oncology" (TCVS/Pulmo) care is the "better" response option for patients with Stage III locally advanced NSCLC, then family medicine as major field of practice was a determinant in likely referring to "oncology" experts

(LR=2.18, 1.35-3.54). The other respondent characteristics did not come out as significant determinants for or against "oncology" experts.

In Stage IV NSCLC patients, the trend was referral to Medical Oncologist and Hospice care specialist, followed by radiation oncologist and pulmonologist, with least referral to TCVS experts.

In *Table IX*, if referral to "oncology" experts vs. "non-oncology" experts is the "better" response options for Stage IV NSCLC patients, then completion of medical training in 1991-1995 was a significant determinant in NOT likely referring to "oncology" experts (LR=0.09, 0.01-0.64). The other respondent characteristics did not come out as significant determinants for or against "oncology" experts.

Discussion

Our survey revealed that there was a significant variability both within and across specialties in the physicians' belief in screening, treatment benefit, and referral patterns for NSCLC patients. These results were consistent with other studies that have identified variability in the management of NSCLC.[4,8,9] Our study further analyzed that respondent characteristics such as current designation, completion of medical training, major field of practice, and annual case load of NSCLC may be determinants in the likelihood of believing in screening, treatment benefit, and referral of NSCLC patients.

Screening. A previous study showed that 75% of the respondents thought that screening was appropriate for patients at high risk for lung cancer, a finding that approximates our study. High risk factors include smoking, chronic obstructive pulmonary disease (COPD), exposure to occupational carcinogens such as asbestos, prior tobacco-related cancer, family history, and female gender.[10] The combination of chest radiography and sputum cytology as screening tools showed no significant reduction in lung cancer mortality in randomized trials.[11] Interest in lung cancer screening was renewed with the use of computed-tomography (CT). The International Early Lung Cancer Action Project (I-ELCAP), a multinational, non-randomized study, accrued patients with a baseline and annual repeat CT scanning. With a median follow up time of approximately 40 months, it revealed a more than 95% survival rates for subjects screened and eventually diagnosed to have Stage I lung cancer.[12,13] A randomized trial initiated by the National Cancer Institute in 2002, to evaluate whether CT screening leads to a significant improvement in lung cancer mortality, finished its accrual last February 2004.[13,14] Results with planned follow up for mortality will be available by 2009. Although these trials showed promising results, definitive evidence that CT screening reduces lung cancer mortality is still lacking. The American Cancer Society still recommends that CT screening should not be performed in asymptomatic high risk patients.[15]

Early Stage (Stage I to IIIA) NSCLC. The study by Raby et al.[9] revealed that 68% of the physicians recommended no adjuvant treatment for early stage lung cancer. Only 1% of the respondents on the same study recommended adjuvant chemotherapy. However, the survey done by Schroen et al.[8] showed the responses of the physicians were essentially divided as to whether adjuvant chemotherapy or radiation offered a survival benefit.

The Postoperative radiotherapy (PORT) meta-analysis Trialist Group for NSCLC concluded that postoperative radiation is detrimental to early stage completely resected NSCLC patients and should not be used in the routine treatment of such patients.[16] A 1995 meta-analysis investigated the role of chemotherapy in the treatment of NSCLC.[17] One of the trials examining the use of postoperative adjuvant chemotherapy in the same study gave a hazard ratio of 0.87 (p=0.08), corresponding to a 13% reduction in the risk of death, and an absolute benefit of 5% at five years. These findings triggered subsequent multiple randomized adjuvant chemotherapy trials for NSCLC. Except for the Adjuvant Lung Project Italy (ALPI),[18] Japanese Clinical Oncology Group Trial 9304 (J9304),[19] and the Big Lung Trial (BLT),[20] all the other trials (the Italian Stage IB Study,[21] International Adjuvant Lung Cancer Trial (IALT),[22] United States Intergroup JBR.10 Trial,[23] Cancer and Leukemia Group B (CALGB) trial 9633,[24] and Uracil-Tegafur Adjuvant Tria1,[25] and the recent Adjuvant Navelbine International Trialist Association (ANITA)[26] showed a survival benefit with adjuvant chemotherapy.

Unresectable locally advanced (Stage IIIA to IIIB) NSCLC. The Canadian study[9] revealed that 65% of the respondents recommended radiotherapy and 16% respondents recommended combined chemo-RT for an asymptomatic Stage IIIB patient. On the other hand, another study[8] showed that 71% physicians espoused the use of chemotherapy plus radiation. This was comparable to our survey of combined chemo-RT of 62%.

Chemotherapy plus radiotherapy given concurrently is the optimal treatment for the group of

patients with locally advanced stage IIIA and IIIB disease.[27] The same meta-analysis[17] showed a survival benefit with locally advanced disease, with a hazard ratio of 0.87 (13% risk reduction of death; absolute benefit of 4% at two years.)

Metastatic (Stage IV) NSCLC. Raby's survey[9] showed that in the management of an asymptomatic Stage IV patient, a quarter recommended chemotherapy while three quarters recommended no active treatment or best supportive care only. Schroen[8] claimed that only 33% of the respondents were convinced that chemotherapy grants a survival benefit in these subset of patients. Another survey conducted by Jennens et al.[28] revealed that 40% of the clinicians were not knowledgeable regarding the role of chemotherapy in metastatic NSCLC. In our study, there were varied responses across specialties regarding survival benefit with chemotherapy.

The cisplatin-based trials showed a benefit of chemotherapy plus best supportive care over best supportive care alone in advanced lung cancer.[17] It gave a hazard ratio of 0.73 ($p<0.001$), a reduction in the risk of death of 27%, equivalent to an absolute improvement in survival of 10% at one year or an increased median survival of 1½ months (1 month to 2½ months). The addition of newer generation agents such as vinorelbine, gemcitabine, paclitaxel, or docetaxel to a platinum agent can improve survival, although no combination have offered significant advantage over the others.[29]

In a review of randomized trials conducted by Socinski et aI, it was shown that chemotherapy improves survival and palliates symptoms, thereby, improving quality of life in patients with Stage IV NSCLC in both the first-line and second-line setting.[30] Performance status was one of the most powerful predictors of survival in metastatic NSCLC.[31] Patients with an ECOG performance status of 0 or 1 are generally considered suitable for chemotherapy, whereas it is not recommended for patients with a performance status of 3 or 4.[30] This was one limitation which was not considered in our survey. Radiotherapy used alone may provide palliation of symptoms and improve quality of life.[32]

Referral Pattern preferences. Schroen's[8] survey on referral patterns indicate that referral to thoracic surgery was deemed appropriate in early stage disease. There was a varied response across designation, completion of training, and specialty in our study. The same survey by Schroen showed a clear majority advocating medical oncology referrals in Stage III and IV disease. This was comparable to our survey, with the addition of hospice care referral for metastatic disease.

All patients with lung cancer should be referred to a specialist.[4] In fact, a multidisciplinary team approach have a greater impact, and is often necessary to provide optimal care. Management by a specialist has been shown to be an independent predictor of access to potentially curative treatment and improved survival in lung cancer.[33] It was also discovered on the same study that patients who were referred to a specialist within 6 months of diagnosis were found to have significantly better survival.[33] Although survival gains with treatment may be small, these will become clinically significant when it is realized that lung cancer is the leading cause of cancer-related mortality in the Philippines.

Conclusion

Physicians, both within and between specialties, have varied opinions regarding screening, referral patterns, and therapeutic approach to non-small cell lung cancer. With the growing number of therapeutic options available, referring physicians should be more vigilant, not be influenced by biases and restricted access to patient care, and give patients the opportunity to consider all of their treatment options. In this way, optimum patient care and prolonged survival outcome is achieved.

Recommendations

The authors would like to make the following recommendations, based on the results of this study:

To educate the physicians, regardless of specialty, about the various therapeutic options available in the management of NSCLC and its survival benefit.

To develop standard protocols or algorithm for the management of NSCLC and, eventually, disseminate these guidelines among oncology and non-oncology physicians for proper screening, treatment and referral practice.

References

1. Parkin DM, Bray F, et al: Estimating the world cancer burden: Globocan 2000. Int J Cancer 94:153-156,2001
2. National Center for Health Statistics, Centers for Disease Control and Prevention 2004. American Cancer Society, Inc, Surveillance Research 2005
3. Laudico A, Esteban D et al. 2005 Philippine Cancer Facts and Estimates.

4. Perez EA: Perceptions of prognosis, treatment and treatment impact on prognosis in non-small cell lung cancer. Chest 1998; 114:593-604
5. Vinod SK, Delaney GP, et al: Lung cancer patterns of care in South Western Sydney, Australia. Thorax 2003; 58:690-694
6. Earle C, Neumann PJ, et al: Impact of Referral Patterns on the Use of chemotherapy for Lung cancer. J Clin Oncol 20: 1786-1792
7. Scheaffer, Richard. Elementary Survey Sampling 1986 3rd edition p209
8. Schroen A, Detterbeck F, et al. Beliefs among Pulmonologists and Thoracic Surgeons in the Therapeutic Approach to Non-small cell lung cancer. Chest July 2000;118:129-137
9. Raby B, Pater J, et al: Does knowledge guide practice? Another look at the assessment ofNSCLC. J Clin Onco11995; 13:1904-11
10. Beisalski HK, Chessm A, et al: European consensus statement on lung cancer: risk factors and prevention. CA Cancer J Clin 1998; 48: 167 -17 6
11. Humphrey LL, Teutsch S, et al: Lung Cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the US Preventive Services Task Force. Ann Intern Med 2004; 140: 740-53
12. Henschke cr, Naidich DP, et al: CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004;231 : 164-8
13. Mulshine JL, Sullivan D. Lung cancer screening. N Engl J Med 2005; 352:27142720
14. Gohagan JK, Marcus PM, et al: Final results of the Lung Screening Study, a randomized feasibility study of spiral CT vs. CXR screening for lung cancer. Lung Cancer 2005; 47:9-15 21
15. Smith RA, Eyre HJ et al: American Cancer Society guidelines for the early detection of cancer, 2004. CA Cancer J Clin 2004;54;41-52
16. Postoperative radiotherapy in NSCLC: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. PORT Metaanalysis Trialists Group. Lancet 352:257-263,1998
17. Non-small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311 :899-909, 1995
18. Scagliotti GV, Torri V et al. Randomized Study of adjuvant chemotherapy for completely resected Stage I, II or IIIA non-small cell lung cancer. J Nat'l Cancer Inst 95:1453-61,2003
19. Tada H, Tsuchiya R, et al.: A randomized trial comparing adjuvant chemotherapy vs. surgery alone for completely resected pN2 non-small cell lung cancer (JCOG 9304). Lung Cancer 43:167-173, 2004
20. Waller D, Peake MD et al: Chemotherapy for patients with non-small cell lung cancer. The surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 26: 173-182, 2004
21. Mineo TC, Ambrogi V, et al: Postoperative adjuvant therapy for Stage ill NSCLC. Eur J Cardiothorac Surg 20:378-384,2001
22. Arrigada R, Bergman B, et al: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. NEJM 350:351-360,2004
23. Winton T, Livingston R, et al: Vinorelbine plus Cisplatin vs. observation III resected non-small cell lung cancer. NEJM 2005;352:2589-97
24. Strauss GM, Herndon J, et al.: Randomized Clinical Trial of Adjuvant chemotherapy with Pac1itaxel and Carboplatin following resection in Stage ill NSCLC: Report of Cancer and Leukemia Group B Protocol 9633. J Clin Oncol 22:621s,2004
25. Kato H, Ohta M, et al: A Randomized trial of Adjuvant chemotherapy with Uracil-Tegafur for Adenocarcinoma of the lung. NEJM 2004;350:1713-21
26. Douillard J, Rosell R, et al: ANITA: Phase III adjuvant vinorelbine and cisplatin vs observation in completely resected (Stage I-III) non-small cell lung cancer patients; Final results after 70-month median follow up. ASCO 2005. Abstract No:7013
27. Farray D, Albain K, et al: Multimodality therapy for Stage III NSCLC. J Clin OncoI23:3257-3269,2005
28. Jennens R, de Boer R, et al.: A survey of knowledge and bias among clinicians regarding the role of chemotherapy in Metastatic NSCLC. Chest Dec 2004. Vol 126 No.6
29. Schiller JH, Harrington D, et al: Comparison of four chemotherapy regimens for advanced NSCLC. NEJM 346:92-98,2002
30. Socinski M, Morris D, et al: Chemotherapeutic management of Stage IV Nonsmall cell lung cancer. Chest 2003;123:226s-243s
31. Finkelstein DM, Ettinger DS, et al.: Long term survivors in metastatic NSCLC: an Eastern Cooperative Oncology Group Study. J Clin Oncol1986;4:702-709
32. 32. Sause W. The Role of Radiotherapy in NSCLC. Chest 1999;116:504s-508s
33. Gregor A, Thomson CS, et al: Management and survival on lung cancer in Scotland diagnosed in 1995: results of a national population based study. Thorax 2001;56:212-7 23

The Outcome of Patients with Non-small Cell cancer at the Lung Center of the Philippines from 2000-2003

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Background: Lung cancer is the cause of 921,000 deaths each year worldwide, accounting for 17.8% of cancer-related deaths. Lung cancer is highly lethal, with the highest recorded 5-year patient survival rates (14%) observed in the United States. In Europe, the 5-year overall survival rate is 8%, similar to that of the developing world.
Objective: This study aims to determine the outcome of patients with non-small cell lung cancer at the Lung Center of the Philippines from 2000-2003
Study Design: This is an ambispective cohort study with 256 subjects.
Methodology: Medical records of patients diagnosed with non small cell lung cancer by histopathology report from January 2000 up to June 2003 were obtained from the Tumor Registry at the Record Section.
Results: The study showed that most of the patients belonged to the 60-69 yrs old (83/257=32%). Majority were males (79%) and 39 (15%) were active smokers. Presenting symptom was mainly dyspnea in 51% (n=131) and on chest xray had a solitary mass 53% (n=137). As to location, most were on the right (132)(51.5%) with 103 (40%) left and 18 (7%) bilateral. Most common diagnostic tool used was fiberoptic bronchoscopy, 76 (29.6%) followed by pleural fluid analysis, 55 (21.4%). For patients with metastasis, majority occurred in the brain, 17 (6.6%) followed by the bone, 15 (5.8%) then contralateral lungs, 10 (3.9%). Clinical stage showed they were mainly in stage IV, 109 (43%) then stage IIIB, 78 (31%) then stage IB, 34 (13%). Majority opted no treatment, 157 (61.3%). TNM staging showed most patients were in stage III B, T4N0M0, 54 (21%). With regards to survival, most have expired, 251 (98%) with only 5 (2%) still alive as of the moment.
Conclusions: Patients diagnosed to have non small cell lung cancer have very low 5 year survival rates (5/258 or 2%) despite various forms of treatment. Most patients are diagnosed in the late sage of the disease, stage III-B or stage IV, and most are only given palliative care. Most patients are active smokers with 30-39 or 40-49 pack years smoking history.
Recommendations: A similar but larger prospective trial should be done. There is also a great need to look for treatment of non small cell lung cancer to improve survival. More public education is needed for earlier detection of lung cancer as well as more vigorous anti- smoking campaign. *Phil Journal Chest Diseases. Vol. 13 No. 1 pp: 10-14*

Keywords: Lung cancer, epidemiology, survival

Introduction

Worldwide, bronchogenic carcinoma is the most common cause of cancer death in both men and in women. The 5-year survival rate is 14%, and it has largely remained unchanged for decades. Lung cancer kills more people than colorectal, breast, and prostate cancers combined.[1] Approximately 45% of lung cancer cases occur in women, and, in North America, the number of deaths resulting from lung cancer has recently surpassed the number of deaths resulting from breast cancer. Approximately 1.04 million new cases of lung cancer were diagnosed in 1990, accounting for 12.8% of the worldwide total cancer incidence. The number of new cases is increasing, each year; a 16% increase occurred between 1985 and 1990. Hispanics, the Japanese, the Chinese, Filipinos, and Koreans have incidence rates of 42-53 cases per 100,000 population. The Vietnamese, Alaskan natives, Hawaiians, and whites have incidence rates of 71-89 cases per 100,000 population.[1]

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Previous studies have been done at LCP by Sinsuat and Naval on Survival of Lung Cancer Patients from 1991-1997 and also by Ares. Both studies showed that most patients were males and diagnosed to have NSCCA at the late stage of the disease either stage III or IV. Despite the various forms of treatment received by the subjects most of them expired as shown by the study of Naval. However it only showed a two year survival for the subjects. This study had a longer follow up of the patients, as much as 5 years. The study of Ares only reviewed the: demographic characteristics of patients with NSCCA. It didn't tackle the issue of survival of these patients. The main difference between this study and the other two previously conducted is that this study has longer follow up of the subjects (5 years) and will review the TNM staging.

Methodology

Study Population: Patients diagnosed to have non small cell lung cancer (NSCLC) by histopathologic report admitted at LCP from January 2000-June 2003

Inclusion Criteria: Patients diagnosed to have non small cell lung cancer by histopathologic report admitted at LCP from 2000-2003.

Exclusion Criteria: 1. Patients with a diagnosis of non small cell carcinoma but who did not reply to the researcher after two letters have been sent and three phone calls done. 2. Patients not contacted due to wrong addresses and telephone numbers

Medical records of patients with NSCLC registered with the Lung Center of the Philippines Tumor Registry from January 2000 up to June 2003 were obtained from the Medical Records Section. Medical charts were then reviewed for data on sex, age, smoking history, presenting symptom, radiographic findings, radiographic location of lesion, diagnostic tool, site of metastasis, clinical stage, TNM stage and treatment received. The current status of the patients, whether dead or living, was determined by calling patients or relatives by phone for up to three times or writing patients by regular mail up to twice until they have responded. If patients can't be contacted by phone or through letters then they were considered as being dropped or lost to follow-up from the study.

Statistical Analysis: This is a descriptive study only so the analysis done is just a summary of the data through presentation of frequency tables and corresponding percentages.

Table I Age Distribution of Patient

Age, (years)	No. of Patients	% .of total population
20-29	1	0.3%
30-39	8	3%
40-49	29	11.3%
50-59	80	31%
60-69	83	32%
70-79	45	17.5%
>80	10	3.9%

Table II Sex Distribution of Patients

SEX	No. of Patients	Percent
Male	203	79%
Female	53	20.5%

Table III Smoking history of patients

Smoking (pack years)	No. of Patients	Percent
<10	19	7.4
10-19	20	7.8
20-29	25	10
30-39	34	13
40-49	34	13
50-59	19	7.3
60-69	19	7.7
70-79	8	3
80-89	6	2.3
90-99	1	0.3
>100	7	2.7
No data	20	7.8
Passive smoker	39	15
Non smoker	5	2

Results

There were a total of 1,200 patients registered in the Tumor Registry during the period from January 2000 to June 2003. A total of 256 patients responded to telephone or mail inquiry and were included in the study.

The study showed majority of the patients belonged to the 60-69 years age group (32%) followed by those in the 50-59 years age group (31 %) then by those in the 70-79 years age group (17.5%).

Most (79%) of the subjects were male (n=203).

Most (75.2%) of the subjects were active smokers, 15% were considered passive smokers, and 2% were non-smokers; in 20 (7.8%), data on smoking was not available. Among the smokers, the greatest percentage (13%) were found in those who smoked 30-39 and 40-49 pack-years.

Majority of the patients sought consult because of dyspnea (51%) followed by cough (12%) then by generalized body weakness (7.4%)

Table IV Presenting symptoms

Symptom	No. of Patients	Percent
dyspnea	131	51
cough	30	12
generalized weakness	19	7.4
hemoptysis	13	5
chest pain	13	5
back pain	10	3.9
mass/es	6	2.3
inability to sleep	6	2.3
hoarseness	4	1.5
sensorial change	3	1.1
vomiting	3	1.1
supraclavicular mass	3	1.1
chest discomfort	2	0.7
abdominal pain	2	0.7
diuresis	2	0.7
superior vena cava syndrome	1	0.3
headache	1	0.3
weight loss	1	0.3
dizziness	1	0.3
unresponsiveness	1	0.3
joint pain	1	0.3
lumbar pain	1	0.3
thigh pain	1	0.3
hip pain	1	0.3

Table V Radiologic findings of patients

Radiologic finding	No. of Patients	Percent
Solitary mass	137	53
Pleural effusion	69	27
Multiple masses	21	8.10
Atelectasis	10	3.8
Bilateral infiltrates	9	3 .4
Solitary infiltrate	4	1.5
Hilar fullness	2	0.8
Double del1sity	1	0.3
Pericardial effusion	1	0.3.

Table VI Location of non-small cell Lung cancer

Location	No. of patients	Percent
Right lesion only	132	51.5
Left lesion only	103	40
Bilateral lesions	18	7

Chest radiographic findings showed the patients mainly had solitary mass, 137 (53%) followed by those with pleural effusion, 69 (27%) then by those with multiple masses, 21 (8%).

Many of the patients showed radiographic abnormalities on the right side of the lungs, 132 (51.5%)

Table VII Metastatic sites of Non-small cell lung cancer

Metastatic site	No. of Patients	Percent
Brain	17	6.6
Bone	15	5.8
Lungs	10	3.9
Cervical lymph node	10	3.9
Liver	6	2.3
Esophagus and mediastinum	3	1.1
Bone and brain	3	1.1
Chest wall	2	0.3
Liver and bone	2	0.8
Esophagus	1	0.3
Pleura	1	0.3
Bone and adrenal	1	0.3
Gastric	1	0.3
Supraclavicular lymph node	1	0.3
Scalene lymph node	1	0.3
Back mass	1	0.3
Brain and adrenal	1	0.3
Adrenal	1	0.3
Laryngeal	1	0.3
Liver and lungs	1	0.3
Bone and liver	1	0.3

Table VIII Diagnostic tools used

Diagnostic Tool	No. of Patients	Percent
FOB	76	29.6.
Pleural fluid analysis	55	21.4
CT	30	11.7
Cervical node biopsy	25	9.7
Percutaneous lymph node biopsy	22	8.5
Fine needle aspiration biopsy	10	3.8
Scalene	10	3.8
Supraclavicular node biopsy	7	2.7
Pleural biopsy	7	2.7
Transthoracic needle biopsy	7	2.7
Not available	6	2.3
Thoracentesis	4	1.8
Sputum cytology	3	1.1
VATS	3	1.1
Axillary node biopsy	1	0.3

For those patients with metastasis, these occurred most commonly in the brain (6.6%) followed by those in the bone (5.8%) then by those in the lungs and cervical nodes 10 (3 .9%).

To diagnose Non small cell carcinoma majority were done using FOB, 76 (29.6%). This is followed by pleural fluid analysis in 55 (21.4%) then by chest CT scan, 30 (11.7%)

Majority of the patients did not receive any form of treatment (157 or 61.3%) followed by those who received chemotherapy alone (39 or 15.2%) then by

Table IX Treatment modalities received by the patients

Treatment Given	No. of Patients	Percent
Chemotherapy	39	15.2
Chemotherapy + Radiotherapy	18	7
Radiotherapy	16	6.2
Surgery	15	5.8
Chemotherapy + Surgery	8	3
Radiotherapy + Surgery	2	0.7
Chemotherapy + Surgery + Radiotherapy	1	0.3
None	157	61.3
Not available	0	

Table X Clinical stage of the patient with Non-small cell lung cancer

Clinical Stage	No. of patients	Percent
IA	2	0.7
IB	34	13
IIA	5	2
IIB	9	3.5
IIIA	16	6
IIIB	78	31
IV	109	43

Table XI Tumor node metastasis staging

Clinical stage	TNM state	No. of Patients	Percent
IA	T1N0M0	1	3
IB	T2N0M0	36	14
IIA	T1N1M0	0	0
IIB	T2N1M0	1	3
	T3N0M0	11	4.2
IIIA	T3N1M0	0	0
	T1N2M0	0	0
	T2N2M0	1	3
	T3N2M0	3	1.1
IIIB	T4N0M0	54	21
	T4N1M0	0	0
	T4N2M0	13	5
	T4N3M0	2	0.7
	T1N3M0	5	1.9
	T3N3M0	4	1.5
IV	T0N0M1	13	1.1
	T1N3M1	1	0.3
	T2N0M1	35	13.6
	T2N1M1	1	0.3
	T2N2M1	3	1.1
	T2N3M1	4	1.5
	T3NoM1	7	2.7
	T3N2M1	4	1.5
	T3N3M1	0	0
	T4N0M1	30	11.7
	T4N1M1	1	0.3
	T4N2M1	7	2.7
	T4N3M1	10	3.9

Table XII Present Health status of the Patient

Health Status	No. of Patients	Percent
Alive	5	2
Expired	251	98

those with combination of chemotherapy plus radiotherapy (18 or 7%) .

As to clinical stage, most of the patients belonged in stage IV, l09 (43 %). Next are those in stage IIIB, 78 (31 %) then those in stage IB, 34 (l3%)

TNM staging revealed majority of the patients were in stage IIIB with 54 (21%) followed) then by stage IB (T2N0M0) with 35 (13.6%) then by stage IV (T2N0M1), 35 (13.6).

Majority of the patients have expired, (251 or 98%). Only 5 (2%) are alive as of the writing of this report.

Discussion

As to age, the results of the study showed majority of the patients were in the 60-69 years of age. Worldwide, lung cancer is uncommon in those younger than 40 years. The incidence increases with advancing age and peaks in persons aged 70-80 years. New cases occur in 1.4% of men and 1.1 % of women aged 40-44 years, and the incidence is 21.5% for men and 19.8% for women aged 70-74 years.[2] The study of Ares showed most patients to be in the 45-54 age group. The study by Naval only showed an age range of 19-89 yrs old.

Most of the subjects in the study were males consistent with studies worldwide and those by Naval and Ares

Results showed that most patients in the study are active smokers. This is consistent with studies done worldwide and those by Ares where cigarette smoking is identified as a single etiologic agent for the development of lung cancer.

Studies on lung cancer internationally reveal that the most common presenting symptom is cough (45-75%) followed by dyspnea (37-58%) and hemoptysis (27-57%).[3] Likewise the study of Ares revealed in descending order the following symptoms: cough (130 cases), dypsnea (129 cases) and hemoptysis (25 cases). This study showed most patients sought consult because of dyspnea (51%) followed by cough (12%), and then generalized body weakness (7%). The result of the study was such because the symptom of dyspnea is more alarming to Filipino patients and this prompts

them to seek medical consult. However the symptom of cough is tolerable and is not considered by Filipinos to be a primary manifestation of lung cancer as it can be a symptom of a variety of pulmonary disorders. This may explain why patients are diagnosed in the late stage of the disease as dyspnea almost always accompanies pleural effusion. And it means patient is already at least stage IIIB of the disease. The third most common symptom generalized body weakness also consistent with the late stage of the disease as most patients already have metastasis, mostly to the bones by the time this symptom presents.

On radiography, most patients presented with a solitary pulmonary (53%) mass followed by pleural effusion (27%) then multiple pulmonary masses (8%). This is consistent with the study of Ares where most patients presented with parenchymal lesions (39%). However, studies worldwide advises us to take precaution in interpreting radiographic findings since up to 5% of smoking patients have a normal chest xray but have lung cancer.[4] Most lesions radiographically in descending order were located on the right (51.5%), left (40%) and bilateral lesions in (7%) of cases. This is the same as that shown by Ares showing most lesions being located in the right (59%), followed by left (37%) and then bilateral (4%).

As to sites of metastasis from lung cancer they are mainly in the brain (6.6%), bone (5.8%) and lungs (3.9%) as revealed by the study. This is consistent with studies worldwide which show most common areas of metastasis are the adrenal, liver, brain and skeletal system.[5] One reason why adrenal metastasis are not as often detected may be because patients can rarely afford abdominal CT scans with particular note of the adrenals. While the one done by Ares showed most had metastasis in lymph node (65%), soft tissue (15%), and CNS (12%). This may be explained because a majority of her patients underwent cervical node biopsy as part of diagnostic work up. Since a cranial CT scan wasn't included in her diagnostic procedures it may explain the lower incidence/detection of brain metastasis.

The subjects were mainly in stage IIIB (31%) and IV (43%) by the time the diagnosis of lung cancer was made. This is not consistent with the study of Naval where majority are in stage IIIB (593 cases) followed by those in stage IV (433 cases) and by Ares where they are mostly stage III (300 cases) followed by stage IV (72 cases). A higher incidence of stage IV in this study could be explained by the fact that most patients seek medical consult only if the symptoms are in the advanced state of disease. Only when their symptoms renders them incapacitating do they feel a need to have a check up. Another reason is, they don't have enough finances thus the delay. Another reason may be unavailability of access to medical help especially for those patients living in the rural areas. In general, the trend is by the time the patients are diagnosed of their disease they are in the advanced stage. The TNM staging of patients showed most of them were in stage IIIB (T4N0M0) (21%) then stage IB (T2N0M0) (14%) then stage IV (T2N0M1) (13.6%). This is consistent with the data gathered on the clinical stage of patients where they are mostly in the late stage of the disease.

As to treatment received most patients opted not to have any form of treatment (61.3%) followed by chemotherapy, (15.2%) and chemotherapy plus radiotherapy (7%). A reason for patients not choosing any form of treatment is because the patients and/or relatives have accepted the eventual outcome of the disease. Another could be financial aspect as any mode of therapy is quiet expensive. The study of Ares also showed most patients didn't receive any form of treatment (56 patients). The study of Naval showed that with combined treatment, survival rate of patients in stage III was 34 months and stage IV was 44 months.

As to survival, the study showed most patients expired (251/258 or 98%) despite any kind of treatment given them. Only five (2%) of them survived. Based on an analysis of large databases in inoperable lung cancer patients, the strongest predictors of survival are good performance score (Karnofsky), lower extent of disease (stage) and absence of weight loss.[6] Lung cancer is the cause of 921,000 deaths each year worldwide, accounting for 17.8% of cancer-related deaths. Lung cancer is highly lethal, with the highest recorded 5-year patient survival rates (14%) observed in the United States. In Europe, the 5-year overall survival rate is 8%, similar to that of the developing world.[7]

Conclusions

Patients diagnosed to have non small cell lung cancer have low 5 year survival rates (2%) despite various forms of treatment received. Most patients are diagnosed in the late sage of the disease, stage III-B or stage IV. Most patients are active smokers with 30-39 or 40-49 pack years smoking history.

Recommendations

A prospective, large scale study similar to the one done should be conducted. There is a great need to

look for non small cell lung cancer treatment to improve its outcome. A greater public education is needed for earlier detection of lung cancer. A more vigorous anti-smoking campaign should be done.

References

1. Ares, Luzviminda , 1988. Bronchogenic Adenocarcinoma: A Review of 420 cases. Scientific Proceedings June 1988 pp 65-75
2. Maghfoor, I et al. 2005. Lung Cancer, Non Small Cell. E medicine-Instant Access to Minds of medicine
3. Murray, et al Bronchogenic carcinoma. Respiratorv Diseases in Medicine Vol 3, 5th ed pp1328-1348 and 1357-1378.
4. Sinsuat, Bai ; Naval, S 1997 Survival of Lung Caner Patients seen at LCP from January 1991-June 1997 Scientific Proceedings pp. 65-75
5. Sharma, S Lung Cancer, Non-Small Cell August 10, 2005

Lung Cancer: Cases seen at the Chinese General Hospital and Medical Center (January 2000-May 2002)

MA. THERESA CRISANTA LIM, MD,[1]

Lung cancer is a leading cause of mortality from malignancies among men in the Philippines and in both sexes in the US. Inspite of this, there seems to be limited data locally. To be able to help elucidate this further, this study was undertaken at the Section of Pulmonary Medicine of the Chinese General Hospital and Medical Center. All patients admitted from January 15, 2001 to May 15, 2002 under the Section of Pulmonary Medicine who were for work-up as well as diagnosed cases of lung cancer were included in the study.

A total number of 64 patients were included in the study with an age range of 38-84 years old and a mean age of 45 years. There were 42 males (66%) and 22 females. Smoking history, associated respiratory illness, type of occupation, symptoms as well as stage at presentation, diagnostic modalities used, and histologic types were further determined and discussed in relation to other local studies. Most of the patients presented with late stage disease, with only three (5%) presenting at Stage IIB and the rest with Stage III and above. The most common histologic type was adenocarcinoma (59%) followed by squamous cell carcinoma (28%). There were few small cell carcinoma (5%) but all presented with extensive disease at the time of diagnosis. Diagnostic modalities were split between CT Scan guided percutaneous needle biopsy (34%) and bronchial biopsy (23%). Most had presented with pulmonary symptoms, chest xray findings and/or weight loss. Smoking remained a common risk factor with either active (52%) or passive exposure (8%). However, the remaining (34%) claimed never to have smoked. *Phil Journal of Chest Diseases. Vol. 13 No.1 pp: 15-20*

Keywords : Lung cancer, diagnosis, management

Introduction

Lung cancer is occurring in epidemic proportions worldwide. It is the leading cause of cancer mortality in both men and women in the United States. Since 1897, more women have died each year of lung cancer than breast cancer. The American Cancer Society estimated that 160,000 people would die of lung cancer in 1998; this would represent 28% of all cancers.[1] One of the eight individuals diagnosed with lung cancer will survive five years.[2] It is considered an epidemic disease that is underrepresented in the research finding for early prevention and chemoprevention arenas. Screening programs have been discouraged for both financial and political reasons. Yet increasing evidence suggests that early screening and detection may improve outcome in lung cancer.[3]

Despite the burden of this disease there seems to be a limited published data on lung cancer in the local setting. This paper aims to determine the clinical profile of pathologically proven cases of bronchogenic carcinoma seen at the Chinese General Hospital and Medical Center over a 22 month period (January 15, 2000 up to October 2001).

Materials and Methods

All patients admitted to the Section of Pulmonary Medicine who were for work-up as well as diagnosed cases of lung cancer were included in the study. The study period started January 15, 2001 to May 15, 2002. The investigator provided a uniform data collection sheet to be filled up.

Results

A total number of 64 patients were registered and included in the study. The age range is 38-84 years old

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Table I. Patients' smoking habits

Type of Smoker	Adeno CA (n=38)	Squamous cell CA (n=18)	Large cell CA (n=5)	Small cell CA (n=3)	Total (n=64, %)
Active	14	17	3	3	37 (52)
Passive	3	1	1		5 (8)
Non-smoker	21		1		22 (34)
Pack year					
< 20	8	1	1		10 (16)
21 – 50	4	9	2	2	17 (27)
51 – 80	2	4		1	7 (11)
> 80		3			3 (47)
Smoking Habit					
Currently smoking	7	9	2	2	20 (31)
Previously smoking	7	8	1	1	17 (27)

Table II Diagnostic modalities

Diagnostic Modality	AdenoCA (n=38)	Squamous cell CA (n=18)	Large cell CA (n=5)	Small cell CA (n=3)	Total (n=64, %)
Cytology					
Bronchial washing		4	1		5 (8)
Biopsy of metastatic site	2				2 (3)
Ultrasound guided biopsy	1				1 (2)
CT-guided biopsy	10	7	2	3	22 (34)
Pleural fluid cytology	14				14 (22)
Biopsy					
Excision biopsy of LN	2	2			4 (6)
Bronchial biopsy	8	5	2		15 (23)
Frozen section/ thoracotomy lobectomy	1				1 (2)

with a mean age of 45 years. There were 42 males (66%), dominating the population. Twenty two were female. The results also agreed with the previous studies done in the local setting.[4,5]

Occupational data was included. The grouping of occupational classification is shown in *Figure 1*. The classification was based on the earlier work of Rosaros and colleagues.[5] There were 24 who were classified as those who have white collar jobs

Table III Stage of presentation according to histologic subtype

Histologic Type	Stage of presentation						
	IA	IB	IIA	IIB	IIIA	IIIB	IV
AdenoCA		2			6	7	23
Squamous cell CA				3		5	10
Large cell CA						2	1
Total	0	2 (3)	0	3 (5)	6 (9)	14 (22)	36 (56)

Table IV Time interval from onset of symptoms to diagnosis

Months	AdenoCA (n=38)	Squamous cell CA (n=18)	Large cell CA (n=5)	Small cell CA (n=3)	Total (n=64, %)
< 1	5	3	2	2	12 (19)
1 – 2	5	8			13 (20)
3 – 4	12	5			17 (27)
5 – 6	10	2	3	1	16 (25)
7 – 8	23				3 (5)
9 – 10					
11 – 12	3				3 (5)
> 12					

(businessman, salesman, office worker) which consisted of 28 % of the total population. Individuals with blue collar jobs category was further subdivided as to those with or without possible exposure. There were 16 patients (25%) who were under the category of blue collar jobs with exposure. Those who belong to the blue collar jobs with exposure were plumbers, construction workers, machine operators, sugarcane workers, painters and farmers. There were nine of the blue collared jobs without exposure comprising 14% of the total population. Fifteen (23%) were unemployed including housewives.

Occurrence of associated respiratory diseases was included as shown in *Figure 2*. There were eight (12%) who had no associated illnesses while 10 or 16 % had more than two identified respiratory illnesses. There were 36 (56%) who had chronic obstructive pulmonary disease and 14 had tuberculosis which comprised 22% of the total population. Six (9%) had bronchial asthma.

Smoking which is the most proven carcinogen associated with lung malignancy is common among the study population. *Table I* shows patients' smoking habits. Thirty seven (52%) of the subjects were active smokers, 20 (31%) of whom were current smokers at the time of admission. Five (8%) and 22 (34%) were

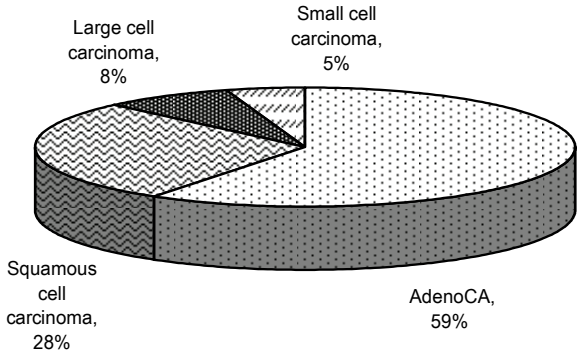

Figure 1 Distribution of subjects according to occupation

passive smokers and non smokers, respectively. Forty three percent of smokers had > 20 pack years smoking history.

Early diagnosis is crucial for early institution of intervention. *Table II* shows the different diagnostic modalities done to come up with the histopathologic diagnosis. There was no standard diagnostic procedure used to establish the disease. Twenty two (34%) were subjected to CT guided percutaneous fine needle aspiration biopsy. Pleural fluid cytology analysis rank second most common diagnostic procedure done comprising 22%. Four (6%) had the diagnosis by lymph node excision biopsy. Bronchial biopsy was done in fourteen (22%) patients. One underwent surgery with frozen section of tissue.

The revised TNM system for staging Lung Cancer was used in this study. This classification was recently revised to better identify' patient groups with similar treatment and prognoses.

Based on clinical experience, the application of new technology and new research findings, the revised system (1) divided stage I and stage II disease into A and B categories and (2) modifies stage IIIA to more accurately reflect the extent of disease and prognostic implications.

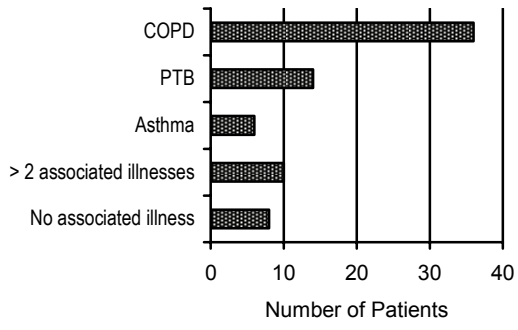

Figure 2 Distribution of subjects according to associated respiratory illnesses

Table V Presenting signs and symptoms of patients

Signs and Symptoms	Adeno CA (n=38)	Squamous cell CA (n=18)	Large cell CA (n=5)	Small cell CA (n=3)	Total (n=64, %)
Pulmonary					
Dyspnea	25	12	2	3	42 (66)
Cough	22	18	2	3	45 (70)
Hemoptysis	1	8		1	10 (16)
Pleural effusion	21				21 (33)
Metastasis					
Bone & chest pains	8	8	4	1	21 (33)
Neck masses					
Neurologic	1	1			2 (3)
Abdominal		3			3 (5)
Chest masses					
Constitutional					
Fever	5	5	2	2	14 (28)
Weight loss	30	17	5	3	55 (86)
Others					
Neck & facial swelling	1	5			6 (9)
Shoulder-hand pain	1	2	1	3	6 (9)
Horseness	8	2		1	12 (19)
CHF					
Osteoarthropathy					
CXR findings	38	10		2	50 (78)

Table VI Non-metastatic extrapulmonary manifestations

Manifestations	Adeno CA (n=38)	Squamous cell CA (n=18)	Large cell CA (n=5)	Small cell CA (n=3)	Total (n=64, %)
Osteoarthropathy		1		1	2 (3)
Myopathy	3	4	2	2	11 (17)
Non-metastatic neuropathy		2		1	3 (5)
Anemia	18	12	2		32 (50)
Leucocytosis	8	5	2		4 (6)

Table VII Location of lesion

Histologic Type	Location		
	Right	Left	Bilateral
AdenoCA	18	14	6
Squamous cell CA	10	6	2
Large cell CA	3	2	
Small cell CA			3
Total (%)	31 (48)	22 (34)	11 (17)

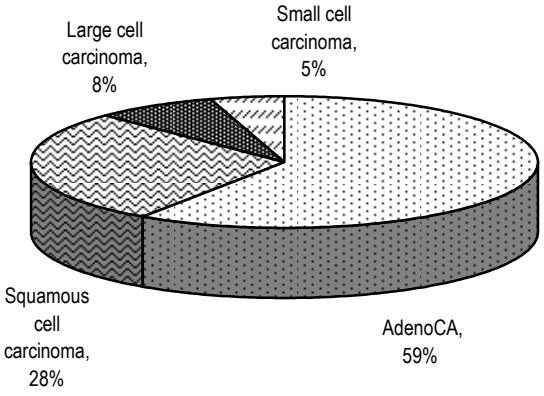

Figure 3 Distribution of subjects according to histologic subtype

Distribution of subjects according to histologic subtype is shown in *Figure 3*. The most common histologic subtype is adenocarcinoma. It was found in 38 patients comprising 59%. Squamous cell carcinoma was second most common type comprising 28% of the total population. Five (9%) was large cell carcinoma. Three (6%) had small cell lung carcinoma.

Majority of the patients, 36 out of the 64 were in stage IV during the time of diagnosis comprising about 56% of cases as shown in *Table III*. Fourteen (22%) patients were in stage IIIB. Six (9%) were in stage IIIA and three (5%) were in stage IIB. All patients with small cell lung carcinoma were at extensive stage disease at the time of diagnosis.

Time interval from the onset of symptoms to the time of diagnosis is shown in *Table IV*. There was a note of a wide range of time interval among the group. Most (91%) of the patients had the symptoms less than six months before the diagnosis while three (5%) had it for about a year.

The grouping of symptoms according to pulmonary, metastatic and constitutional manifestations were done based on earlier work of Mendoza-Wi and colleagues.[4] Pulmonary manifestation was still the most common clinical presentation as shown in *Table V*. Dyspnea was seen in 42 (66%) patients and cough in 45 (70%) patients. Thirty three percent had symptoms of bone and chest pains. Two (4%) had neck masses while three had seizures with brain metastasis on cranial CT scan.

Non-metastatic extrapulmonary symptoms were also noted and the most common of which is anemia which was found in 50% of cases as shown in *Table VI*. Myopathy was also seen in eleven cases (1 7%).

There was predilection for the right lung which was seen in 48%. It was bilateral in eleven (17%) cases.

Discussion

Lung cancer is a silent epidemic. It is a growing problem worldwide. It is a crippling disease which carries a poor prognosis when diagnosed late in the course that even the vast armamentaria developed could not handle. In the United States it is the most common cause of death for both men & women. In the Philippines it has been reported as the number one killer in the adult male and second to breast cancer among females.[6] The burden of this disease will grow substantially in the coming years as shown in the increasing incidence annually.

Histopathology appearance of lung carcinoma is an important guide to prognosis and treatment. The most widely accepted lung tumor classification schema is that of the World Health Organization. This classification system is the result of years of collaborative effort by a panel of pathologists internationally recognized for their lung cancer expertise. The classification system is periodically updated, and the most recent update was published in 1999. The aim of this panel has been to define criteria for diagnostic categories that reflect the biology of lung cancer and at the same time can be reproducibly applied virtually all anatomic pathology laboratories. The new revision includes the elimination of the small cell intermediate cell type category; the addition of the large neuroendocrine and spindle/giant cell categories, and an extensive consideration of paraneoplastic lesions. The histopathologic classification of lung cancer is expected to continue to change as clinical practice and biological understanding of these tumors change.[7]

Retrospective reviews of local studies revealed squamous cell carcinoma as the most common histologic type followed by adenocarcinoma. Recent reports however revealed a changing trend with adenocarcinoma replacing squamous cell as the most common histologic type. This study reinforces prior findings that adenocarcinoma is seen in 38 out of the 64 patients comprising 59% of cases followed by squamous cell carcinoma in 28%. Out of the 38 cases of adenocarcinoma 14 were female and the 12 were non smokers while the two were passive smokers. Studies have shown that adenocarcinoma is the most common type of lung cancer in most recently reported series, and is the most frequent histologic type in

women and nonsmokers of either sex. A five-year survival for resected adenocarcinoma is approximately 30-40%. The second most common cancer in this study is squamous cell carcinoma. This type was the most frequent histologic type of lung tumor in nearly all studies done prior to mid-1980. Most recent reports have noted a shift in the relative frequency of lung carcinoma tumor types such that adenocarcinoma now is more common than squamous cell carcinoma, particularly in women. As an example, a series of almost 5,000 patients entered into a tumor registry between 1964 and 1985 documented that adenocarcinoma was the most common lung tumor in women, accounting for approximately 40% of cases.[8] During the same time period, squamous cell carcinoma remained the predominant histologic type in men, but its incidence decreases from 50 to 37 percent, while the incidence of adenocarcinoma increased from 13 to 27 percent. More recent data from large cooperative group studies in the United States, Europe, and Asia, show that adenocarcinoma now exceeds squamous cell cancer in frequency. The increasing female population involved in cigarette smoking adds up to this result. There also appears to be a trend toward decreasing incidence of small cell cancer which was also noted in this study wherein small cell cancer accounted only for 5%.

Rational treatment and prognosis depend largely on the stage of disease at the time of diagnosis. Staging is the measurement of the extent of tumor that allows rational grouping of patients with similar disease for prognostic, analytic or therapeutic purposes. In the preoperative setting, staging will define patients most likely to benefit from pulmonary resection, while ensuring that no individual is denied the chance of curative resection based on radiologic or clinical findings alone. In this study, the revised TNM staging was used for non small cell lung carcinoma. Seventy eight percent of patients presented with stage IIIB and IV at the time of diagnosis. Little could be offered expect for palliation. The two patients at stage IB and two of IIB underwent surgical resection. There were six patients belonging to stage IIIA comprising only 9%. Three patients included were small cell lung cancer cases. They all have at extensive stage of the disease at the time of diagnosis.

Percutaneous needle biopsy with the aid of computed tomography was the most common diagnostic modality used. In this study, 34% had CT guide percutaneous needle biopsy. This could be attributed to the preference of the family to subject their patient to less invasive procedure like bronchoscopy. High incidence of a positive pleural fluid cytology result was noted. Fourteen cases (22%) underwent diagnostic thoracentesis and were found to be positive for adenocarcinoma.

Imaging plays an integral role in diagnosis, staging and follow-up of lung cancer. Most tumors are detected on chest radiographs, but unfortunately, the majority of patients have advanced stage disease at presentation. ‘. Lung cancer is often considered a differential diagnosis for a spectrum of thoracic radiographic abnormalities. When an abnormality is detected, an important next step is comparison of old radiographs. Most consider a two year interval without change as good evidence for benignancy. If no old radiographs are available, or if the abnormality is new, computed tomography may further characterize the lesion. While CT is extremely specific for certain benign lesions, most abnormalities remain indeterminate and lung cancer cannot be excluded.

The epidemic of lung cancer followed the widespread adaptation of cigarette smoking, allowing for a lag time of about 20-30 years. The initial epidemiologic evidence for an association between cigarette smoking and lung cancer began to appear around 1950 and was based primarily on studies of men. This study showed that smoking played a major role in the development of lung cancer.

Fifty two percent are active smokers and eight percent are passive smokers. Women smokers are noted to be increasing by being passive smokers. A multicenter population based case study done in five metropolitan areas in the United States on Environmental Tobacco Smoke & Lung Cancer in Nonsmoking women showed that exposure to smoking increase the risk of lung cancer in lifetime nonsmokers to about 30% to all types of lung carcinoma. These results confirm earlier findings that the risk from major lung cancer types is consistently higher for women than men. It is a well established fact that cigarette smoking is the principal cause of lung cancer in both men and women. The continued higher incidence rates in men reflect their longer and greater exposure to cigarette tar.

Female lung cancer mortality rates have increased dramatically by 500% since 1950, and in 1987 lung cancer surpassed breast cancer as the leading cause of cancer death among US women. The epidemic in women, as in men, is attributable to cigarette smoking. Today, the disease accounts for 22% of female cancer deaths compared with only 3% in 1950.[12] Smoking

clearly increases the risk of all histologic types of lung cancer, although the defect appears greatest for small cell carcinoma followed by squamous cell carcinoma and then adenocarcinoma. This current study revealed almost the same trend. All cases of small cell carcinoma were smokers. This was followed by squamous cell lung carcinoma then large cell carcinoma.

Although genetic, dietary and other environmental factors play a role in the etiology of lung cancer, cigarette smoking is primarily responsible for the dramatic twentieth century epidemic of the disease in women as well as in men. Research on smoking has increased in the past years and there are many new therapeutic modalities available. We have the behavioral therapy which demonstrated cessation rates of approximately 20% for those willing to participate. Drug therapy remains attractive for many patients but this has monetary considerations. In a country like us where the majority hardly subsist on their daily wage this seems to be a problem. So we are left with the effort of physicians to give advice in any way they can.

Dyspnea and cough was the most common clinical feature on presentation. Other common symptoms noted were fever and weight loss. Regardless of the presentation these patients had the complaints for less than two months. This shows the importance of extensive evaluation of patients with recurrent complaints despite adequate medical intervention.

Bone is the most common site of metastasis, followed by central nervous system. Of the 64 cases, only 40 (63%) had intervention in the form of chemotherapy and radiotherapy.

Conclusion

Genetic and environmental factors play a role in the etiology of lung cancer. Among the many culprits, cigarette smoking is primarily responsible for the dramatic twentieth century epidemic of the disease in women as well as in men.

The medical profession has been struggling with the question of what to do about smoking and its various risks. What about the authorities? Probably they are still in an ambiguous position since political campaigns are funded by tobacco companies, cigarettes are a major source of tax revenues, and most of all this industry employs many people. There are clearly still a large numbers of people who continue to smoke, and we don't seem to be making any headway. It is about time that we have to move on. The big tobacco companies probably have to be aware that there seems to be a very good reason to put a stop on business on poison. Tobacco for many years is responsible for many deaths and so much disability from lung cancer and others cancers, COPD, coronary artery diseases and name it. They have nevertheless continued making large profits up to this date and it's the youth that they target and the third world of course like the Philippines. The anticipated growth in the number of smokers and failure of smoking cessation programs will dramatically increase the national burden of this disease in the near future. When one person could give spare time to explain the hazards of cigarette smoking to each patient probably it will make a big difference in their lives.

Prevention is better than raging a battle against lung cancer when it is already there. Among the identified risk factor cigarette smoking is the best target to intervene. Regarding cancer screening probably we could revise strategy to be able to do early diagnosis. In its early stage lung cancer still has hope of treatment & cure.

References

1. Cancer Facts and Figures-1998.Atrlanta, GA: American Cancer Society; 1998.
2. Wingo PA, Tong T. BoldenJ. Cancer statistic, 1995. CA Cancer J 1995; 45;8-30
3. Timothy C. et a! CHEST 2000; 117:725-795.
4. Mendoza-Wi J. et al, Bronchogenic carcinoma characterization. Phil J Internal Medicine; 1984
5. Rosaros et a!. A Review of Histologically Proven Bronchogenic Carcinoma Cases Seen at UP- PGH (1992-1997)
6. Montevirgen. RM. Et al. 1984. Lung Cancer Epidemiology & Pathogenesis, CHEST DISEASES. 31-45.
7. WilburA. Franklin. Diagnosis of lUng Cance. CHEST: 80S-89S April 2000.
8. Edward F. Patz Jr. Imaging Bronchogenic carcinoma. CHEST 2000;1 17:90S-95S.
9. Elizabeth T.H. et al. Environmental Tobacco Smoke and Lung Cancer in Non Smoking Women.JAMA June 1994 Vol 27:22.
10. Healthy People 2000 Review. Washington (D.C.): US Dcpartment of Health & I-luman Services-Public Health Service, 1 992:102
11. Virginia L Eraster. The Epidemiology of Lung Cancer in Women. Annals of Epidemiology AEP/. Vol 4 :10. 1994

LUNG CANCER EPIDEMIOLOGIC STUDY: January 1, 2002 – December 31, 2002

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Lung cancer is known to be the most lethal of all malignancies known to mankind. In the Philippines, lung cancer is now the third leading cause of death among Filipinos. This study was therefore conducted to conduct an epidemiologic data collection in order to establish the prevalence of, and compare NSCLC and SCLC among admitted patients at St Luke's Medical Center. Included in the study were patients admitted and referred to the pulmonary service from January 1 2002 up to December 31, 2002 for work up of a possible lung carcinoma.

There were a total of 120 medical records with eventually 62 patients diagnosed with primary lung cancer, 4 cases (6.45%) of which are Small Cell Lung Cancer (SCLC) and 58 cases (93.54%) of Non-small Cell Lung Cancer (NSCLC). Among the histologic cases of NSCLC, the most frequent type was adenocarcinoma (25.86%), followed by squamous cell CA (20.68%), then large cell CA (12.06%), bronchioalveolar (6.89%) and adenosquamous (1.72%). All patients were more than 40 years old with the overall incidence of lung cancer in both NSCLC and SCLC groups most prominent in the 50-69 year-old subjects. Most of the subjects were smokers as seen in 62.06% of the NSCLC population but 50% of the SCLC group did not specify any smoking history. Interestingly, in the Adenocarcinoma group, there was a relatively large subset of smokers (60%). There was no significant family history of cancer that correlates with increased incidence in lung cancer. The most common presenting symptoms were cough (41.93%), dyspnea (20.96%) and bone pain (9.67%) for both groups. All patients with SCLC had an extensive stage at the time of diagnosis; while in NSCLC, majority of cases were diagnosed at an advanced stage. The predominant sites of metastasis were that of the bone (34.48%) and brain (20.68%).

Among the cases reviewed, the most frequently utilized method of obtaining tissue diagnosis was by CT guided fine needle aspiration biopsy (74.19%) followed by fiberoptic bronchoscopy (17.74%) although there were further differences depending on histologic subtype. *Phil Journal of Chest Diseases. Vol. 13 No.1 pp: 21-25*

Keywords: Lung cancer, diagnosis, management

Introduction

Worldwide, Lung Cancer is known to be the most lethal of all malignancies known to mankind due to its high incidence and with a high case fatality ratio. In the United States lung cancer constitutes 13% of all malignant tumors and accounts for 28% of all cancer deaths each year.

In the Philippines, lung cancer is now the third leading cause of death among Filipinos, ranking next only to communicable and cardiovascular disease. To date Lung cancer is at its peak compared to previous years with about 11,123 new cases reported each year and with about 9,710 associated deaths.

Smoking is still among the many identified risk factors for the development of lung cancer. In fact the duration of smoking is strongly correlated with the risk of lung cancer and there is evidence that smoking one pack of cigarettes per day for 40 years is associated with a higher risk of lung cancer than smoking two packs per day for 20 years.

The main objective therefore of this study is to conduct an epidemiologic data collection in order to establish the prevalence of Non-small Cell Lung Cancer (NSCLC) and small cell lung cancer (SCLC) among admitted patients at St Luke's Medical Center.

1 Institute of Pulmonary Medicine St. Luke's Medical Center

Table I Distribution of Patients according to Sex and Histologic type of NSCLC

SEX	NSCLC	Squamous	Adeno	Large cell CA	Adeno-squamous	Broncho-alveolar	Total
Male	16	9	9	1	0	3	38
Female	3	3	6	6	1	1	20
TOTAL	19	12	15	7	1	4	58

Table II Distribution according to Gender of all Patients with Lung Cancer.

Sex	NSCLC	SCLC	Total
Male	38	3	41
Female	20	1	21
Total	58	4	62

Table III Distribution of Patients according to Age and Histologic cell type of NSCLC

Age	NSCLC	Squamous	AdenoCA	Large cell CA	Adeno-squamous	Broncho-alveolar	TOTAL
20-29							
30-39							
40-49	2	1	2	1			6
50-59	6	4	5	5	1	3	24
60-69	3	5	5			1	14
70-79	5	1	3	1			10
>80	3	1					4
TOTAL	19	12 (20.68%)	15 (25.86%)	7 (12.06%)	1 (1.72%)	4 (6.89%)	58

Table IV Distribution of Patients according to Age and types of Cancer

Age	NSCLC	SCLC	Total
20-29	0	0	
30-39	0	0	
40-49	6	0	6
50-59	24	1	25
60-69	14	1	15
70-79	10	1	11
>80	4	1	5
Total	58	4	62

Table V Smoking History of Patients according to Pack years

Pack years	NSCLC	SCLC
None	16	0
<1	0	0
1-9	0	0
1 0-1 9	5	1
20-29	4	0
30-39	9	0
40-49	6	0
>50	12	1
Not specified	6	2

Table VI Smoking History According to Histologic Cell type of NSCLC

Pack years	NSCLC	Squamous	AdenoCA	Large cell CA	Adeno-squamous	Broncho-alveolar
None	1	3	6	4	1	1
<1						
1-9						
1 0-19	3		2			
20-29	1	1	2	1		
30-39	2	3	1			2
40-49	4	1	1			
>50	3	4	3	2		
Not specified	5					1

Methodology

Included in the study were patients admitted and referred to the pulmonary service from the study period January 1, 2002 up to December 31, 2002 for work-up of a possible lung carcinoma. The records of the said patients were reviewed and their hospital course was followed through. Analysis of cases was carried out to establish the following: the baseline characteristics of patients with Lung Cancer using various demographic parameters: age, sex, smoking history, family history of cancer, previous history of cancer other than the lungs, and presence or absence of co-morbid illness.

The frequency of clinical symptoms of the disease; distribution of cases across different stages of the disease at time of clinical presentation and diagnosis; and the sites of involvement as well as metastasis to other organ, with the frequency of diagnostic procedures which were used to diagnose lung cancer were also determined.

Results

There were a total of 120 medical records (admissions and referrals to the pulmonary service) reviewed for this study. There were eventually 62 patients diagnosed with primary lung cancer, 4 cases (6.45%) of which are Small Cell Lung Cancer (SCLC) and 58 cases (93.54%) of Non-small Cell Lung Cancer (NSCLC). Among the histologic cases of NSCLC, the most frequent type was adenocarcinoma (25.86%), followed by squamous cell carcinoma (20.68%), then large cell carcinoma (12.06%), bronchioalveolar (6.89%) and adenosquamous (1.72%).

There were 41 males and 21 females among the study subjects. (*Table II*). Likewise there was a male

Table VII Distribution according to Familial History of Cancer

Family History	NSCLC	SCLC
None	53	4
Breast	0	
Lung	1	
Ovarian	1	
Liver	1	
Colon	1	
Renal	0	
Prostate	1	

Table VIII Comparison of Medical History for Cancer and Co-Morbid Illness

Co-morbid	NSCLC	SCLC
None	23	1
Lung	0	
Prostate	2	
Renal	0	
Breast CA	0	
Tongue CA	0	1
PTB	6	1
COPD	7	
OM	15	1
HTN	23	1
Liver Cirrhosis	0	
Asthma	4	

Table IX Distribution of Presenting Symptoms in Patients with NSCLC

Presenting symptoms	NSCLC	Squamous	Adeno CA	Large cell CA	Adeno-squamous	Broncho-alveolar
Cough	9	2	7	5	0	1
Hemoptysis	1	0	1	0	0	0
Chest pain	3	1	0	0	0	0
Dyspnea	2	3	6	0	0	2
Bone pain	3	0	3	0	0	0
Weight Loss	0	1	0	0	0	0
Fatigue	3	2	0	0	1	0
Hoarseness	0	0	0	0	0	1
Asymptomatic	1	0	0	1	0	0

Table X Distribution of Patients with NSCLC by Stage Classification

Stage	NSCLC	Squamous	Adeno	Large Cell	Adeno-squamous	Broncho-alveolar	Total
IA							
IB							
2B							
3A	1	3	1	1			6
3B	2	2	2	1		1	8
4	16	5	9	4	1	3	38
Not specified	2	1	2	1			6

Table XI Sites of Metastasis in Patients with NSCLC

Site	NSCLC	Squamous	Adeno	Large Cell	Adeno-squamous	Broncho-alveolar	Total
Bone	9	2	7	2	0	0	20
Brain	3	3	3	2	1	0	12
Liver	2	0	0	1	0	0	3
Intra-pulmonary	3	0	0	1	0	0	4
Adrenal	1	0	0	1	0	0	2
Pancreas	0	1	0	0	0	0	1
Cord	1	0	0	0	0	0	1

preponderance among both groups of lung cancer patients. However, it is noteworthy that there were actually more females in the large cell carcinoma group. While the rest of the cell types was predominantly more of males. The above findings were consistent with current literatures where there is relative and absolute prevalence of Lung Adenocarcinoma as the frequent cell type.

Comparison of SCLC and NSCLC. Bv Age Group All patients were more than 40 years old. Incidence of SCLC was evenly distributed above the fourth decade. In contrast, in the NSCLC group, the 50-59 year old group had the most number of subjects. Nonetheless the overall incidence of lung cancer in both groups was more prominent in the group of 50-69 year-old subjects (*Tables III and IV*).

Smoking History. Most of the subjects were smokers as seen in 62.06% of the NSCLC population but 50% of the SCLC group did not specify any smoking history. However, in the Adenocarcinoma group, there was a relatively large subset of smokers (60%) which is contrary to previous findings that it is the histologic type that nonsmokers tend to have most (*Tables V and VI*).

Familv History. Overall, there was no significant family history of cancer that correlates with increased incidence in lung CA None of the patients with SCLC had a family history of cancer. In NSCLC, 1.72% of patients has a family history for lung cancer, ovarian CA, Liver CA, colon CA, and prostate respectively. (*Table VII*)

Medical History. Among the patients with NSCLC, the most common co-morbid illness was hypertension (39.65%) followed by Diabetes Mellitus (25.86%). This may relate to the fact that majority of our subjects belong to the fourth decade and above age group (*Table VIII*).

Presenting Symptoms at Time of Diagnosis. Most common presenting symptoms were cough (41.93%),

dyspnea (20.96%) and bone pain (9.67%) for both groups (*Table IX*). There were two subjects (3.22%) who were apparently asymptomatic and were diagnosed incidentally on routine work-ups.

Staging Classification and Site of Metastasis. All patients with SCLC had an extensive stage at the time of diagnosis While in NSCLC, majority of cases were diagnosed at an advanced stage, as 65.51% of cases belong to stage IV. The predominant site of metastasis were that of the bone (34.48%) and brain (20.68%) Other sites of metastasis include intrapulmonary, adrenal, pancreas, and the spinal cord (*Tables X and XI*).

Method of Diagnosis. Among the cases reviewed, the most frequently utilized method of obtaining tissue diagnosis was by CT guided fine needle aspiration biopsy (74.19%) followed by fiberoptic bronchoscopy (17.74%). In NSCLC subgroup adenocarcinoma was mainly documented via FNAB while squamous was diagnosed thru fiberoptic bronchoscopy although a significant number of patients with squamous carcinoma were documented thru FNAB. The above findings correlate well with the dictum, that the approach to diagnosis depends on the location of the lesion whether it is centrally or peripherally accessible.

Table XII Method of Obtaining Tissue Diagnosis

Method	SCLC	NSCLC	Total
FNAB	3	43	46
FOB	1	10	11
VATS	0	2	2
LN Biopsy	0	3	3
Pleural fluid	0	0	0
Pericardial Fluid	0	0	0
Total	4	58	62

Table XIII Methods of Diagnosis in NSCLC

	Large Cell	Broncho-alveolar	Squamous	Adeno-squamous	NSCLC	AdenoCA	Total
FNAB	7	2	7	0	15	12	43
FOB	0	1	4	1	2	2	10
VATS	0	0	0	0	2	0	2
LN Biopsy	0	0	1	0	2	0	3
Pleural fluid	0	0	0	0	0	0	0
Pericardial	0	0	0	0	0	0	0
Fluid							
Total	7	3	12	1	21	14	

Discussion

Age. It is a well known fact that the risk of lung cancer goes up with age. Rates of the disease are low in people under 40; they then increase significantly from age 40 until after 75. Although most cases of lung cancer occur in the sixth through eighth decades of life, 5 to 10% are diagnosed in patients <50 years of age. Several studies have suggested that a more aggressive disease course and a worse prognosis exist among younger patients with lung cancer than older patients. However, similar prognosis of lung cancer in younger and older patient cohorts have also been reported by other investigators.[5] In this study, the peak incidence was noted at ages 50- 59 years old.

Sex. Previously, lung cancer has been known as exclusively affecting men or so called a men's disease. This study reflects such truth as more men than women had the disease overall. Among NSCLC and even among patients diagnosed with Small cell lung cancer, the males still predominates. However, the tide is turning, as increasing number of women are being reported to have the illness. The gender difference in epidemiology of lung cancer has been postulated to be due to the higher susceptibility of women to risk factors especially tobacco smoking. Alternatively, such difference may also be explained by some unknown gender-specific etiological factors. Other postulates attribute the modern lifestyle and chic image associated with smoking, plus the burden on people confined to closed spaces with smokers.

Smoking Cigarette smoking is the leading cause of lung cancer. The rise in lung cancer over the last half century is directly related to cigarette smoking. The role played by smoking in the development of lung cancer is well substantiated. The proposed link between lung cancer and smoking is the potent mutagen released into cigarette smoke from tars in the tobacco. Tobacco smoke contains more than one hundred diverse mutagens and carcinogens, including polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines. The metabolites of these carcinogens are direct mutagens and may cause DNA damage. These chemicals in cigarette smoke cause the mutations inducing lung cancer. Studies suggest that cigarette smoking can act as both an initiator and a promoter of lung carcinogenesis. The initiation and promotion of lung cancer is thought to result from a series of genetic mutations, including point mutations, chromosomal abnormalities, gene amplification, and altered gene expression.[4]

In this study, it was found that there was a high prevalence of smokers in this series. And as little as 10 pack years smoking history, lung cancer has been

evident among the studied cases. Although majority of the subjects have been identified to have smoked more than 20 pack years.

Cigarette smoking is a stronger risk factor for squamous cell carcinoma and small cell carcinoma. This study corroborates the above findings.

Conversely, adenocarcinoma has been the most common type of lung cancer occurring in nonsmokers.[3] Ironically, in this study, a significant number of cases of adenocarcinoma were smokers .

Non-smokers. Clinical and experimental evidence suggests a various links between the non-smoker and lung cancer. A few of these suspected causes were: family history of lung cancer, air pollution, passive smoking, environmental or occupational respiratory carcinogens; exposure to radiation and the like. However, strong associations for these factors have yet to be established. In this study, adenocarcinoma is still the predominant histologic cell type among non-smokers.

Histologic type. In this study, among the different histologic cell types, majority of the patients have Non-Small cell type - of which, adenocarcinoma is the most frequently occurring histologic type followed by squamous cell carcinoma. With regards to histological differences, in the older patients of this series there was a high frequency of squamous cell carcinomas and adenocarcinomas.

Diagnostic approach. Fine needle aspiration cytology in cancer diagnosis is quick, cheap, and accurate when used appropriately. This study has shown that FNAB has a high yield among study subjects.

Subjects with a centrally located lesion, bronchoscopy is still the most sensitive way to obtain tissue diagnosis and to confirm cancer. In a patient with central lesion that is suspicious for lung cancer, further testing to definitely rule out cancer must follow a nonspecific benign result on bronchoscopy.[6] The sensitivity of bronchoscopy is low in patients with peripheral lesion. Therefore a nonspecific result on bronchoscopy of a peripheral lesion that is suspicious for lung cancer requires further testing to definitely rule out cancer. Trans-thoracic needle aspiration (TTNA) has a much higher sensitivity than bronchoscopy in cases of peripheral lung lesion for which it is the procedure of choice for confirmation. A nonspecific result on TTNA of a lesion that is suspicious of being a lung cancer carries a high false negative rate. However, further testing is needed in order to establish a definitive diagnosis in cases of a nonspecific result of TTNA.[6]

Recommendations

Additional research needs to be done to clarify the reasons for changes in the distribution of the major histologic types during the past decades.

References

1. F Barbone, M Bovenzi, F Cavallieri and G Stanta. 1997. cigarette smoking and histologic type of lung cancer in men. Chest. Vol 112, 1474-1479
2. SA Khuder and AB Mutgi. 2001. Effect of smoking cessation on major histologic types of lung cancer. Chest. 120: 1577-1583
3. LT Nordquist, GR Simon, A Cantor, WM Alberts and G Bepler. 2004. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. Chest. 126:347-351
4. SA Khuder and AB Mutgi. 2001. Effect of smoking cessation on major histologic types of lung cancer. Chest. 120: 1577-1583
5. SM Gadgeel, S Ramalingam, G Cummings, MJ Kraut, AJ Wozniak, LE Gaspar, and GP Kalemkerian. 1999. Lung cancer in patients less than 50 years of age. Chest. 5:
6. MP Rivera, F Detterbeck and AC Mehta. 2003. Diagnosis of lung cancer: the guidelines. Chest. 123 (1 suppl): 129s-36s
7. MP Rivera, FC Detterbeck and DP Loomis. 2001. Epidemiology and classification of lung cancer. Diagnosis and treatment of lung cancer an evidence based guide for practicing clinician.

Diagnostic Value of Fiberoptic Bronchoscopy and Fine Needle Aspiration Biopsy in the Diagnosis of Lung Cancer: A Philippine Heart Center Experience

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Lung cancer is the leading cause of cancer deaths in the United States as well as in the Philippines. This study seeks to discover the diagnostic yields of fiberoptic bronchoscopy and fine needle aspiration biopsy on centrally and peripherally located lung lesions. This is a retrospective comparative study of 44 patients with pulmonary mass by chest x ray and/or chest CT scan suspected for lung carcinoma and who underwent fiberoptic bronchoscopy (FOB) and CT scan guided fine needle aspiration biopsy at the Philippine Heart Center from January 1998 to September 2002. Data collected included age, sex, location of pulmonary mass (whether peripherally or centrally located), and bronchoscopic findings of intraluminal mass. Likewise, histopathologic results of fiberoptic bronchoscopy, CT scan guided biopsy, and biopsies of the excised pulmonary mass were gathered. No significant difference in the diagnostic yield of central and peripheral lung lesions combined was noted between FOB and FNAB ($p = 0.134$). However, the diagnostic yield between FOB and FNAB in relation to the location of the lung lesion is statistically significant. Thus, this study showed that fine needle aspiration biopsy has a better diagnostic value in peripheral lung lesions whereas fiberoptic bronchoscopy had a better diagnostic value in centrally located lung. Fiberoptic bronchoscopy has a better diagnostic value regardless of the location of the lesion. *Phil Journal of Chest Diseases. Vol. 13 No. 1 pp: 26-30*

KEYWORDS: fiberoptic bronchoscopy, fine needle aspiration biopsy, lung cancer

Introduction

Lung cancer is the leading cause of cancer deaths in the United States as well as in the Philippines. The individual therapeutic approaches and prognoses depend on accurate diagnosis and staging.[1,2] In a third world country, cost of diagnostic modality is one major hindrance in the proper management of patients with suspected lung carcinoma. There are various diagnostic modalities that can be done. One is sputum cytology. However, studies have shown that this is one test that is not cost effective in clinical practice except when the patient has a large clinically unresectable lesion.[3] The sensitivity of sputum cytology in screening studies are usually in the 20% to 30% range.[4]

Fiberoptic bronchoscopy (FOB) is utilized extensively in the initial evaluation of patients suspected of lung carcinoma. The role of FOB in the evaluation of bronchogenic carcinoma is twofold: (1) It confirms the diagnosis of cancer and determines the cell type, and (2) Inspection of the proximal airways for the presence of endobronchial tumor for tumor staging. Fiberoptic bronchoscopy has a high yield when there is clinical evidence of endobronchial disease, like hemoptysis and/or radiographic findings like lobar atelectasis. However, the role of fiberoptic bronchoscopy in the preoperative evaluation of a peripheral pulmonary nodule or mass without other evidence of endobronchial disease is uncertain.[5]

Transthoracic needle aspiration biopsy (TNAB) for the diagnosis of lung cancer has progressed over the past 35 years. Technical advances and experiences gave way to early concerns about the safety and yield of this technique. Improvements in imaging, biopsy equipment, technique, and cytopathology have allowed the indications for this procedure to expand to include lesions that are smaller and more difficult to approach but many questions and room for advancement remain. Most research regarding the use of transthoracic needle biopsy has been in the form of case series. The patient populations and techniques in these series vary,

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making some results difficult to apply to a given patient. Transthoracic needle biopsy and complimentary diagnostic procedures, such as bronchoscopy, have not been subjected to significant outcomes research; fueling debate about their position in the diagnostic algorithm for lung cancer.[1] FOB and TNAB are by far the most commonly used diagnostic modalities for lung carcinoma. These two modalities, if combined, may lead to a better diagnostic yield, but the question is, will it be cost effective?

The aim of this study is to determine and compare the diagnostic yield of the two modalities in general and try to delineate their specific role in peripheral or central lung carcinoma base on our local experience. Furthermore, this paper will attempt to determine the diagnostic yield of combining FOB and TNAB.

Methodology

A retrospective comparative study of all patients with a pulmonary mass suspected for lung carcinoma by chest x ray and/or chest CT scan and underwent fiberoptic bronchoscopy and CT scan guided fine needle aspiration biopsy at the Philippine Heart Center from January 1998 to September 2002 were included. Data were collected from the bronchoscopy registry of the Division of Pulmonary and Critical Care Medicine and from the CT scan registry of the Division of Radiology. Records were reviewed. Data collected were the age, sex, location of pulmonary mass (whether peripherally or centrally located), and bronchoscopic findings of intraluminal mass. Likewise, histopathologic results of Fiberoptic bronchoscopy, CT scan guided biopsy, and biopsies of the excised pulmonary mass were gathered. Data were analyzed using McNemar's Test via *SPSS 7.5* and *Epi-Info 6* software to determine the diagnostic yields of fiberoptic bronchoscopy and fine needle aspiration biopsy and its specificity and sensitivity in the diagnosis of peripheral and central lung carcinoma as compared to the histopathologic result of the excised pulmonary mass as the gold standard. A p value < 0.05 was considered to be significant.

Results

From 1998 to 2002, 228 patients underwent fiberoptic bronchoscopy (FOB) while 277 patients had CT guided fine needle aspiration biopsy (FNAB) for evaluation of lung masses for malignancy. Among these, 44 patients underwent both procedures, hence were included in the study. The demographic data of all subjects included according to the location of their lung lesion are shown in *Table I.* The group with peripheral lung lesions was older compared to those with central lung lesions (60.84 vs 44.68 years respectively, p value = 0.000). In general, majority of patients presenting with lung mass were males (M = 37; F = 7). However, no significant difference in gender was noted between those with peripheral in contrast to those with central lung lesions (p = 0.6912).

Majority of the histologic types of lung cancer are adenocarcinoma, undifferentiated non-small cell carcinoma, and squamous cell carcinoma, the distribution of which is shown in *Table II*. Curiously,

Table I Demographic data

Parameter	Peripheral Lung Lesions	Central Lung Lesions
Age (Mean ± SD)	60.84 ± 1.66	44.68 ± 12.52
Sex (n, %)		
Male	22 (50)	15 (34)
Female	3 (7)	4 (9)

Table II Histologic types of peripheral and central lung lesions

Histologic Type	Peripheral Lung Lesions	Central Lung Lesions	Total
Small cell CA	0	0	0
Non-small cell CA			
Undifferentiated	10	0	10
Squamous cell CA	7	2	9
AdenoCA	2	9	11
Bronchoalveolar CA	1	1	2
Adenosquamous CA	1	1	2
Sarcoma	0	1	1

Table III Comparison of diagnostic yield between FOB and FNAB in peripheral lung lesions, central lung lesions and both peripheral and central lung lesions (n=positive for malignancy)

Location	Fiberoptic Bronchoscopy	Fine Needle Aspiration Biopsy	*p* Value
Peripheral	6 (24)	20 (80)	0.001
Central	12 (63.2)	6 (31.6)	0.031
Both	18 (40.9)	26 (59.1)	0.134

Table IV Comparison of diagnostic yield of FOB and FNAB in relation to the presence of an intraluminal mass

Intraluminal mass	Fiberoptic Bronchoscopy	Fine Needle Aspiration Biopsy	*p* Value
Positive	5 (55.6)	3 (33.3)	0.688
Negative	13 (37.1)	23 (65.7)	0.021

Table V Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FOB and FNAB in the diagnosis of lung cancer

Overall	Gold Standard		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	+	-				
FOB Positive Negative	12 4	0 5	73.5 (49.8, 88.6)	91.7 (51.7, 99.1)	96.2 (71.7, 99.6)	55 (27.4, 79.9)
FNAB Positive Negative	9 7	2 3	56.3 (33.2, 76.9)	60 (23.1, 88.2)	81.8 (52.3, 94.9)	30 (10.8, 60.3)
Peripheral Lung Lesion						
FOB Positive Negative	3 2	0 3	58.3 (24.1, 86.1)	87.5 (39.6, 98.7)	87.5 (39.6, 98.7)	58.3 (24.1, 86.1)
FNAB Positive Negative	3 2	2 1	60 (23.1, 88.2)	33.3 (1.7, 79.2)	60 (23.1, 88.2)	33.3 (1.7, 79.2)
Central Lung Lesion						
FOB Positive Negative	9 2	0 2	79.2 (50.9, 93.3)	83.3 (31, 98.2)	95 (65.5, 99.5)	50 (17, 83)
FNAB Positive Negative	6 2	0 2	54.2 (28.6, 77.7)	83.3 (31, 98.2)	92.9 (56.1, 99.2)	31.3 (10.2, 64.4)

Table V Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FOB and FNAB in the diagnosis of lung cancer

Overall	Gold Standard		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	+	-				
Combined Positive Negative	13 2	2 3	81.3 (57, 93.4)	60 (23.1, 88.2)	86.7 (62.1, 96.3)	50 (18.8, 82.2)
Peripheral Lung Lesion						
Combined Positive Negative	4 1	2 1	80 (37.6, 99)	33.3 (1.7, 79)	66.7 (30,. 90.3)	50 (2.6, 97.4)
Central Lung Lesion						
Combined Positive Negative	9 2	0 2	79.2 (50.9, 93.3)	83.3 (31, 98.2)	95 (65.5, 99.5)	50 (17, 83)

all undifferentiated, and majority of squamous lung carcinonomas presented as peripheral lung lesions. Adenocarcinomas, on the other hand, presented more as central lesions.

The comparison of the diagnostic yields between FOB and FNAB in peripheral lung lesions (PLL), central lung lesions (CLL), and both peripheral and central lung lesions (BLL) are shown in *Table III*. No significant difference in the diagnostic yield of both peripheral and central lung lesions combined was noted between FOB and FNAB ($p = 0.134$). However, the diagnostic yield between FOB and FNAB in relation to the location of the lung lesion is statistically significant. FOB had more positive diagnostic yield in the centrally located lung lesions compared to the peripherally located lung lesions (63.2% vs 31.6%, $p = 0.031$). On the other hand, FNAB had more positive diagnostic yield in the peripherally located lung lesions compared to the centrally located lung lesions (80% vs 24%, $p = 0.0001$).

The presence of an intraluminal mass during bronchoscopy was analyzed for correlation to diagnostic yield, and findings showed that there were more positive yields among patients who underwent FOB than those who underwent FNAB but this was not statistically significant ($p = 0.688$). However, there were more negative yields among patients who underwent FNAB than those who underwent FOB and this was statistically significant ($p = 0.021$) as seen in *Table IV*.

Among the 44 subjects included in the study only 21 subjects underwent open thoracotomy for excision of the pulmonary mass. Sensitivity, specificity and positive and negative predictive value of FOB and FNAB were computed. Regardless of the location of lung lesion, FOB had better diagnostic yield with a sensitivity of 73.5% with 95% confidence interval from 49.8% to 88.6%, specificity of 91.7% (95% CI 51.7% to 99.1%), positive predictive value of 96.2%

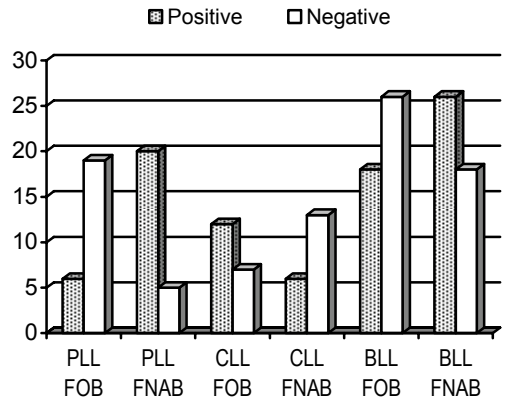

Figure 1 Diagnostic yield of fiberoptic bronchoscopy (FOB) and fine needle aspiration biopsy (FNAB) in peripheral lung lesion (PLL), central lung lesion (CLL) and both peripheral and central lung lesion (BLL)

(95% CI 71.7% to 99.6%) and a negative predictive value of 55% (95% CI 27.4% to 79.9%) compared to CT guided FNAB with a sensitivity of 56.3% (95% CI 33.2% to 76.9%), specificity of 60% (95% CI 23.1% to 88.2%), positive predictive value of 81.8% (95% CI 52.3% to 94.9%), and a negative predictive value of 30% (95% CI 10.8% to 60.3%).

For peripherally located lung lesions, FOB had a sensitivity of 58.3% (95% CI 24.1% to 86.1%), specificity of 87.5% (95% CI 39.6% to 98.7%), positive predictive value of 87.5% (95% CI 39.6% to 98.7%) and a negative predictive value of 58.3% (95% CI 24.1% to 86.1%), while CT guided FNAB had lower yield with a sensitivity of 60% (95% CI 23.1% to 88.2%), specificity of 33.3% (95% CI 1.7% to 79.2%), positive predictive value of 60% (95% CI 23.1% to 88.2%), and a negative predictive value of 33.3% (95% CI 1.7% to 79.2%). In centrally located lung lesions, FOB had better diagnostic yield with a sensitivity of 79.2% (95% CI 50.9% to 93.3%), specificity of 83.3% (95% CI 31% to 98.2%), positive predictive value of 95% (95% CI 65.5% to 99.5%) and a negative predictive value of 50% (95% CI 17% to 83%), while CT guided FNAB had a sensitivity of 54.2% (95% CT 28.6% to 77.7%), specificity of 83.3% (95% CI 31% to 98.2%), positive predictive value of 92.9% (95% CI 56.1% to 99.2%), and a negative predictive value of 3l.3% (95% CI 10.2% to 64.4%).

Use of both modality, FOB and FNAB were also computed. In general, combined modality has a sensitivity of 81.3% (95% CI 57% to 93.4%), specificity of 60% (95% CI 23.1% to 88.2%), positive predictive value of 86.7% (95% CT 62.1% to 96.3%), and negative predictive value of 50% (95% CI 18.8% to 82.2%). In peripherally located lung lesions use of both modality had a sensitivity of 80% (95% CI 37.6% to 99%), specificity of 33.3% (95% CI 1.7% to 79%), positive predictive value of 66.7% (95% CI 30% to 90.3%), and negative predictive value of 50% (95% CI 2.6% to 97.4%). On the other hand, combined modalities had a sensitivity of 79.2% (95% CI 50.9% to 93.3%), specificity 83.3% (95% CI 31% to 98.2%), positive predictive value of 95% (95% CI 65.5% to 99.5%), and negative predictive value of 50% (95% CI 1 7% to 83%) in centrally located lung lesion.

To test the difference in agreement of using both FOB and FNAB versus FOB alone or FNAB alone, kappa test was done and results showed that there is no significant difference in diagnostic value between using a combined FOB and FNAB versus FOB alone with $p > 0.05$, likewise between combined FOB and FNAB versus FNAB alone with $p > 0.05$.

Discussion

The results of this study indicate that in centrally located pulmonary mass fiberoptic bronchoscopy had a better yield in the diagnosis of lung cancer as compared to fine needle aspiration biopsy. The sensitivity of FOB in this study was a little bit low at 79.2%, comparable to other studies with sensitivities ranging from 61% to 94%. Its specificity is a little higher at 83.3% with positive predictive value of 95% and negative predictive value of 50%.

Fine needle aspiration biopsy is sometimes being utilized to diagnose centrally located lung cancers. Despite the fact that literature showed that this modality has a low diagnostic value, it is still being used specially for those with huge central lung masses on chest x ray. This study revealed that FNAB had a poor sensitivity of 54.2% which is in agreement with other studies with regards to diagnosis of centrally located lung carcinoma.

In peripherally located lung lesion, Fine needle aspiration biopsy (FNAB) had higher diagnostic yield compared to FOB (80% vs. 24%, $p < 0.001$). Although our result showed that fine needle aspiration biopsy had a better diagnostic yield in peripheral lung cancer, its sensitivity is not comparable to other studies, with a sensitivity for malignancy ranged from 72% to 99%, specificity ranged from 91% to 100%, positive predictive value ranged from 95% to 100%, and negative predictive value ranged from 48% to 98% as reported in the summary of case series done from 1980 to 1998.[1] FOB had a sensitivity of 58.3% in peripheral lung carcinoma which is almost comparable to FNAB and in fact had a better specificity, positive predictive value and negative predictive value than FNAB (*Table V*). This may be due to the fact that in the evaluation of patients with peripheral lung lesions during FOB and in the absence of an intraluminal mass, bronchial brushings and bronchial washings are being done in the area of the lesion as a standard diagnostic tool. Other studies also reported that the combination of bronchial lavage, bronchial biopsy, and bronchial brushing has significantly increased the accuracy of FOB in the diagnosis of lung cancer.[6] One study even recommends doing a blind forceps biopsy of the main carina and upper lobe carina ipsilateral to the lesion site, because their results showed that the operability of a patient with lung lesion were decreased from 36.4% to 27.3% due to the positive findings of carcinoma diagnosed solely on the blind biopsy results.[7] Peripheral tumors that are not visible on endobronchial examination are diagnosed less readily by fiberoptic bronchoscopy. However literature showed that

fiberoptic bronchoscopy still provides a diagnosis in 48% to 80%, with an average of 69% in 15 studies of patients with peripheral lung cancers. Our result is comparable with that of foreign literatures with FOB carrying a sensitivity of 58.3%.[1,11,12] Chechani reported that lung lesions not visible through the bronchoscope can be diagnosed with accuracy in most patients by FOB.[8]

Overall, regardless of location of lung lesion fiberoptic bronchoscopy has a better diagnostic value with sensitivity of 73.5%, specificity of 91.7%, positive predictive value of 96.2%, and a negative predictive value of 55%, comparable to studies done from 1970 to 2000. Fine needle aspiration biopsy has an overall sensitivity of 56.3%, specificity of 60%, positive predictive value of 81.8%, and a negative predictive value of 30%. This is maybe due to the fact that, even if fine needle aspiration biopsy is being done under CT guidance, radiologists are still cautious of possible complications after transthoracic needling, especially pneumothorax. Studies from 1976 to 1993 revealed a pneumothorax rate from 11% to 67%. Also, FOB guided biopsy, even though it is more invasive, is still better because the bronchoscopist has a good picture of the lesion three dimensionally.

Combined modalities had a better diagnostic sensitivity being 81.3% in this study. Other studies had an 88% yield.[10] However, when combined procedure were compared to using FNAB alone or FOB alone, there was no significant difference statistically in diagnostic value.

Adenocarcinoma was the most common histologic type, and is commonly seen centrally, followed by undifferentiated carcinoma. Squamous cell carcinoma was the third in incidence and presents as a peripheral lung lesion. This finding is not congruent to previous findings that adenocarcinoma is generally located peripherally and squamous cell carcinoma is often seen centrally. The changing pattern of lung cancer by histologic type were also reviewed in many studies in the 1990's and findings showed that the proportion of adenocarcinomas among lung cancers has been increasing.[14,15] The reason for the shift in the proportions of the various histologic types of lung cancer has not been clearly identified. However, circumstantial evidence points to changes in smoking habits as a plausible explanation.[14, 16]

Conclusion

This study concludes that fine needle aspiration biopsy has a higher diagnostic value in peripheral lung carcinoma as compared to fiberoptic bronchoscopy and that fiberoptic bronchoscopy has a better diagnostic value in central lung carcinoma as compared to fine needle aspiration biopsy. But overall, regardless of whether the lesion is centrally or peripherally located, fiberoptic bronchoscopy has a better diagnostic value.

Recommendation

We recommend that in a developing country, it is better to adapt the use of fine needle aspiration biopsy in the diagnosis of peripherally located lung cancers and fiberoptic bronchoscopy to centrally located lung cancers to save on costing but not sacrificing outcome of diagnosis of lung cancer.

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References

1. Peter J. et al. Bronchoscopy and Needle Biopsy Technique for Diagnosis and Staging of Lung Cancer. Clinic in Chest Medicine Mar 2002; 23:1
2. Laudico AV. et al. Philippine Cancer Facts and Estimates, 1993. Philippine Cancer Society Inc. UP Manila
3. Goldberg-Kahn B. et al. The Cost of Diagnosis. A Comparison of Four Different Strategies in the Workup of Solitary Radiographic Lung Lesions. Chest 1997; 111: 870-76
4. Lam S, Shibuya H, Early Diagnosis of Lung Cancer. Clinics in Chest Medicine. 1999; 20:1:53-61
5. Aristizabal IF. et al. Can Chest. CT Decrease the Use of Preoperative Bronchoscopy in the Evaluation of Suspected Bronchogenic Carcinoma? Chest. 1998; 113:5
6. Gaber KA. et al. Cytological Examination of the Whole Endobronchial Brush in Bronchoscopic Diagnosis of Lung Cancer. Respiratory Medicine. April 2002; 96:4
7. Gunen H. et al. Utility of Blind Forceps Biopsy of the Main Carina and Upper- Lobe Carina in Patients With Non-small Cell Lung Cancer. Chest. February 2001; 119:2
8. Chechani V. et al. Bronchoscopic Diagnosis of Solitary Pulmonary Nodules and Lung Masses in the Absence of Endobronchial Abnormality. Chest. 1996; 109:620-25
9. Hill PC. et al. Pneumothorax with fine Needle Aspiration of Thoracic Lesions. Chest. October 1993; 104:1017-20
10. Wallace JM. et al. Flexible Bronchoscopy and Percutaneous Needle Lung Aspiration for Evaluating the Solitary Pulmonary Nodule. Chest. June 1982; 81:6
11. Cortese DA. et al. Biopsy and Brushing of Peripheral Lung Cancer with Fluoroscopic Guidance. Chest. 1979; 75:2:141-145
12. Radke JR et al. Diagnostic Accuracy in Peripheral; Lung Lesions. Factors Predicting Success with Flexible Fiberoptic Bronchoscopy. Chest. 1979; 76:2:176- 179
13. Kvale PA. et al. Diagnostic Accuracy in Lung Cancer. Comparison of Technique Used in association with Flexible Fiberoptic Bronchoscopy. Chest. 1976; 69:6:752-75 7
14. Zheng T, Holford Tr, Boyle P, et at. Time trend and the age period cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989. Cancer. 1994;74: 1556-1567.
15. Valaitis L, Warren S, Gamble D. Increasing incidence of adenocarcinoma of the lung. Cancer. 1981;47:1042-1046

16. Wynder EL, Hoffman D. Smoking and lung cancer: Scientific challenges and opportunities. Cancer Res. 1994; 54:5284-5295
17. LoCicero J. Does Every Patient With Enigmatic Lung Disease Deserve a Lung Biopsy? Chest. 1994; 106:706-08
18. Torrington KG. et al. The Utility of Fiberoptic Bronchoscopy in the Evaluation of the Solitary Pulmonary Nodule. Chest. October 1993; 104:4:1021-24
19. Baaklini WA. et al. Diagnostic Yield of Fiberoptic Bronchoscopy in Evaluating Solitary Pulmonary Nodules. Chest. April 2000; 117:4

A Comparative Study of Induced Sputum versus Spontaneous Sputum for Cytologic Examination in the Diagnosis of Lung Cancer

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To determine the method of sputum collection that will give a higher yield in diagnosing lung cancer by sputum cytology, 54 patients suspected of having lung cancer were prospectively studied. After randomization, 27 had induced sputum cytology, 27 had spontaneous sputum cytology, all done thrice. Specimens were stained by Papanicolau technique and reported using method of Papanicolau. The same set of patients underwent bronchoscopy for definitive pathologic diagnosis. Results obtained revealed a higher yield in multiple induced sputum cytology as compared to multiple spontaneous sputum cytology. No significant adverse effects were noted on both groups. The cost benefit ratio of multiple induced sputum cytology is at PhP 6,649.64 while multiple spontaneous sputum cytology is at PhP 7,599.28. Though statistically insignificant, multiple induced sputum cytology has a higher yield in the diagnosis of lung cancer as compared to multiple spontaneous sputum cytology. Induced sputum cytology is generally safe and has a better cost benefit ratio as compared to spontaneous sputum cytology. Multiple induced sputum cytology is an option for patients undergoing lung cancer evaluation who are poor candidates for invasive procedures. *Phil Journal of Chest Diseases. Vol. 13 No. 1 pp: 31-35*

Keywords: Lung cancer, diagnosis, sputum cytology

Introduction

In the process of diagnosing lung cancer, most patients have chest radiograph that reveal pulmonary lesions suggesting presence of malignancy. For pathological diagnosis, patients often undergo additional testing such as bronchoscopy, fine needle aspiration, thoracoscopy, and thoracotomy; and less commonly, sputum cytology. In the 1960's, sputum cytology was dubbed as the best initial test in diagnostic evaluation of patients with chest radiograph suggesting a malignancy.[1] It's the least invasive method of obtaining a cytologic diagnosis in a patient suspected of harboring lung cancer. Sputum cytology sensitivity for diagnosis of lung malignancies has been declining steadily over time. At present, foreign literature cited its sensitivity to only 30-60%,[2,3] local data at 5-30%.[4,5] This can be secondary to changes in relative proportion of lung cancer cell types at present, an increase of adenocarcinoma cases as compared to previously predominant squamous cell bronchogenic carcinoma.

Bronchoscopy and fine needle aspiration at present had replaced sputum cytologic testing in the initial evaluation of lung cancer suspects. It has a higher probability of obtaining pathologic diagnosis, but it has its inherent disadvantages such as greater risk of morbidity, mortality and is more costly per test.

Sputum induction had been proven useful in diagnosing mycobacterial infections and *Pneumocystis carinii* pneumonia,[6] but there are scant data on its use in the diagnosis of lung malignancy. Sputum induction could result to respiratory failure, especially in patients with hyperactive airways. It can also lead to hemoptysis in some cases.

Since no study, both local and foreign, has been done proving the utility of induced sputum cytology in diagnosing lung malignancy, this study attempts to know its usefulness on initial evaluation of lung cancer suspects.

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Table I Demographic characteristics of patients

Parameter	Induced (n=27)	Spontaneous (n=27)	*p* Value
Age, mean (SD)	54.11 (10.26)	60.4 (9.39)	0.02
Sex, male (%)	20 (74)	25 (93)	0.14
Smoker (%)	19 (70)	26 (96)	0.02
Pack years, median (range)	40 (10-125)	37.5 (5-60)	0.31

Table II Presenting symptoms of patients

Symptoms	Induced (n=27)	Spontaneous (n=27)	*p* Value
Weight loss	13 (48)	14 (52)	0.78
Hemoptysis	8 (30)	9 (33)	0.77
Cough	25 (92)	26 (92)	1.00
Back pain	9 (33)	9 (33)	1.00

Table III Histologic diagnosis based on fiberoptic bronchoscopy

Histologic type	Induced (n=15)	Spontaneous (n=14)	*p* Value
Small cell CA	4 (27)	2 (14)	
Non-small cell CA	2 (13)	3 (21)	
AdenoCA	2 (13)	4 (28)	
Squamous cell CA	7 (47)	5 (36)	
Total	15	14	0.664

The objective of this study is to compare the usefulness of multiple induced sputum cytology versus multiple spontaneous sputum cytology in the diagnosis of lung cancer. The secondary objectives are to determine the yield, safety and cost benefit of multiple induced vs. spontaneous sputum cytology in lung cancer diagnosis.

Materials and Methods

*Subject Selection***.** Patients seen at Lung Center of the Philippines, with chest radiograph revealing centrally located pulmonary lesions suggestive of the presence of lung malignancy, giving consent for bronchoscopy for histologic diagnosis, were included in the study. Centrally located pulmonary lesions are lesions within the medial two-thirds of chest radiograph or with evidence of partial atelectasis or presence of cutoff sign.

Lung cancer suspects in respiratory failure/insufficiency, presenting with massive hemoptysis, completely atelectatic lung, known hyperactive airway needing regular dose of bronchodilator and/or steroids, or with performance scale of at least Zubrod III were excluded from the study. Patients undergoing histologic diagnosis through metastatic node biopsy were also excluded.

Procedure Patients included in the study, after an informed/written consent, were randomly assigned, using a computer generated randomization schedule, into two groups. The first group had sputum induction done thrice. The second group had spontaneous sputum collection done thrice. The first samples were collected on the day of consultation, second on the following morning and third sample collected immediately prior to a scheduled bronchoscopy.

Sputum induction was done using 3% hypertonic saline solution, delivered by jet ultrasonic nebulization for a period of 12 minutes. Subjects were instructed to do tidal breathing by mouth during the period and cough out any phlegm produced. As a safety feature, a bronchodilator, salbutamol MDI, was administered 10 minutes prior to the procedure. A pulmonary fellow-in-training examined patients prior to sputum induction and monitored patients during the procedure for any adverse effects. Vital signs were recorded prior, during and every 15 minutes for the next 2 hours after the procedure.

For spontaneous sputum collection, after thoroughly rinsing mouth with water, patients were instructed to breathe deeply three times. After the third breath, patients were asked to cough hard and try to bring up sputum from deep in the lungs. At least one tablespoon of sputum, not saliva, was collected and submitted for cytology. Any adverse effects on

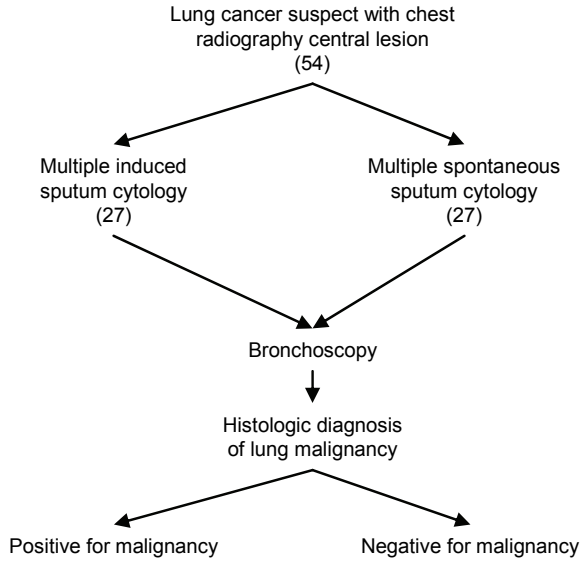

Figure 1 Flow chart of procedures

Table IV Visual findings on fiberoptic bronchoscopy

Visual Findings	Induced (n=27)	Spontaneous (n=27)	*p* Value
(+) Mass	11	12	
(-) Mass	9	8	
Narrowing/stenosis	7	7	
Total	27	27	0.95

Table V Diagnostic yield of multiple induced sputum cytology

Induced sputum	(+) by FOB	(-) by FOB	Total
Positive	3	1	4 (14.8)
Negative	12	11	23 (85.2)
Total	15	12	27

Table VI Diagnostic yield of multiple spontaneous sputum cytology

Induced sputum	(+) by FOB	(-) by FOB	Total
Positive	1	0	1 (3.7)
Negative	13	13	26 (96.3)
Total	14	13	27

spontaneous sputum specimen gathering were noted.

Both the induced and spontaneous sputum specimens were placed on a clean container with a well-fitted cap. Specimens were then brought to the Department of Pathology of Lung Center of the Philippines for cytology.

Specimens were smeared in slides and stained using Papanicolau technique.

Results were then reported using the method of Papanicolau. After sputum collection, definite histologic diagnosis was obtained through bronchoscopy. Bronchial aspirate, washing, and brushing were done if there is no intraluminal mass noted or bronchial bite biopsy, done at least three times, for intraluminal mass. Visual findings were also noted and reported. Patients were monitored with a pulse oximeter during the procedure. All specimens for cytology and histopathology were brought to the Department of Pathology of the Lung Center of the Philippines and read by a consultant pathologist (*Figure 1*).

Outcome Measures The two groups were compared in terms of diagnostic yield based on the percentage of positive test for the procedure. Safety was determined by the presence of adverse events noted after each procedure. Assessment of the cost-benefit ratio for each method of sputum cytology was done by assuming a hypothetical diagnostic protocol which utilizes sputum cytology, either induced or spontaneous, as an initial procedure followed by fiberoptic bronchoscopy in cases where cytology is negative. The cost of induced sputum cytology, spontaneous sputum cytology and fiberoptic bronchoscopy were based on average charges in the Lung Center of the Philippines. The cost of every definitive case of lung cancer diagnosed was used as the measure of the cost-benefit of each method. This was calculated by determining the total cost incurred by all 27 patients in each group if the diagnostic protocol was used divided by the number of cases with a definitive diagnosis of lung cancer.

Statistical Analysis Descriptive statistics were used to summarize mean, standard deviation for quantitative variables and percentages for qualitative variables. Comparability of the two groups in terms of demographic and clinical data was assessed using t-test and chi-square. *Fischer's* exact test was used when appropriate. A statistical package (*STATA*) was used for the calculations. A $p < 0.05$ was considered significant. Cost was based on society's perspective.

Results

A total of 54 patients (27 induced sputum and 27 spontaneous sputum) were included in the study. Mean age of both groups was at 57 years old. Spontaneous sputum cytology group comprised of statistically significant older age (60.4 yrs) and a largely smoking group as compared to induced sputum cytology group (*Table I*).

The most common presenting symptom of patients

Table VII Histologic diagnosis based on sputum cytology

Histologic type	Induced (n=4)	Spontaneous (n=1)
Small cell CA		
Non-small cell CA		
AdenoCA	1 (25)	1 (100)
Squamous cell CA	3 (75)	
Total	4	1

Table VIII Adverse effects

Adverse effects	Induced (n=27)	Spontaneous (n=27)
Hemoptysis	1 (3.7)	0
Dyspnea	6 (22.2)	6 (22.2)
Chest pains	1 (3.7)	1 (3.7)

Table IX Comparative cost of procedures (in Philippine pesos)

Procedure	Induced (n=4)	Spontaneous (n=1)
Sputum cytology (3x)	540	540
Sputum induction (3x)	330	
Nebulizing kit	56.25	
Sputum canister	30	30
Salbutamol inhaler	2.80	
Bronchoscopy	3500	3500
Total (x 27 pts)	106,394.35	106,390
Cost per definitive diagnosis	6649.64	7599.28

is cough, followed by weight loss on both groups (*Table II*). The most common histologic diagnosis on fiberoptic bronchoscopy was squamous cell carcinoma in both groups (46% for induced sputum, 36% for spontaneous sputum) (*Table III*). Visual findings on bronchoscopy had almost similar frequencies on both groups (*Table IV*). Bronchoscopy had an overall yield of only 53% (15/27 for induced sputum cytology group, 14/27 for spontaneous sputum group) on both sets of patients. The differences were all not statistically significant.

Induced sputum cytology had a 14.8% positive yield as compared to a 3.7% positive yield of spontaneous sputum cytology (*Tables V and VI*). Its difference was also not statistically significant (*p=0.351*).

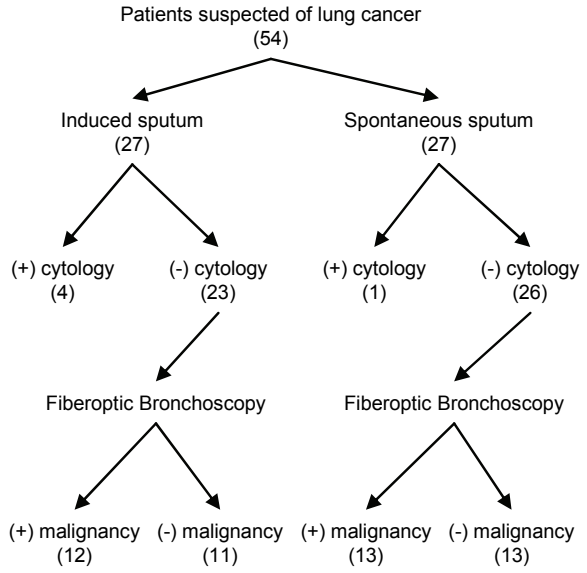

Figure 2 Summary of diagnostic yield of diagnostic protocol using sputum cytology followed by fiberoptic bronchoscopy

Squamous cell carcinoma was also the most common histologic findings in the induced sputum group (*Table VII*). All of the histologic findings of induced sputum had the same corresponding histology from specimens obtained through bronchoscopy except for one subject. This subject had squamous cell carcinoma by sputum cytology but no intraluminal mass noted on bronchoscopy. Subsequent aspirate/brushing cytologies revealed only metaplasia (class III).

Identified adverse effects were slight dyspnea, chest pains and an episode of non-massive hemoptysis (*Table VIII*). The single episode of non- massive hemoptysis was noted on a patient under the induced sputum group. It amounted to about 2 tbsps of fresh blood while undergoing sputum induction, not requiring any emergency intervention nor need for special care.

The overall cost of multiple induced sputum cytology on 27 patients was at PhP 25,894.35 (PhP 959.05 each) while multiple spontaneous sputum cytology on 27 patients was at PhP 15,390.00 (PhP 570.00 each). Using a diagnostic protocol utilizing sputum cytology followed by fiberoptic bronchoscopy for negative yield, induced sputum saved a total of four fiberoptic bronchoscopies while spontaneous sputum saved only one fiberoptic bronchoscopy (*Figure 2*). At an estimated average expense of PhP 3,500.00 for fiberoptic bronchoscopy with histology, cytology cost per correct diagnosis for induced sputum cytology was at PhP 6,649.64. Spontaneous sputum cytology cost per correct diagnosis is at PhP 7,599.28 (*Table IX*).

Discussion

Sputum cytology is considered the simplest and least invasive technique of lung cancer evaluation, with the dual purpose of determining the presence of tumor and classifying tumor as accurately as possible. Sputum induction is proven useful in the diagnosis of *Pneumocystis carinii* pneumonia and mycobacterial infections[6] but there are scant data on its use in the diagnosis of lung cancer. Available research done on sputum induction didn't show much benefit from its use aside from patients who are asymptomatic from cough.

In a study by Gerschman et al[7] in 1999, he recommended 12 minutes sputum induction as the optimal duration for sputum induction. The duration affects the cellular/biochemical composition of induced sputum. The large airways are sampled at the beginning of sputum induction, while the peripheral

airways/alveoli are sampled at later time period. Macrophages predominate at the end, while eosinophils/neutrophils are higher at the beginning of sputum induction.

In 1986, Chavez[4] made a research on which method of collection and staining would give the highest yield in sputum cytology. Results showed a trend for a 24 hour spontaneous sputum collection and staining with Saccomanno method for a better malignant detection. A follow-up study in 1989 by Edrozo[5] compared the diagnostic yield of a three day versus a 24 hour sputum collection. It was concluded that the three day early morning sputum collection produced a significant higher diagnostic yield than the 24 hours sputum collection.

Randomization failed to provide an almost similar baseline characteristic of both groups in this study. The spontaneous sputum cytology group comprised of a much older group with a higher percentage of smokers, both known risk factors for lung cancer. This could have increased the yield of multiple spontaneous sputum cytology but results obtained were the opposite. Endobronchial symptoms, and cough, predominate in both groups. This is secondary to the inclusion criteria of a central pulmonary mass, which is expected to increase the yield of sputum cytology. Definitive histologic diagnosis based on specimens obtained through fiberoptic bronchoscopy revealed predominance of squamous cell carcinoma in both groups. This supports previous conclusions that squamous cell carcinoma predominates in centrally located lesions.

In general, sputum cytology is highly specific but less sensitive in diagnosing lung malignancy. The diagnostic yield of both multiple induced and spontaneous sputum cytology in this study is lower as compared to the 40% yield in the study of Chavez in 1986. This can be secondary to the overall low yield of lung cancer diagnosis (53%) on both sets of patients even after obtaining specimens for pathologic diagnosis after bronchoscopy.

Only minor adverse effects were noted on both groups. Induced sputum collection is as safe as spontaneous sputum collection on this particular set of patient population. The cost benefit ratio of induced sputum cytology is much cheaper as compared to the spontaneous sputum cytology. This can be translated to a to a lower direct cost of obtaining a correct diagnosis for lung cancer in clinical practice.

Though statistically insignificant, induced sputum cytology has a higher yield, generally safe and has a better cost benefit ratio as compared to spontaneous sputum cytology in the diagnosis of lung cancer. Multiple induced sputum cytology remains as an option for patients undergoing lung cancer evaluation who are poor candidates for invasive procedures.

References

1. Johnston et al. Comprehensive Cytopathology. Philadelphia: WB Saunders, 1991. 320-98
2. Raab S.S. et al. The Importance of Sputum Cytology in the diagnosis of Lung Cancer. Chest 1997. 112:937-45
3. Bechtel JJ et al. Outcome of 51 patients with Roentgenographically Occult Lung Cancer detected by Sputum Cytologic Testing, A Community Hospital Program: Archives of Internal Medicine. May 1994; 154(9):975-980.
4. Chavez J.R. Sputum Cytology in the Diagnosis of Bronchogenic Carcinoma. Chest Diseases; June 1986; 3-12
5. Edrozo VS. A Comparative Study of Early Morning Sputum versus 24-Hour Sputum Collection in the Cytologic Diagnosis of Carcinoma of the Lung. LCP Scientific Proceedings; December 1989; 256-259
6. Bandyopadhyay T. et al; A Comparison of Induced and Expectorated Sputum for the Microbiological Diagnosis of Community Acquired Pneumonia. Respiration; 2000; 67(2):173-6
7. Gerschman N., et al; Fractional Analysis of Sequential Induced Sputum Samples During Sputum Induction. Journal of Allergy and Clinical Immunology. Aug 1999. 104:322-8.

Glutathione S - Transferase Polymorphisms as Biomarkers of Lung Cancer Risk among Filipinos

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Background: Glutathione S - transferase (GST) is a phase II enzyme which catalyzes reactions between glutathione and a variety of electrophilic compounds. Its isoenzymes display several polymorphisms (GSTT1, GSTM1, and GSTP1) which have been found in some studies to be associated with an increased risk for developing lung cancer, particularly among smokers. Few such studies have been done in the Asian population.
Objectives: This study determined the interaction between the GST genotypes and smoking history on lung cancer susceptibility among Filipinos.
Methodology: From 2002 to 2005, via a case control study design, we analyzed blood, pleural fluid, bronchia or lymph node biopsy or lung mass specimen taken from patients with histologically proven lung cancer and compared these with similar specimen obtained from non-cancer pulmonary subjects. GST polymorphisms were identified using PCR analysis (Institute of Human Genetics, UP-NIH, Manila). Statistical analysis was done using *SPSS* software.
Results: 201 lung cancer cases (mean age = 58.8y; ever-smokers 80.1%) and 110 controls (mean age = 53.3y ever-smokers 48.1 %) were entered into the study. There was no significant association between the presence of GSTT1 (OR=1.049; 95% CI: 0.59-1.86; *p*=0.8695), GSTP1 (OR=1.49; 95% CI: 0.77-2.89; *p*=0.2376) and GSTM1 (OR=1.25; 95% CI: 0.61-2.58; *p*=0.5400) null genotypes and lung cancer risk irrespective of the smoking history.
Conclusion: The association between GSTT1, GSTM1 or GSTP1-null genotypes and lung cancer susceptibility is weak among Filipinos. *Phil Journal of Chest Diseases. Vol. 13 No. 1 pp: 36-39*

Keywords: Lung cancer, Diagnosis, genetic polymorphism

Introduction

Over the past century, lung cancer has become one of the leading causes of cancer death worldwide.

Initially an epidemic disease among men, lung cancer now has become the leading cancer killer in both sexes in the United States and increasingly in developing countries.[1] In the Philippines, lung cancer is the most common cancer in males and third most common among females. It has claimed the lives of more than ten thousand people in year 2000 alone.[2] The World Health Organization has estimated that by the year 2025, worldwide lung cancer deaths will increase several folds, primarily in the third world countries like the Philippines.[3]

Tobacco smoking has been established as the most important etiologic factor of lung cancer for both men and women. However, only a fraction of smokers, approximately 20%, will eventually develop lung cancer.[4] This finding leads to the notion that there may be genetic factors that affect individual susceptibility to develop the cancer. Other factors that have been attributed are gender, race, environmental factors, occupational exposures and pre existing non-malignant lung disease.[1]

Studies of familial clustering of lung cancer cases and novel in molecular epidemiology provide us with knowledge on the genetic susceptibility for the disease. There has been much interest in determining the polymorphisms that are hypothesized to affect lung cancer risk, particularly focusing on molecules associated with carcinogen handling and deoxyribonucleic acid (DNA) repair. This includes polymorphisms of the genes encoding Phase I and Phase II xenobiotic metabolizing enzymes. An individual's susceptibility to cancer may be affected by the balance between the capacity to activate inhaled

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pro-carcinogens (Phase I enzymes) and the capacity to detoxify carcinogens (Phase II enzymes). The genetic variations thought to be important in lung cancer include polymorphisms at cytochrome P 450 gene loci (CYP 450) such as CYP1A1 and CYP2DE; and the glutathione- s- transferase gene cluster (GST).[5]

The Glutathione S - Transferase is a phase II enzyme that catalyzes reactions between glutathione and a variety of eosinophilic compounds. Its isoenzymes display several polymorphisms (GSTT1, GSTM1, and GSTP1) which have been found in some studies to be associated with an increased risk for developing lung cancer, particularly among smokers. In a study by Hung et al, loss of GSTM1 enzyme activity (GSTM1 null genotype) has been associated with host susceptibility in smoking-related lung cancer.[6] This finding was also supported by Sweeney et a1.[7] Wenzlaff AS et al documented that among never-smoker individuals with high environmental tobacco smoke exposure category carrying GSTM1 null genotype and GSTP1 polymorphism, the risk of developing lung cancer is four-fold (OR=4.56, 95% CI=1.21, 17.21). [8,10-12] Sorensen et al's investigation suggested that the GSTT1 null genotype was associated with an increased risk of lung cancer, especially in younger individuals (OR=2.4, 95% CI=1.31,4.41). Contrary to the previously mentioned report, his findings did not show significant effects on polymorphisms in GSTM1 and GSTP1.[9] On the other hand, the study of Schneider et al showed that the polymorphisms of the GSTM1, GSTTI or GSTP1 had no relevant modifying effect on lung cancer risk.[13]

Table I Demographics and Characteristics of Patients

Characteristic	Case (n=201)	Control (n=110)	Total (n=311)
Age, Mean in years	58.8	53.3	
SEX, No. (%)			
Male	160 (79.6%)	61 (55.45%)	221 (71.06%)
Female	41 (20.4%)	49 (44.45%)	90 (28.9%)
SMOKING HISTORY. No. (%)			
Smoker	161 (80.1%)	53 (48.1%)	214 (68.8%)
Nonsmoker	40 (19.9%)	57 (51.9%)	335 (31.2%)

Table II Glutathione S - Transferase Genotypes, null vs wild

Genotypes	Chi Square	Odds Ratio	Confidence Interval	*p* value
GSTT1	0.027	1.049	0.059 - 1.86	0.8695
GSTM1	0.368	1.25	0.605 - 2.580	0.54
GSTP1	1.395	1.49	0.77 - 2.89	0.2376

Taken together, the above mentioned findings prompted us to further investigate the potential role of GST in lung cancer susceptibility.

The intense effort of determining the molecular epidemiology of individual susceptibility to tobacco smoke carcinogens may guide us to focus on the highest risk groups. In the presence of newer screening technologies, which are now capable of detecting very small nodules, we can detect lung cancer in its early stage. Knowing the paucity of such studies conducted among Asian population, it was therefore the objective of this study to determine the interaction between the GST genotypes and smoking history on lung cancer susceptibility among Filipinos. Few such studies have been done in the Asian population.

Materials and Methods

Study Design and Population. This is a case-control study involving patients from the Philippine General Hospital from 2002 to 2005. The Ethics and Review Research Board of the hospital approved the study. Eligible cases included patients who consented to participate in the study, histologically/cytologically proven bronchogenic carcinoma for the case group and patients with other respiratory complaints without cancer for the control group. Subjects with prior exposure to chemotherapy or radiotherapy and those with medical condition prohibiting molecular genetics specimen collection were excluded.

Sample Analysis. An informed written consent was obtained in all subjects. Specimens such as blood, pleural fluid, bronchial and lymph node biopsy or lung mass were taken for GST genotypes analysis (wild and null). GST genotypes were assayed by Polymerase Chain Reaction based Restriction Fragment Length Polymorphism (PCR-RFLP). The molecular studies were done at the Institute of Human Genetics, University of the Philippines - National Institute for Health.

Statistical Analysis. The statistical analysis was done using SPSS software. Odds ratio (OR) and the 95% Confidence Interval (CI) were computed. A *p* value of 0.05 was considered significant.

Results

Two hundred one lung cancer cases and 110 controls were included in the study (Total subjects=311). Demographics of subjects are shown in *Table I.* The mean age for the case group was 58.8 years with the predominance of male population

Table III Glutathione S - Transferase Genotypes, null vs wild, Among Smokers

Genotypes	Chi Square	Odds Ratio	Confidence Interval	*p* value
GSTT1	0.422	1.303	0.58 - 2.91	0.5161
GSTM1	0.439	0.708	0.25 - 1.97	0.5077
GSTP1	0.189	1.227	0.488 - 3.082	0.6636

Table IV Glutathione S - Transferase Genotypes, null vs wild, Among Non-Smokers

Genotypes	Chi Square	Odds Ratio	Confidence Interval	*p* value
GSTT1	0.489	0.71	0.27 - 1.84	0.4842
GSTM1	1. 797	2.204	0.68 - 7.065	0.1801
GSTP1	0.321	1.364	0.466 - 3.993	0.5711

(79.6%). Majority were smokers (80.1%). For the control group, the mean age was 53.3 years with the male population predominating (55.45%). Fifty percent were non- smokers.

Odds ratio and Confidence Interval were computed for all the GST genotypes (*Table II*).

Subjects were stratified into smoker and non-smoker groups (*Tables III and IV*).

There was no significant association between the presence of GSTT1 (OR=1.049; 95% CI: 0.59-1.86; *p*=0.8695), GSTP1 (OR=1.49; 95% CI: 0.77-2.89; *p*=0.2376) and GSTM1 (OR=1.25; 95% CI: 0.61-2.58; *p*=0.5400) null genotypes and lung cancer risk, irrespective of the smoking history.

Discussion

Lung cancer has become one of the leading causes of death worldwide. In the Philippines, it is the most common cancer in males and the third most common among females.[2] Several etiologic factors have been attributed such as gender, race, age, cigarette smoking, environmental factors, occupational carcinogens, pre-existing non-malignant lung disease and genetic factors. Tobacco smoking has been established as the most important etiologic factor of lung cancer for both men and women. However, only approximately 20% of smokers will eventually develop lung cancer.[4] This finding could be explained by the various etiologic factors as mentioned earlier, one of which is the genetic factor.

Several studies have reported the association of gene polymorphisms with lung cancer risk particularly among Caucasian. Sweeney et al found that patients with GSTM1 null genotypes had shorter overall survival. This finding was not found to be true for GSTT1 or GSTP1 genotype.[7] Cote ML et al did a study in 2005 involving African Americans and Caucasians. African Americans with either one or two risk genotypes at the GSTM1 and GSTP1 loci were at increased risk of having lung cancer compared with those having fully functional GSTM1 and GSTP1 genes (OR 2.8, 95% CI: 1.1-7.2 and OR 4.0, 95% CI: 1.3-12.2, respectively). No significant single gene associations between GSTM1, GSTTI or GSTP1 and early-onset lung cancer were identified in Caucasians.[14] As previously mentioned, Wenzelaff et al and Sorensen et al also proved the associations of GST polymorphisms with the, disease.[7-9] In contrast, the study of Schneider showed otherwise.[13]

In our study, GSTT1, GSTP1 and GSTM1 polymorphisms did not show significant association with lung cancer risk, irrespective of smoking history. This has been supported by few studies done among Asian population. Yang XR et al in 2004 concluded that GSTM1 null genotype is not associated with lung carcinogenesis.[15] Belogubova et al did a study among the Russian population. He concluded that there is no significant effect in the lung cancer proneness for the GSTT1 genotypes. As mentioned earlier, the study of Schneider showed that polymorphisms of the GSTT1, GSTM1 or GSTP1 had no relevant modifying effect on lung cancer risk.[13] However, other studies conducted among the Asian population concluded significant association. Wang et al had concluded that the combination of GSTM1 and GSTP1 polymorphisms was significantly associated with elevated lung cancer risk (OR 2.4, 95% CI 1.5-5.1).[10] Lin et al documented that GSTP1 polymorphism alone was associated with increased risk among Taiwanese (OR 1.63, 95% CI 0.96-2.7).

Conclusion

The association between GSTT1, GSTM1, or GSTP1 null genotypes and lung cancer susceptibility is weak among Filipinos.

References

1. Billelo KS, Murin S, Mathay R. Epidemiology, Etiology, and Prevention of Lung Cancer. Clinics in Chest Medicine. March 2002; 23 (1): 1-24
2. Globocan 2000. Cancer Incidence, Mortality and Prevalence

3. World Health Organization: World Health Report 1997: Executive Summary, Geneva. WHO, 1997: 1 - 13
4. Wright GS. Early Detection and Prevention of Lung Cancer. Curr Opinion Onco1. 12: 143- 148
5. Fong et a1. Molecular Biology of Lung Cancer: Clinical Implications. Clinics in Chest Medicine. March 2002; 23(1): 83
6. Hung et a1. CYF1A1 and GSTM1 Genetic Polymorphisms and Lung Cancer Risk in Caucasian Non Smokers. 2003; 24(5): 875 - 882
7. Sweeney et a1. Glutathione S-Transferase M1, T1 and PI polymorphisms and Survival Among Lung Cancer Patients. Cancer 2003; 12(6): 527 - 533
8. Wenzlaff et a1. GSTM1, GSTT1 and GSTP1 polymorphisms, Environmental Tobacco Smoke Exposure and Risk of Lung Cancer Among Never Smokers: A population - based study. Carcinogenesis. Feb 2005; 26(2): 395 - 401
9. Sorensen et al. Glutathione S-Transferase T1 null genotype is Associated with an Increased Risk of Lung Cancer. June 2004; 110(2): 219 - 224
10. Wang et a1. GST Genetic Po1ymorphisms and Lung Cancer Adenocarcinoma Susceptibility in a Chinese Population. Nov 2003; 201(2): 185 - 193
11. Reszka et al. Glutathione S-Transferase M1 and PI Metabolic Polymorphism and Lung Cancer Predisposition. Neoplasma. Jan 2003; 50(5): 357 - 362
12. Stucker et a1. Genetic Polymorphisms of Glutathione S-Transferase as Modulator of Lung Cancer Susceptibility. Sept 2002; 23(9): 1475 - 1481
13. Schneider et al. GSTM1, GSTT1 and GSTP1 polymorphism and Lung Cancer Risk in Relation to Tobacco Smoking. Cancer Lett. May 2004; 208(1): 65 -74
14. Cote ML et a1. Combinations of Glutathione S - Transferase Genotypes and Risk of Early Onset Lung Cancer in Caucasians and African Americans: a population - based study. Carcinogenesis. April 2005; 26(4): 811- 819
15. Yang XR et a1. CYFIA1 and GST Polymorphisms in Relation to Luna Cancer Risk in Chinese Women.
16. Cancer LeU. October 2004; 214(2): 197 - 204
17. Belogubova et a1. A Novel Approach for Assessment of Cancer Predisposing Roles of GSTM1 and GSTT1 Genes: Use of Putatively Cancer Resistant Elderly Tumor-Free Smokers as the Referents. Lung Cancer. March 2004: 43(3): 259 - 266
18. Lin P et at Analysis of NQ01, GSTP1, and MnSOD Genetic Polymorphisms on Lung Cancer Risk in Taiwan. Lung Cancer. May 2003; 40(2): 123 - 129

A Study on the Clinical Profile of COPD Patients in VMMC COPD Clinic in Correlation with Exacerbation and Mortality

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Chronic obstructive pulmonary disease is still a major cause of morbidity and mortality in the Philippines as well as the whole world. In order to be able to better understand this disease, this study was conducted at the VMMC COPD Clinic on patients seen from June 2004 to 2005. Two-hundred ten patients with records from the ER, OPD and Ward were obtained and analyzed for several demographic factors such as age, sex, frequency of exacerbations, basal metabolic index (BMI), duration of COPD, stage of COPD, and mortality. Other factors were also looked at such as relationship between smoking duration and smoking cessation with the stage of COPD, the stage of COPD and frequency of exacerbations; ER visits and hospitalizations, the medications commonly used by our COPD patients, the most common causes of death of our COPD patients and the percentage of COPD patients enrolled in and completed our Pulmonary rehabilitation program.

Among other findings, BMI, duration of COPD, frequency of exacerbations and frequency of hospitalizations have statistically significant correlation with morbidity, but it has no significant association with the stage of COPD. When the stage of COPD is linked to frequency of exacerbations and ER visits the relationship is significant. *Phil Journal of Chest Diseases. Vol. 13 No. 1 pp: 40-45*

Keywords: COPD, mortality, risk factors

Introduction

Chronic Obstructive Pulmonary Disease is a disease state characterized by airflow limitation that is not fully reversible.[1] It is one of the commonest respiratory conditions of adults in the developed world.[2] It is progressive and associated with abnormal inflammatory response due to exposure to inhaled noxious particles and gases.[1] Cigarette smoking is the most common cause of COPD. Most people with COPD are smokers or former smokers.[3]

It is currently the fourth leading cause of death in the world[4] and significant cause of morbidity and mortality in developing countries.[5] In our local setting it is the seventh leading cause of mortality in the 1998 census of the Department of Health.[6]

People who are afflicted with the condition are more likely to be limited in activities and less likely to be working with higher rates of health care service.[7] These include physician visits, emergency department visits and hospitalizations.

Management of COPD includes a variety of treatment approaches such as avoidance of risk factors, pharmacotherapy, patient education and counseling, nutritional advice and pulmonary rehabilitation. The latter is widely accepted, the primary goal is to optimize function and improve the quality of life in patients with COPD.

With the growing case of COPD in the country, this study is conducted in our institution to give an overview of the clinical profile of COPD patients in our very own setting at VMMC COPD Clinic.

The study therefore aims to determine the clinical profile of COPD patients in VMMC COPD Clinic from June 2004 to June 2005. In addition, the demographic parameters of COPD patients seen at the COPD Clinic were investigated. We also correlated BMI, duration of COPD, stage of COPD, frequency of exacerbations, ER visits and number of hospitalizations with mortality. Other factors were also looked at such as relationship between smoking duration and smoking cessation with the stage of COPD, the stage of COPD

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and frequency of exacerbations; ER visits and hospitalizations, the medications commonly used by our COPD patients, the most common causes of death of our COPD patients and the percentage of COPD patients enrolled in our Pulmonary rehabilitation and those who completed the program.

Materials and Methods

Type of Study: Descriptive Retrospective

Study Population The subjects in this study were the COPD patients enrolled in the VMMC COPD Clinic (Ward 18) from June 2004 and June 2005 and those previously enrolled that have followed up during this period. Diagnosis of COPD was based on the criteria set by the GOLD guideline on severity of COPD.[1]

Stage	Category	Characteristics
0	At Risk	Normal Spirometry Chronic Symptoms (cough, sputum production)
I	Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without chronic symptoms (cough and sputum production
II	Moderate COPD	$FEV_1/FVC < 70\%$ $> 50\%$ $FEV_1 \leq 80\%$ predicted With or without chronic symptoms (cough and sputum production
III	Severe COPD	$FEV_1/FVC < 70\%$ $> 30\%$ $FEV_1 \leq 50\%$ predicted With or without chronic symptoms (cough and sputum production
IV	Very severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 \leq 30\%$ predicted Plus chronic respiratory failure, pulmonary insufficiency and cor pulmonale

Inclusion Criteria: 1. Patients who have enrolled in the COPD clinic who meet the criteria set by the GOLD guideline. A review of records in the VMMC COPD Clinic was done from June 2004 to June 2005, including ER and Mortality records and some admission charts.

Table I Characteristics of patients

Characteristics	No. (%)
Age	
< 65 years	23 (10.95)
≥ 65 years	187 (89.05)
Sex	
Male	188 (79)
Female	44 (21)
Address	
Within Metro Manila	151 (71.9)
Outside Metro Manila	59 (28.1)
Duration of COPD	
< 1 year	34 (16.2)
1-2 years	114 (54.3)
3-4 years	43 (20.5)
5-7 years	8 (3.8)
8-10 years	4 (1.9)
> 10 years	7 (3.3)
BMI	
< 18.5	42 (20)
18.5 – 24.9	124 (59)
25 – 29.9	36 (17)
30 – 39.5	8 (4)
Duration of smoking	
Non-smoker	13 (6.2)
Passive smoker	8 (3.8)
0 – 20 pack years	50 (23.8)
21 – 40 pack years	64 (30.5)
41 – 60 pack years	38 (18.1)
> 60 pack years	37 (17.6)
Duration of smoking cessation	
1 – 10 years	109 (51.9)
11 – 20 years	31 (14.8)
21 – 40 years	15 (7.1)
> 40 years	9 (4.3)
Not known	25 (11.9)
Non-smoker	11 (5.2)
Co-morbid illness	
Without co-morbid illness	51 (24.3)
With co-morbid illness	159 (75.7)
Stage of COPD	
0	8 (3.8)
1	7 (3.3)
2	79 (37.6)
3	77 (36.7)
4	39 (18.6)

The following data were gathered: age, sex, residence, civil status, height and weight to compute for the BMI, duration of COPD, smoking history, medications, presence or absence of co-morbid illnesses. The spirometry was reviewed and the stage of COPD and FEV_1 were determined. Frequency of exacerbations, ER visits and hospitalizations for the past six months were noted. Mortality of COPD patients was retrieved at the medical records, the place and causes of death were determined. The number of patients who enrolled in pulmonary rehabilitation and those who completed the program were taken.

Table II Exacerbations, ER visits and hospitalization characteristics

Characteristics	No. (%)
Frequency of exacerbation	
0	12 (5.7)
1 - 2	73 (34.8)
3 - 4	52 (24.8)
5 - 6	19 (9)
7 - 8	16 (7.6)
9 - 10	6 (32)
> 10	32 (15.2)
ER Visits within the last 6 months	
0	52 (24.8)
1 – 2	109 (51.9)
3 – 4	33 (15.7)
5 – 6	10 (4.8)
7 – 8	3 (1.4)
> 10	3 (1.4)
Frequency of hospitalization	
0	61 (29)
1 – 2	118 (56.2)
3 – 4	25 (11.9)
5 – 6	5 (2.4)
> 10	1 (0.48)

Statistical Analysis With in group analysis, paired *t-test* was done while between group analysis *Mann Whitney* U Test ,and *Spearman's rho* was carried out, a *p* value of 0.050 was considered significant.

Results

There were 210 patients included in the study. Data were retrieved from COPD clinic from June 2004 to June 2005. Out of 210 patients 89.05 % were older than 65 years old and 10.95% are younger than 65 years (*Table I*) with age ranges between 45-88 years old. Male consist of 71.9% (151) and 21% (44) are females, 1-2 years duration of COPD comprises the largest size of patients at 54.3% (114) followed by 3-4 years duration at 20.5 % (43) while 8-10 years duration of COPD is the least number of patients at around 1.9%

Around 71.9% (151) lives in Metro Manila while 28.1% (59) resides outside Metro Manila. Body Mass Index (BMI) of COPD patients (*Table I*) are normal (18.5-24.9) in 59% (124) of cases followed by underweight ($\leq$18.5) at 20% (42). The obese group, with a BMI of 30 kg/m^2 and above was only 3.8 % (8).

Majority of COPD patients have concomitant medical illness in 75.7% (159) while 24.3% (51) have none as seen in *Table I*.

Table III Relationship of several characteristics to mortality

Characteristics	Alive	Dead	Total
BMI			
< 18.5	36	6	42
18.5 – 24.9	118	6	124
25 – 29.9	36	0	36
30 – 39.5	7	1	8
Total	197	13	210
Duration of COPD			
< 1 year	34	6	34
1-2 years	108	3	114
3-4 years	40	2	43
5-7 years	6	2	8
8-10 years	2	0	4
> 10 years	7	0	7
Total	197	13	210
Stage of COPD			
0	8		9
1	7		7
2	75	4	79
3	72	5	77
4	35	4	39
Total	197	13	210
Frequency of exacerbation			
0	12	0	12
1 - 2	71	2	73
3 - 4	49	3	52
5 - 6	19	0	19
7 - 8	15	1	16
9 - 10	5	1	6
> 10	36	6	32
Total	197	13	210
Frequency of hospitalization			
0	61	0	61
1 – 2	108	10	118
3 – 4	23	2	25
5 – 6	4	1	5
> 10	1	0	1
Total	197	13	210

For the duration of smoking, the bulk of COPD patients are seen on 21-40 years duration at 30.5% (64) while passive smoker comprises the lowest at 3.8%

There are 51.9% (109) of patients who have stopped smoking for 1-10 years followed by 11-20 years at 14.8% (31) and > 40 years duration of smoking cessation is the least at 4.3% (9) (*Table I)*.

Patients were subjected to spirometric studies; FEV_1 was obtained to stage the severity of COPD patients. *Table I* showed 37.6% of patients (79) are Stage 2 followed by Stage 3 at 36.7% (77) with Stage 1 as the least at 3.3% (7).

With the additional data gathered from ER records and Admission charts, frequency of exacerbations, ER visits and hospitalizations for the past six months were recorded. *Table II* showed 34.8% (73) have 1-2

exacerbations followed by 24.8% (52) with 3-4 exacerbations and 2.9% (6) with 9-10 exacerbations as the least. It is noteworthy that 15.2% (32) of patients have greater than 10 times exacerbations.

Table II showed that the peak ER visits occur at 1-2 times for 6 months at 51.9% (109) , followed by no ER visits at 24.8% (52), with 7-8 times and greater than 10 times ER visits got similar rank at 1.4% and the lowest rank.

The trend in frequency of hospitalization is almost the same with the frequency of exacerbations and ER visits. The top rank still on 1-2 times hospitalization for six months at 56.2% (118) followed by 29% (61) with out hospitalization and only 48% (1) for more than 10 times hospitalizations (*Table II*).

Table III showed the relationship of BMI and mortality with 6/42 deaths on the underweight (BMI< 18.5) and 6/124 on normal BMI (BMI=18.5-24.5) and only 1/8 on obese (BMI=30-39.5) with *p* value of 0.029 using *Mann Whitney* U Test suggesting statistically significant result.

The relationship of COPD duration and mortality is seen also in *Table III.* One to two years duration of COPD has 6/114 deaths with 5-7 and 8-10 years COPD duration had 2/6 and 2/2 deaths, respectively with *p* value of 0.013 using *Mann Whitney* U Test, indicating statistically significant result.

The relationship of COPD stage and mortality

Table IV Relationship of some characteristics to Stage of COPD

Characteristics	Stage of COPD					Total
	0	1	2	3	4	
Duration of smoking						
Non-smoker	1	0	6	5	1	13
Passive smoker	1	0	3	3	1	8
0 – 20 pack years	0	0	23	18	9	50
21 – 40 pack years	3	3	21	26	11	64
41 – 60 pack years	2	1	14	15	6	38
> 60 pack years	1	3	12	10	11	37
Total	8	7	79	77	39	210
Duration of smoking cessation						
<1 year	0	1	2	4	3	10
1 – 10 years	3	5	36	43	22	109
11 – 20 years	3	0	9	13	6	31
21 – 40 years	0	0	6	6	3	15
> 40 years	1	0	4	1	3	9
Non-smoker	1	1	16	6	1	25
Not known	0	0	6	4	1	11
Total	8	7	79	77	39	210
Frequency of exacerbation						
0	2	1	6	3	0	12
1 - 2	5	2	34	25	7	73
3 - 4	1	3	21	17	10	52
5 - 6	0	0	10	6	3	19
7 - 8	0	0	2	9	5	16
9 - 10	0	0	2	3	1	6
> 10	0	1	4	14	13	32
Total	8	7	79	77	39	210
ER Visits within the last 6 months						
0	5	2	19	23	3	52
1 – 2	2	4	45	35	23	109
3 – 4	1	1	11	10	10	33
5 – 6	0	0	2	5	3	10
7 – 8	0	0	3	3	0	3
> 10	0	0	0	1	0	3
Total	8	7	79	77	39	210
Frequency of hospitalization						
0	5	3	23	24	6	61
1 – 2	2	4	46	42	24	118
3 – 4	1	0	7	9	8	25
5 – 6	0	0	2	2	1	5
> 10	0	0	1	0	0	1
Total	8	7	79	77	39	210

Table V Maintenance medications of patients

Medications	No. (%)
1 SABA: Tab/Neb/MDI	18 (8.6)
2 Short Acting Anticholinergic: Neb/MDI	2 (1.0)
3 Theophylline, Doxofylline, Bambuterol	2 (1.0)
4 Combination of LABA & ICS	23 (11.0)
5 Long Acting Anticholinergic: *Handihaler*	14 (6.7)
6 LABA: MDI, *Turbohaler*, Tab	2 (1.0)
7 Combination of 1 & 4	22 (10.5)
8 Combination of 1 & 5	8 (3.8)
9 Combination of 2 & 4	11 (5.2)
10 Combination of 2 & 5	8 (3.8)
11 Combination of 4 & 5	52 (24.8)
12 Combination of 1, 4 & 5	4 (1.9)
13 Combination of 2, 4 & 5	9 (4.3)
14 Combination of 3, 4 & 5	7 (3.3)
15 Combination of 4, 5 & 6	1 (0.5)
16 Other Combinations	27 (12.9)
Total	210 (100)

(*Table III*) showed 5/77 deaths on stage 3; 4/79 and 4/39 on stage 2 and 4, respectively with a *p* value of 0.166 using the *Mann Whitney* U Test which is not statistically significant.

Table III further demonstrates the relationship of frequency of exacerbation and mortality with 6/32 deaths on more than 10 times frequency of exacerbation which is the highest in this group followed by 3/52 on three to four times and 1/6 on nine to ten times frequency of exacerbations with a *p* value of 0.006 . The relationship of frequency of hospitalization and mortality is also seen with 10/118 deaths on 1-2 times frequency of exacerbations and 2/25 on 3-4 times and lastly 1/5 on more than 10 times hospitalization with a *p* value of 0.0025 using the *Mann Whitney* U Test.

The relationship of smoking duration and the stage of COPD (*Table IV*) reveal stage 2 with the highest number of COPD patients followed by stage 3 with 79 and 77 respectively. The bulk of duration of smoking is at 21-40 years duration followed by 11-20 years duration with 64 and 50 patients, respectively; with a *p* value of 0.475 using *Spearman's* rho which is not statistically significant. Likewise, the relationship of smoking cessation and the stage of COPD as seen in *Table IV* illustrate 109/210 patients have ceased smoking with 1-10 years followed by 11-20 years (31/210) and > 40 (9/210) with a *p* value of 0.037 using *Spearman's* rho which is significant.

Table IV also showed the relationship between frequency of exacerbation with the stage of COPD. The bulk of exacerbations were 1-2 times in 6 months with stage 2 as the highest followed by Stage 3 with *p* value of .000 indicating statistically significant results.

The relationship between ER visits and the Stage of COPD (*Table IV*) showed that most of the ER visits are concentrated on 1-2 times in 6 months led by stage 2 and preceded by Stage 3. Using 2 tailed test (*Spearman's* rho) *p* value 0.012 indicating statistically significant result.

Correlation between frequencies of hospitalization with the stage of COPD also seen in *Table IV* still showed 1-2 hospitalization in 6 months as the highest frequency with stage 2 and 3 as the first and second level respectively.

The maintenance medications commonly used by our COPD patients (*Table V*) includes combination of LABA + ICS (*Seretide, Symbicort*) and long acting anticholinergic (*Spiriva*) at 24.8% followed by other medications not specified at 12.9% and combination of LABA + ICS in one container either MDI, *Discus* and *Turbohaler* rank third at 11 %.

Mortality of patients in the study was 6.25% with death related to COPD is at 61.5% and 38.5% are due to co- morbid conditions of the patient.

There were 31% of patients who underwent pulmonary rehabilitation. The percentage of patients who completed the program was 23.4% and 7.6% started the rehabilitation but did not reach completion while 69% did not enroll.

Discussion

Our population is elderly with age range between 45-88 years old, 71.9% is > 65. As age advances lung function also begins to decline in a slowly accelerating manner with faster decline on smoker, with an average of about 40 ml/year.[3] As stated by K. Groenewegen et al, older age could be identified as risk factor associated with higher mortality.[8] Duration of COPD was based upon spirometric studies, as most of the patients were symptomatic before referral to our clinic, it is believed that disease develop earlier than what is reflected in the study. Its relationship to mortality is significant. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2), and was categorized into 4 groups: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (30 kg/m^2 and above). A study done by Charlotte Landbo et al,[9] states that effect of BMI on mortality

depended on the stage of disease, with significant effect present in subjects with severe COPD but she later concluded that underweight is an important independent risk factor for mortality. BMI has significant relationship to mortality together with frequency of exacerbations, and hospitalization. The role of low BMI as a determinant of poor survival in these patients could have been due to several factors, such as respiratory muscle weakness,[10] impaired gas exchange,[11] and impaired immune response,[12] all of which have been related to malnutrition of COPD patients. Hypoxia and hypercapnea are related to the severity of COPD and have been linked to malnutrition.[13] Patients admitted to the hospital for acute exacerbation has poor prognosis as stated by K. Groenewegen et al.[8] COPD exacerbations increase FEV_1 deterioration[14] as does mortality[15] leading to increase frequency of hospitalization and ER visits since the reduction of FEV_1 place the patient at risk for life threatening exacerbations.[1] In contrast, the relationship between stage of COPD and mortality is not significant. Duration of smoking leads to decrements in lung function in a dose dependent manner,[3] it has a greater annual rate of decline of FEV_1 and a greater mortality rate than non-smokers.[1] However, the relationship between smoking duration and stage of COPD is not significant as seen in this study. On the other hand, smoking cessation when correlated with decline in FEV_1 revealed a significant result. In a study conducted by Anthonisen, smoking cessation in adulthood can slow the rate of decline of FEV_1 among individuals with mild COPD.[16] Whether such benefit is true among individuals with more severe disease or in the elderly is unclear.[17] Smoking cessation is associated with a reduction in the risk of COPD morbidity of approximately 40%,[18] with longer duration of discontinuation CD8 cell numbers decrease and plasma cell numbers increase.[19] Survival of the patients have been influenced by their maintenance medications, in 24.8% of patient utilize combination of LABA + ICS (*Seretide, Symbicort*) and long acting anticholinergic (*Spiriva*). Thirty one percent of patient enrolled to pulmonary rehabilitation with only 23.4% completing the program.

Conclusion

This study provides information on the clinical profile of COPD patients enrolled in the COPD clinic of Veterans Memorial Medical Center. Basal metabolic indexes, duration of COPD, frequency of exacerbations and frequency of hospitalizations have statistically significant correlation with morbidity, but it has no significant association with the stage of COPD. When the stage of COPD is linked to frequency of exacerbations and ER visits the relationship is significant. With the aforementioned data, this will help us predict the frequency of exacerbations and its prognosis.

References

1. Global Initiative for Chronic Obstructive Lung Disease, National Institute of Health, Health Organization: Nikokai Khaltev, .MD July, 2003.
2. JAMA 2003:290-2362
3. Murray and Nadels Textbook of Respiratory Medicine, 4th Edition, Volume 2, J.
4. Murray et al, Copyright 2005 p 116-1128.
5. World Health Organization. World Health Report. Geneva: World Health Organization; 2000. Available from: URL:http://www.who.int/whr 2000/enlstatistics.htm
6. Singh V. Khandelwal DC, et al, Pulmonary Rehabilitation in patients with COPD, Indian Chest Dis Allied Sci, 2003 Jan-March, 45 (1):137
7. Philippines Health Statistics 1998.
8. National Institute of Health, National Heart and Lung and Blood Institute (2002) Morbidity and Mortality:2002
9. Karin H. Groenewegen, MD et al., Mortality and Mortality-Related Factors After Hospitalization for Acute Exacerbation of COPD, Eur Respir J 2003;21;58-67
10. Charlotte Landbo et al., Prognostic Value of Nutritional Status in COPD, Am. J. Respir. Crit. Care Med., Volume 160, Number 6, Dec 1999, 1856-1861.
11. Donahoe,M., et al. 1989. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 140: 385-391.
12. Braun, S.R.,et al., 1984. The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease: predictive clinical value of nutritional assessment factors in COPD. Chest 8:353-357.
13. Hunter, A. M., et al, 1981. The nutritional status of patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 124:376-381.
14. Schols, A., et al., 1989. Inventory of nutritional status in patients in COPD. Chest 96: 247-249.
15. Burge PS, Calvery PM, et al, Prednisolone response in patients with chronic obstructive pulmonary disease: Results from ISOLDE study. Thorax 58:654-658,
16. Mannino DM, Buist AS, Petty TL, et al: Lung function and mortality in the United States: Data from the First National Health and Nutrition Examination Survey follow up study. Thorax 58:388-393, 2003.
17. Anthonisen NR, Connett JE, Murray RP: Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 166:675-679, 2002.
18. Camili AE, Burrows B,et al., Longitudinal Changes in forced expiratory volume in one second in adults. Am Rev Respir Dis 135:794-799,1987.
19. Thorax 2004; 59:713-721.
20. Thorax 2002; 57:967-972.

Quality of Care Assessment in Adult Patients with Bronchial Asthma in Exacerbation Admitted at the St Luke's Medical Center from January 2003 to December 2003

Objective: To review the quality of care rendered by physicians to asthmatic patients admitted for bronchial asthma in exacerbation at the Philippine General Hospital for the period of January 2003 to December 2003, according to guidelines set in the 2002 Global initiative for Asthma (GINA)
Study Design: Retrospective descriptive study
Study Setting: Tertiary hospital in Quezon City
Participants: Adult patients with bronchial asthma in exacerbation admitted at SLMC from January 2003 to December 2003
Methods: Quality of care indicators for three areas (diagnostic quality indicator, acute management quality of care indicator, and quality of care for discharge planning) were assessed.
Results: None of the patients had peak expiratory flow rate (PEFR) monitoring at home to be able to document if their PEFR was <80% of their personal best or predicted, or > 70% if no response to bronchodilator. Eighty percent of patients had baseline and periodic monitoring of PEFR. PEFR variability was not computed. Beta-2 agonists and systemic steroids were given to all patients on admission. Fifty two percent of patients were instructed on proper inhaler technique prior to discharge. Medical records did not note any discharge instructions regarding home PEFR monitoring, instructions on avoidance of trigger factors and formulation of asthma action plan for the patient. All patients were given a follow-up schedule after discharge.
Conclusion: The quality of care for diagnosis, acute management and discharge planning for asthma exacerbation as recommended by GINA guidelines were not being followed. *Phil Journal of Chest Diseases. Vol 13 No. 1 pp: 46-51*

Keywords: Bronchial asthma, Quality of care, Asthma guidelines

Introduction

Asthma is prevalent in the Philippines affecting 10 to 15% of our young adult population. Available data from the Philippine General Hospital outpatient department census shows that 50% of asthmatic patients are aged 15 years and below.[1] The limited reports gathered showed a prevalence of 12% in children aged 13 to 14 years and 17 to 22% in older age groups.[2] The worldwide trend is also the same. The prevalence of severe asthma in 12 countries was reported, with the United States showing the highest prevalence rate (10%) and Sweden showing the lowest prevalence rate (2%). Asthma mortality rate was likewise compared for these 12 countries, and it showed that Australia, despite having a prevalence rate of 8.3%, had the highest mortality rate (86%), while Sweden had the lowest mortality rate for asthma (12%).[3] Asthma also caused considerable morbidity in the Asia-Pacific region, with 15% of teenagers troubled by exercise-induced symptoms.[4] There is every reason to believe that the substantial global burden of asthma can be dramatically reduced through collective efforts, thus the need for improving quality of care for asthma.

The Global Initiative for Asthma (GINA) developed by the World Health Organization (WHO) in collaboration with the US National Heart, Lung, and Blood Institute (NHLBI), established diagnostic and management recommendations that are now generally accepted worldwide. The Asthma Insights and Reality in Asia-Pacific (AIRIAP) Study[4] was conducted to document the experience of a wide cross-section of patients with asthma in the community and to assess whether asthma management in the region met the goals proposed by the GINA guidelines. The AIRIAP findings demonstrate that, as in other regions of the world, asthma is sub-optimally controlled in the Asia-Pacific region. The considerable asthma morbidity and reported management practices fall markedly short of

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standards recommended by GINA. Similar to studies in US and Europe, the AIRIAP study highlights the discrepancy between accepted goals for asthma management and the actual degree of-asthma control in the Asia-Pacific region.

This study was therefore conducted to review the quality of care rendered by physicians to asthmatic patients admitted for bronchial asthma in exacerbation at the St Luke's Medical Center for the period of January 2003 to December 2003 according to the guidelines set in the 2002 Global Initiative for Asthma (GINA). Furthermore, we reviewed the practice of physicians as providers of effective care based on diagnostic quality indicators. The practice of physicians as providers of effective care based on acute management quality of care indicators was also looked into. Lastly, we reviewed the practice of physicians as providers of effective care based on quality of care for discharge planning.

Materials and Methods

Study Design. Retrospective, descriptive study

Study setting St Luke's Medical Center, a 675 bed capacity tertiary center in Quezon City.

Study Population Patients were included in the analysis if they were 18 years old and above, previously diagnosed to have bronchial asthma, and admitted with a diagnosis of bronchial asthma in exacerbation.

Patients were excluded from the study if they had other major chest diseases such as lung cancer, bronchiectasis, chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis. Those with a history of cardiac, hepatic, renal or neuromuscular diseases were likewise excluded from the study.

Pregnant women were also not included.

Data Collection Data collection forms were developed and each medical record was reviewed in order to identify patients who met the study criteria and to collect the appropriate information. All charts of eligible patients underwent audit of quality of care indicators. From a total of 480 medical charts of patients admitted for the period of January 2003 to December 2003 with a diagnosis of bronchial asthma in exacerbation, only 286 patients were eligible for the study. One hundred ninety four patients were excluded because the medical record indicated pregnancy in 12 patients, coronary artery disease in 75, COPD in 65, acute bronchitis in 26, lung cancer in 12, and chronic renal failure in 4 patients.

Audit Criteria The study was divided into 3 areas with the assessment of care provided by physicians as the quality of care indicators. A quality of care indicator is a process of care measure that is clearly linked to improve outcomes by clinical trials and can be measured through existing data sources. The three areas for the assessment of quality of care were: diagnostic quality indicator, acute management quality of care indicator, and quality of care for discharge planning. All the indicators with Level 1 evidence, Grade A recommendation were used in this study.

A. Diagnostic Qualitv Indicators to diagnose asthma exacerbation

   1 PEFR < 80% personal best or predicted on 2 successive days, or > 70% if no response to bronchodilator.

B. Acute Management Qualitv of Care Indicators

   1 Baseline and periodic monitoring of peak expiratory flow rate (PEFR) to assess PEF variability.
   2 Administration of inhaled short-acting beta-2 agonists on admission.
   3 Administration of systemic steroids on admission.

C Quality of Care for Discharge Planning

   1 Checking inhaler technique.
   2 PEFR monitoring at home.
   3 Instructions on avoidance of trigger factors.
   4 Formulation of asthma action plan.
   5 Regular follow-up visits.

Table I Clinical presentation on admission establishing the diagnosis of Asthma exacerbation

Clinical presentation on admission	No.	%
Cough	58	20
Dyspnea	90	31
Wheezing	98	34
Nocturnal cough or wheeze	40	14
Persistent PEF < 80% personal best or predicted on 2 successive days or > 70% if no response to bronchodilator	0	0

Table II Acute management of Asthma exacerbation

Parameter	No.	%
Baseline PEFR and PEFR monitoring	230	80
Computation of PEFR variability	0	0
Administration of beta-2 aqonist Inhaled Nebulized	 68 191	 24 67
Administration of beta-2 agonist + anticholinergic via nebulization	27	9
Administration of systemic steroids Oral Intravenous	 26 260	 9 91
Assessment of the severity of exacerbation	10	3
Pulse oximetry monitoring	35	12
Chest x-ray	286	100
Arterial blood gas	286	100
Administration of oxygen (nasal cannula/face mask)	246	86

Table III Discharge instructions given to patients

Discharge instructions	No.	%
Checking inhaler technique	150	52
PEFR monitoring at home	0	0
Instructions on avoidance of trigger factors	0	0
Formulation of asthma action plan	0	0
Regular follow-up visits	286	100

Results

Audit of Quality of Care Indicators

Diagnostic Quality Indicators Two hundred eighty six patients were admitted for asthma exacerbation based on their symptoms (*Table I)*. None of these patients had PEFR monitoring at home to be able to document if their PEFR was < 80% of their personal best of predicted, or > 70% if no response to bronchodilator.

Acute Management Quality of Care Indicators

Two hundred thirty (230) patients (80%) had baseline and periodic monitoring of PEFR. PEFR variability was not computed for. Beta-2 agonists were given to all patients on admission on a regular basis. 197 (67%) were given nebulization using beta-2 agonist alone, 27 (9%) were given nebulization using combined beta-2 agonist + anticholinergic, and 68 (24%) were given beta-2 agonist via inhaler. Systemic steroids were given to all patients on admission as well. Two hundred sixty (91 %) were given steroids via the intravenous route, and 26 (9%) were given steroids via the oral route. Intravenous steroid given was usually in the form of Hydrocortisone 200 mg loading followed by 100 mg every 6 to 8 hours. Oral steroid given was usually in the form of Methylprednisolone 16 mg given twice or thrice a day. Those initially on IV steroids were shifted to oral steroids once symptoms have improved (*Table II*).

In addition, it was found out that severity of asthma exacerbation was recorded in only 10 (3%) of patients. Pulse oximetry monitoring was done for 35 (12%) of patients, while chest x-ray and arterial blood gas were done on admission for all 286 patients. Two hundred forty six (86%) of patients were given oxygen via nasal canula or face mask on admission, regardless of whether the arterial blood gas result showed adequate oxygenation. Oxygen was titrated based on spot check of oxygen saturation for those not on continuous pulse oximetry monitoring (Table II).

Quality of Care for Discharge Planning

Only 150 (52%) of patients were instructed on proper inhaler technique prior to discharge. Medical records did not note any discharge instructions regarding home PEFR monitoring, instructions on avoidance of trigger factors, and formulation of asthma action plan for the patient. All were given a follow-up schedule ranging from 5 to 7 days after discharge (*Table III*).

Discussion

Quality indicator(s) for diagnosis of asthma exacerbation: Results of this study showed that none of the patients had home PEF monitoring. Instead, all patients were admitted based on their symptomatology (cough, dyspnea, wheezing, nocturnal cough or wheeze). Lack of home PEF monitoring may be the reason why most patients fail to recognize asthma exacerbation at the onset, and instead come to the emergency room or physician's clinic for apparent worsening of symptoms. By using a combination of regular symptom recording and PEF measurement, patients can be provided with treatment plans that are responsive to asthma severity, and the course of asthma can be effectively monitored. A patient's adherence to treatment may be enhanced by observing objectively his/her responses to therapy. Long-term monitoring is particularly recommended for those patients with severe asthma, for those with poor perception of severity, and for those who have ever been

hospitalized. A persistent PEF < 80% personal best or predicted on two successive days or > 70% if no response to bronchodilator requires immediate treatment.[3]

Exacerbations of asthma are episodes of rapidly progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow that can be quantified by measurement of lung function (PEF or FEV_1).[3] These measurements are more reliable indicators of the severity of airflow limitation than is the degree of symptoms because a minority of patients perceive symptoms poorly, and may have a significant decline in lung function without a significant change in symptoms.[5] In patients with asthma, clinical symptoms may not always correlate with the degree of airway obstruction, thus objective measures of airway obstruction are needed (Grade A).[2] Asthma symptoms, the visual analog scale and dyspnea scores do not correlate with the level of FEV_1 and PEF (Level 1).[2] In one study, a specialist's assessment of long-term asthma severity did not correlate at all with asthma symptoms.[6] Likewise, two separate studies conducted on intra-patient assessment of severity of their own symptoms before and after treatment showed no correlation with FEV_1 and PEF.[7,8] Poor perception of the severity of asthma on the part of the patient has been cited as a major factor causing delay in treatment and thus may contribute to increased severity and mortality from asthma exacerbations.[9]

Quality indicator(s) for management of asthma exacerbation in the hospital: Results of this study showed that severity of asthma exacerbation was not assessed, except for 10 (3%) patients who presented in acute respiratory failure and were intubated. The severity of asthma exacerbations may range from mild to life-threatening.[3] Deterioration usually progresses over hours or days, but may occasionally occur precipitously over some minutes. Physicians should always assess the severity of asthma exacerbation as this determines the treatment to be administered. Morbidity and mortality are most often associated with failure to recognize the severity of the exacerbation, inadequate action at its onset, and under-treatment of it.

In this study, 80% of patients had baseline and periodic monitoring of PEFR, however, PEF variability was not computed for. Hospital-based management of asthma exacerbations require baseline PEF measurement, if possible, before initiation of treatment, without unduly delaying treatment.[3] Subsequent measurements should be made at intervals until a clear response to treatment has occurred. The measurement of PEFR provides useful information on the severity of asthma attack, response to therapy, need for hospital admission, and risk of early relapse.[2] In studies involving patients treated for acute asthma exacerbation in the emergency department setting, PEF before and after treatment were taken and compared for admitted and discharged patients. Patients who eventually needed hospitalization have lower PEF both at the beginning and at the end of treatment, indicating a greater severity of airflow obstruction in those who need in-patient care. Other studies suggest that failure of FEV_1 or PEF to improve promptly after bronchodilator administration predicts longer emergency department stay and more frequent need for hospital admission (Level 2).[2] The severity of asthma is reflected not only in the level of baseline airflow limitation, but also in its variability particularly across 24 hours. Ideally, PEF should be measured first thing in the morning when values are usually close to their lowest and last thing at night when values are usually at their highest. One method of computing for diurnal PEF variability is the mean percentage difference between the post-bronchodilator evening value and pre-bronchodilator morning value over a period of several weeks. Another method is the minimum morning pre-bronchodilator PEF over one week, expressed as a percent of the recent best.[10] A diurnal variation in PEF of more than 20% is considered to be diagnostic of asthma, the magnitude of the variability being broadly proportional to disease severity.[3] Population-based studies show that excessive diurnal PEF variation correlated with a higher incidence of respiratory symptoms, poor asthma control, and sudden death.[1] In this study, the failure to compute for PEFR variability during the course of the patient's hospital stay did not provide any objective measure of improvement in lung function.

Results of this study also showed that the physicians involved in the primary care complied with the GINA guidelines for the treatment of asthma exacerbation in terms of giving beta-2 agonists and systemic steroids. The schedule for giving beta-2 agonists and the doses of systemic steroids given were also within the recommendation set for in the GINA guidelines. However, most of the patients received beta-2 agonists via nebulization rather than by metered-dose inhaler (MDI), and most of them received intravenous steroids rather than oral steroids. GINA guidelines did not state whether loading doses for systemic steroids should be given.

GINA guidelines recommend the treatment of asthma exacerbation with rapid-acting inhaled beta-2 agonists to achieve rapid reversal of airflow limitation. Bronchodilator therapy delivered via a MDI, ideally with a spacer, produces at least an equivalent improvement in lung function at the same dose delivered via a nebulizer (Evidence A).[3] Studies showed that in patients with severe asthma, bronchodilation achieved was equivalent regardless of whether beta-2 agonist was administered by either MDI with spacer or nebulization. However, the groups given nebulization showed greater side-effects most likely due to increased systemic absorption and higher plasma levels. Hence, the nebulization route should only be used if the patient cannot adequately perform the MDI technique.[12,13] A combination of nebulized beta-2 agonist with an anticholinergic may produce better bronchodilation than either drug alone (Evidence B).[3] The addition of nebulized ipratropium bromide to salbutamol further improved the FEV_1 or PEFR in the initial treatment of acute asthma attacks (Grade A).[2] One study found that on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations, and fewer palpitations when compared with regular therapy given every 4 hours. A reasonable approach to inhaled therapy in exacerbations would be the initial use of continuous therapy, followed by on-demand therapy, which was done in this study.[3]

Systemic glucocorticoids speed resolution of exacerbations (Evidence A).[3] The use of systemic steroids has been shown to shorten duration of attacks, prevent relapse in the outpatient treatment of asthma exacerbations, and reduce subsequent hospital admissions (Grade A).[2] Systemic steroids administered by ingestion are usually as effective as those administered intravenously and are preferred because this route of delivery is less invasive and less expensive. In this study, 9% received systemic oral steroids versus 91% who were given the steroids via the parenteral route. Intravenous administration may be considered if IV access is desirable, or if there is possible impairment of gastrointestinal absorption.[3] Comparative studies have not shown a significant benefit of IV over oral administration in the initial treatment of severe asthma.[15,16] There are no convincing data on the proper duration of oral steroid treatment, although a 10 to 14 day course in adults is usually considered appropriate (Grade D).[3] Doses of systemic glucocorticoids equivalent to 60 mg to 80 mg Methylprednisolone or 300 mg to 400 mg Hydrocortisone per day are adequate for hospitalized patients, and even 40 mg Methylprednisolone or 200 mg Hydrocortisone is probably adequate.[3] All patients received doses of systemic steroids according to the recommendation.

In this study, only 12% of patients had their oxygen saturation monitored by pulse oximetry. Oxygen saturation should be closely monitored, preferably by pulse oximetry to achieve oxygen saturation of greater than or equal to 90% (Grade C).[3]

A chest x-ray is not routinely required, but should be carried out if a complicating cardiopulmonary process is suspected, in patients requiring hospitalization, and in those not responding to treatment where a pneumothorax may be difficult to diagnose clinically (Evidence C).[3] Despite this level of evidence, all patients had a chest x-ray taken on admission.

Arterial blood gas measurements are not routinely required but should be done for patients with a PEF of 30 to 50% predicted and in those who do not respond to initial treatment. A PaO_2 less than 60 mm Hg and a normal or increased $PaCO_2$ especially greater than 45 mm Hg, indicates the potential for or presence of respiratory failure (Evidence 0).[3] All patients had an ABG measurement on admission, regardless of the response to initial treatment.

In 86% of patients, the recommendation of GINA guidelines on the administration of oxygen was complied with. To achieve arterial oxygen saturation of greater than or equal to 90%, oxygen was administered by nasal cannulae or by mask and titrated according to oximetry (Evidence D).[3] For those not on continuous pulse oximetry monitoring, oxygen was titrated based on spot check of oxygen saturation.

Quality indicator(s) for discharge planning: Results of this study showed that inhaler technique was checked in only 52% of patients. Records did not state whether the patients were advised on home PEFR monitoring, instructions on avoidance of trigger factors, and formulation of an asthma action plan. Failure to educate patients on proper inhaler technique, home PEFR monitoring, avoidance of trigger factors, and failure to provide an asthma action plan, can lead to more asthma exacerbations and subsequent hospital admissions. All patients were given a schedule for follow-up visit 5 to 7 days from the date of discharge. Continual monitoring is essential to ensure that therapeutic goals are met. Frequent follow-up visits are necessary to review home PEF records, the techniques in using medication, risk factors and methods to control them, and treatment plans. Once control is established, regular follow-up visits (at 1- to 6- month intervals as appropriate) continue to be

essential. Ideally, all patients should have a written action plan with both a symptom and peak flow component that outlines how and when to recognize signs of deterioration, modify or augment the treatment, assess the severity of the attack, and obtain more specialized care if appropriate.[3]

Conclusion

The quality of care for diagnosis, acute management and discharge planning for asthma exacerbation as recommended by GINA guidelines were not followed. An understanding of the pathophysiology of asthma and implementation of treatment programs such as those in the GINA can help improve the quality of care for patients. The physician's choice of diagnostic and treatment modalities will be greatly influenced by available resources and the priority given to these modalities. Although consensus statements are meant to be used as guides in diagnosis and management, and individualized treatment of patients remains the norm, proper education and good compliance of guideline~ will significantly improve care providers' performance.

Recommendations

Standardization of asthma care as recommended by the guidelines should be implemented.

A proper understanding of the fundamentals of asthma care as reflected by validated quality indicators should be conducted through education and dissemination of guidelines.

A follow-up study to determine (1) compliance with the agreed upon standardization of asthma care and (2) the effect of this on short and long term control of asthma attacks should be done.

References

1. Liwag, Aretha, et al Validation of the Asthma Quality of Life Questionnaire in Adult Filipino Patients. Phil J Internal Medicine, 40: 16, Jan-Feb 2002.
2. Philippine Consensus Report on Asthma Diagnosis and Management, an evidence-based update. Philippine College of Chest Physicians Council on Asthma Report. Revised 2004.
3. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. Revised 2002.
4. Lai, Christopher, et a/. Asthma Control in the Asia-Pacific Region: The Asthma Insights and Reality in Asia-Pacific Study. J Allergy Clin Immunol 2003; 111: 263-8.
5. Kerrebijn KF, et a/. Effect and long-term treatment of inhaled corticosteroids and beta agonists on the bronchial responsiveness in children with asthma. J Allergy Clin Immunol1987; 79: 653-9.
6. Osborne ML, et a/. Lack of correlation of symptoms with specialistassessed long-term asthma severity. Chest. 1999; 115: 85-91.
7. McFadden ER, et a/. Acute bronchial asthma: relations between clinical and physiologic manifestations. N Engl J Med 1973; 288: 221-5.
8. Teether JG, et a/. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. Chest 1998; 113: 272-7.
9. Nowak RM, et a/. Comparison of peak expiratory flow and FEV1 admission criteria for acute bronchial asthma. Ann Emerg Med 1982; 11: 64-9.
10. Reddel HK, et a/. Which index of peak expiratory flow is most useful in the management of stable asthma? Am J Respir Crit Care
11. Med 1995; 151: 1320-5.
12. Quackenboss JJ, et al. The normal range of diurnal changes in peak expiratory flow rates: relationship to symptoms and respiratory disease. Am Rev Respir Dis 1991; 143: 323-30.
13. Rodrigo C, Rodrigo G. Salbutamol treatment of acute severe asthma in the emergency department: MOl vs. handheld nebulizer. Am J Emerg Med 1998; 16 (7)
14. Mandelberg A, et a/. Nebulized wet aerosol treatment in emergency department - is it essential? Comparison with large spacer device for metered dose inhaler. Chest 1997; 12: 1501-5.
15. Bradding P, et a/. As required vs. regular nebiulized salbutamol for the treatment of acute severe asthma. Eur Respir J 1999; 13: 290-4.
16. Rowe B, et a/. Steroid use in the emergency department for treatment of asthma exacerbation: a meta-analysis. Am J Emerg Med 1992; 10: 301-10.
17. Fanta SB, et a/. Glucocorticoids in acute asthma: a clinical controlled trial. Am J Med 1983; 74: 845-51.

Effectiveness of 12 Weeks of Supplementary Oral Nutrition in Improving Functional Capacity of Outpatients with Chronic Obstructive Pulmonary Disease at the Veterans Memorial Medical Center

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Background Information: Two problems of nutritional consequence that are frequently noted in patients with COPD are weight loss and infection. Results of studies concerned with dietary intake and weight changes in COPD patients have suggested that nutrient intake and nutritional status are compromised in the population. Hence, it seems especially appropriate to consider exactly how malnutrition may affect respiratory muscle function and to what extent nutritional repletion can help.
Objectives: To determine the effectiveness of 12 weeks of supplementary oral nutrition in improving the functional capacity of COPD patients.
Methods: 80 COPD patients with moderate to severe chronic airflow obstruction who are receiving regular care at the COPD Clinic of the Department of Pulmonary Diseases of the Veterans Memorial Medical Center, all men 71 to 77 years of age were included in the study. They were randomly allocated to 1 of 2 groups: 40 patients to Group 1 (Control Group), received their normal diet and the other 40 patients to Group 2 (Supplemented Group), received a high calorie/high protein supplemented diet for 12 weeks. Baseline measurements such as weight, height, triceps skinfold thickness, mid-upper arm muscle circumference and waist and hip circumferences were taken on entry to study and monthly thereafter for a period of 12 weeks or 3 months. Likewise, their FEV_1 and FVC were measured and their Dyspnea Score were determined.
Statistics: Dependent t-test was done in evaluating each patient within the 2 groups while independent t-test was used in comparing the 2 groups. Linear regression analysis and analysis of covariance were used in determining within group and between-group correlation of data, respectively.
Results: Statistically, no significant changes in anthropometric measurements as well as in FEV_1 & FVC and Dyspnea Score were identified in the subjects when both groups were compared during the 12-week period. However, when each group was evaluated, the subjects in Group 2 seemed to have improved FEV_1 with a parallel slight weight gain. No definite correlation however can be found between the severity of their nutritional status and their lung capacity.
Conclusion: This study has not successfully demonstrated the effectiveness of oral supplementary nutrition in COPD patients. Factors such as the natural course of COPD, calorie intake, duration of study period and socioeconomic differences could have contributed to this and might have affected the outcome of results of this study. The need for a long-term study to look into the problem of COPD nutrition is inevitable. *Phil Journal of Chest Diseases Vol 13 No. 1 pp: 52-56*

Keywords: Oral nutrition, COPD, Pulmonary function

Introduction

Two problems of nutritional consequence that are frequently noted in patients with chronic obstructive pulmonary disease (COPD) are weight loss and infection.[1] Results of studies have shown that with advancing COPD, weight progressively declines, that weight loss in COPD has a negative effect on lung function and that mortality rates are higher and heart failure occurs more frequently in patients with COPD who have lost weight compared with patients with COPD without a weight change.[2,3] Results of studies concerned with dietary intake and weight changes in

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patients with COPD have suggested that nutrient intake and nutritional status are compromised in the population.[2,3,6] The incidence of significant weight loss may be as high as 71% in hospitalized patients with COPD.[7] Moreover, approximately 50% of hospitalized patients with COPD have lost 10% or more of their ideal body weight, with associated abnormalities of anthropometric, biochemical and immunologic indices of poor nutritional status. However, none of the previous studies has evaluated the nutritional status of patients with COPD by using a comprehensive nutritional profile nor has the concomitant existence of protein calorie malnutrition with COPD been identified. In patients with COPD, it seems especially appropriate to consider exactly how malnutrition may affect respiratory muscle function and to what extent nutritional repletion can help.

Malnutrition is associated with more severe outflow obstruction and predisposes to respiratory failure and death in patients with COPD, and has therefore been regarded as an important prognostic indicator.[8] There are many potential reasons why malnutrition may be detrimental in patients with COPD. These include decreased respiratory muscle mass and ventilatory endurance leading to the premature development of ventilatory failure, decreased ventilatory response to hypoxia, and impairment of local pulmonary as well as systemic immunologic defense mechanisms.

To date, however, there has been little information on the value of nutritional repletion in patients with COPD. In one uncontrolled study, six hospitalized patients received an orally supplemented diet for three weeks, which resulted in improvements in nutritional status and respiratory muscle strength, and in a controlled study in 21 outpatients receiving an orally supplemented diet for eight weeks, there was no significant improvement in nutritional status or respiratory muscle strength.[9] With these contradicting results, we decided to carry out a prospective, randomized, controlled trial that would investigate the effect of twelve weeks of supplementary oral nutrition in COPD patients.

This prospective, randomized controlled trial was carried out at the Department of Pulmonary Diseases of the Veterans Memorial Medical Center to determine the effectiveness of 12 weeks of supplementary oral nutrition in improving the functional capacity of COPD outpatients. Furthermore, we wanted to examine the nutritional status of these COPD patients by measuring their body mass index (BMI), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC) and waist-to-hip ratio; to evaluate their functional capacity by measuring their FEV_1 and FVC and by getting their dyspnea score using the British Medical Research Council Dyspnea Scale,[10] and to determine if severity of malnutrition is associated with severity of airflow obstruction among these patients.

Methods

Eighty COPD outpatients seen in the COPD Clinic of the Department of Pulmonary Diseases of the Veterans Memorial Medical Center, all men 71 to 77 years of age (mean ± SD, 72 ± 5 yrs.) were studied January to March 2003. The sample size was obtained by assuming 71% of the subjects having weight loss with a confidence interval (CI) of 20%, α=0.05, β=0.20. All were ex-smokers and had moderate to severe chronic airflow obstruction (*Table I*). None of the patients had asthma, cancer, neuromuscular disease, or any specific medical or surgical disorder. All patients were randomly allocated to one of two groups: Forty patients assigned to Group 2 (Supplemented Group), received a high calorie/high protein supplemented diet for 12 weeks.

Subjects During the 12-week study period, all were receiving regular care as outpatients in the COPD Clinic at the Veterans Memorial Medical Center. Half of the patients were using tiotropium inhaler, one-fourth were taking a combination of β2-agonist and steroid, and the remaining one-fourth were also taking sustained release oral theophylline preparations. None was taking oral corticosteroids.

Study Design. The study was designed as a prospective, randomized, controlled trial to determine whether 12 weeks of supplementary oral nutrition improved the functional capacity of COPD outpatients. All patients had their baseline parameters taken on entry to the study enabling the investigator to note any effects the supplemented diet produced. The study was performed single blind in that Group 2 patients were obviously appreciated since they were taking a supplemented diet.

Furthermore, none of the investigators making the measurements was aware of which patients were taking the supplemented diet, apart from the principal dietician who was solely responsible for the allocation of diets.

Measurements of weight, height, body mass index (BMI), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), waist-to-hip ratio, dyspnea score and pulmonary function were made on

Table I Baseline Anthropometric Data and Lung Function of Control Subjects (Group 1) and Subjects with Supplemented Diet (Group 2) using Analysis of Covariance

	Group 1 (n=40)	Group 2 (n=40)
Anthropometric Data		
Age, yr.	71 ± 5.1	72 ± 4.6
Sex,M/F	40/0	40/0
Weight, kg	47±11.04	46 ± 10.9
Height, m	1.61± 0.07	1.60 ± 0.05
BMI	26± 7.04	25 ± 6.6
MUAC	22 ± 3.4	21± 3.08
TSF	13 ± 7.2	11 ± 6.06
MAMC	18 ± 2.7	18 ± 2.2
Waist, cm	74 ± 17.2	75 ± 10.9
Hip, cm	78 ± 10.6	79 ± 12.6
Waist-to-hip ratio	0.94 ± 0.05	0.95 ± 0.05
Lung Function		
FEV_1 % pred	52 ± 6.8	47 ± 8.1
FVC, % pred	58 ± 7.7	54 ± 10
FEV1, L	0.75 ± 0.03	0.74 ± 0.03
FVC, L	2 ± 0.07	2 ± 0.08
FEV_1/FVC, %	36 ± 1.5	3 6 ± 5. 1

Note: Comparisons of all parameters between the 2 groups showed no significant differences, p>0.05, not significant.

Table II Anthropometric Data and Lung Function of Control Subjects (Group 1) and Subjects with Supplemented Diet (Group 2), Second Month using Analysis of Covariance

	Group 1 (n=40)	Group 2 (n=40)
Anthropometric Data		
Weight, kg	47 ± 11.4	46 ± 11.2
Height, m	1.62 ± 0.07	1.61 ± 0.06
BMI	26 ± 7.07	26 ± 6.6
MUAC	22 ± 3.5	21 ± 3.08
TSF	12 ± 7.3	11 ± 6.06
MAMC	18 ± 2.7	18 ± 2.2
Waist, cm	74 ± 11.3	75 ± 10.9
Hip, cm	79 ± 12.6	79 ± 10.6
Waist-to-hip ratio	0.94 ± 0.05	0.95 ± 0.05
Lung Function		
FEV_1 % pred	51 ± 6.6	47 ± 7.8
FVC, % pred	57 ± 7.4	54 ± 9.7
FEV1, L	0.98 ± 1.25	0.78 ± 0.03
FVC, L	1.99 ± 0.03	1.99 ± 0.05
FEV_1/FVC, %	39 ± 1.56	39 ± 1.82

Note: Comparisons of all parameters between the 2 groups at 2nu month of study showed no significant differences, p>0.05, not significant.

entry to the study and monthly for the entire 12-week study period. Informed consent was obtained from all patients. The study was approved by the Veterans Memorial Medical Center Committee on Research.

Table III Anthropometric Data and Lung Function of Control Subjects (Group 1) and Subjects with Supplemented Diet (Group 2), 3rd month using Analysis of Covariance

	Group 1 (n=40)	Group 2 (n=40)
Anthropometric Data		
Weight, kg	47 ± 11.4	47 ± 11.2
Height, m	1.62 ± 0.07	1.61 ± 0.06
BMI	26 ± 7.2	26 ± 6.9
MUAC	22 ± 3.5	21 ± 3.08
TSF	13 ± 7.3	11 ± 6.06
MAMC	18 ± 2.7	18 ± 2.2
Waist, cm	74 ± 11	75 ± 10.9
Hip, cm	79 ± 12.6	79 ±10.6
Waist-to-hip ratio	0.94 ± 0.05	0.95 ± 0.05
Lung Function		
FEV_1 % pred	52 ± 6.7	48 ± 9.4
FVC, % pred	58 ± 7.7	54 ± 10
FEV1, L	0.79 ± 0.02	0.81 ± 0.15
FVC, L	2 ± 0.03	2 ± 0.02
FEV_1/FVC, %	39 ± 1.2	3 9 ± 1.7

Note: Comparisons of all parameters between the 2 groups at third month of study showed no significant differences, p>0.05, not significant.

Anthropometric measurements made at each monthly visit included body weight, height, triceps skin-fold thickness (TSF), and mid-arm muscle circumference (MAMC). The weight was obtained using the beam balance or clinical scale. The left mid-arm circumference and triceps skinfold thickness were measured, always by the same investigator using the Holtain skinfold calipers. The site of measurement for the triceps skinfold thickness and mid-arm circumference was located at the midpoint between the acromion and the olecranon process. The MAMC was calculated from the TSF using a standard equation, and the BMl from the weight and height. Measurement of lung function included FEV_1 and FVC using the Knudson normal values during a maximal expiratory flow-volume maneuver. The patient's own subjective assessment of breathlessness was determined by means of the British Medical Research Council Dyspnea Scale[10] with a Grade of 0 to 4, with Grade 4 being most severe feeling of breathlessness.

Statistics. The means of data for each month during the 12-week study period within each patient group were compared using the dependent *t-test* or *Wilcoxon* Matched-Pairs Signed-Ranks test. Between groups comparisons were made using the independent *t-test* or the *Mann-Whitney* U test. Within-group correlation of data was made using simple linear

regression analysis. Between-group correlation of data was made using the analysis of covariance.

Results

Forty COPD patients were randomized to Group 1, receiving their normal diets and the other forty patients into Group 2, taking their supplemented diets prescribed by the principal dietician. All Group 2 patients tolerated the supplemented diet without complication. The supplemented diet consisted of 13 g of protein, 12.6 g of fat, and 47.3 g of carbohydrate, which provided 355 kcal. There were significant increases in the mean daily calorie intakes of Group 2 during the 12-week study period to 1,800 ± 155 kcal with 50% carbohydrates, 30% proteins and 20% fats which were higher than those of Group 1, which received a daily calorie intake of 1,600 kcal computed based on their ideal or desirable body weight (IBW or DBW). All patients in Group 2 maintained their own dietary intake while receiving the supplemented diet. Likewise, all patients in Group 2 were able to comply with their own dietary intake. Baseline measurements of age, height, weight, BMI, MAMC, TSF, waist-to-hip ratio in Groups 1 and 2 were almost similar (*Table I*). The mean age in Group 1 was 71 ± 5.1 years compared with 72 ± 4.6 years in Group 2. The desirable or ideal body weight (DBW or IBW) in Group 1 was 79.5 ± 3.2% compared with 81.3 ± 2.1% in Group 2. The mean weight in Group 1 was 47 ± 11.04 kg compared with 46 ± 10.9 kg in Group 2. The mean height in both Groups 1 and 2 were similar, 1.61 ± 0.07 m and 1.60 ± 0.05 m, respectively. The mean BMI in Group 1 was 26 ± 7.04 and that of Group 2 was 25 ± 6.6. Measurements of MAMC for both Groups 1 and 2 were below the acceptable standard (< 85%). Measurements of TSF were likewise below the acceptable standard except for a number of patients who had values within the acceptable percentile (>50%). The mean waist-to-hip ratios were likewise similar for both groups.

No significant change in weight among patients in Group 1 was noted throughout the entire 12-week study period. This was in contrast with the patients in Group 2, who received supplemented diets. As regard the BMI, there was likewise a parallel increase among patients in Group 2. It was noted however, that when both groups were compared, there was no significant difference in their weights. The mean measurements of MAMC and TSF during the second and third months of study showed no difference from those of the baseline measurements.

Table IV Dyspnea scores of control subjects (Group 1) and subjects with supplemented diet (Group 2) using the British Medical Research Council Dyspnea scale.

Dyspnea Score	Group 1 (n=40)	Group 2 (n=40)	*p* value
1st month			
2	35 (87.5)	37 (93)	0.712
3	5 (12.5)	3 (7.5)	
2nd month			
2	32 (80)	34 (85)	0.768
3	8 (20)	6 (15)	
3rd month			
2	30 (75)	33 (82.5)	0.585
3	10 (25)	7 (17.5)	

The mean baseline FEV_1 and FVC in Group 1 were similar to those in Group 2 (FEV_1 = 0.75 ± 0.03 L, FVC = 2.05 ± 0.07 L, FEV_1 % pred = 52 ± 6.8, FVC % pred = 58 ±7.7 and FEV_1 = 0.74 ± 0.02 L, FVC = 2.03 ± 0.08, FEV_1 % pred = 47 ± 8.1, FVC % pred = 54 ± 10 respectively). Hence, no significant difference between the two groups was observed. There were no statistically significant changes in FEV_1 and FVC in Group 2 patients who received supplemented diets during the entire 12-week study period.

Statistically, there were also no significant changes in any of these tests in Group 1 throughout the 12-week study period. There was however a slight degree of improvement in the FEV_1 (% pred) of Group 2 at the 3rd month of study. The FVC (% pred) in the 3rd month, on the other hand remained the same if not a little less compared to that in the first and second months. These all could have been caused by certain confounders in the study. No significant correlation was observed between the severities of nutritional status among COPD patients in Group 1 and the degree of airflow obstruction they have as shown in the graphs of BMI and FEV_1. But in Group 2, there could be some degree of correlation between the severity of their nutritional status and their lung capacity.

Using the British Medical Research Council Dyspnea Scale, most patients in both Groups 1 and 2 on entry to the study had Grade 2 dyspnea score, i.e., they had to stop for breath when walking on the level. A number of patients in both Groups 1 and 2, however also had Grade 3 dyspnea score, i.e., they had to stop after walking about 100 yards or after a few minutes on the level. (*Table IV*)

No improvement was noted in the dyspnea scores of patients in Group 2 during the second and third

months that they received a supplemented diet, a few even deteriorated to some extent (*Table IV*).

Discussion

This study has not shown that a supplementary oral nutrition given for twelve weeks can result in a significant increase in weight gain and in improvement of nutritional status of patients with COPD. Basing on our data, no significant increase in their weight, MAMC, TSF measurements were noted. Likewise, no concurrent improvement in their pulmonary function was seen during the 12-week supplemented diet. Estimates of clinical improvement such as the subjective scores of dyspnea did not also improve significantly.

Despite the 12-week oral supplementary nutrition, the patients did not demonstrate improvement in the clinical parameters that were measured. The patients neither showed any marked deterioration during the period that they received the supplemented diet. Indeed, it has previously been suggested that the weight loss accompanying COPD might be due to a reduced calorie intake or to increased caloric utilization. This could very well explain why these patients did not improve in their nutritional status despite the supplementation. They could have been continuously expending energy due to respiratory muscle fatigue from their COPD. The results of the anthropometric measurements for triceps skinfold, mid-arm circumference, and mid-arm muscle circumference indicated that the morphologic root of the weight loss in COPD is subcutaneous fat stores and lean body mass. As evidenced in this study, both of these compartments were overtly depleted, that is, well below the acceptable range. Socioeconomic differences such as family support, social class and personal wealth and depression could have also contributed, although these were not examined in detail on entry to the study.

There have also been three other comparable attempts in COPD patients which failed to show any benefit in giving oral supplementary nutrition. In these studies the baseline calorie intake was high but was given for a shorter period of time, 30 to 56 days.[11] In our study, the calorie intake was similar to these studies, though given for a longer period of time, i.e., 12 weeks or 90 days. In contrast to our study, Efthimiou et aI, found out that oral supplementary nutrition for twelve weeks improved the nutritional as well as the pulmonary status of the COPD patients.[9] It is quite interesting to note that the calorie intake and protein distribution given to their subjects were much higher.

Although it is generally agreed that progressive weight loss exists in COPD, the cause of the weight loss is often considered an enigma. Decrease caloric intake is frequently mentioned as a causative agent in the weight loss experienced by COPD patients. Thus, the severity of dietary impairment and the extent of calorie increase as well as its duration may also be key factors and may be crucial in nutritional repletion in COPD patients.

Conclusion

Our data did not conclusively demonstrate the effectiveness of supplementary nutrition in COPD outpatients possibly because of confounding factors such as the amount of calorie intake, the duration of the study period, socioeconomic differences and, the natural course of COPD and its pathophysiology being the most important factor. Hence, it is of sufficient importance that long-term studies in COPD nutrition be done to improve both the quality of life and survival of these COPD patients.

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References

1. Mitchell, RS, Filley GF. Chronic obstructive pulmonary disease: clinical features. Am Rev Respir Dis 1964; 89:360-7L
2. Barrows, BA, Niden, AH, Barclay, WR, Kasik, SI. Chronic obstructive lung disease: relationship of clinical and physiologic findings to the symptoms of airway obstruction. Am Rev Respir 1965; 91:665-78.
3. Rondenberg E, van de Woestijne KP, Gyselen, RD. Weight changes in the terminal stages of Chronic obstructive pulmonary disease: relation of respiratory function and prognosis. Am Rev Respir Dis 1967; 95-556-66.
4. Fowler, J, Godese, R. Empysema of the lungs. In Disease of the lungs. London: Longmans, Green, 1898; 171.
5. Driver, AG, McAlevy, MT, Smith, JL. Nutritional assessment of patients with chronic obstructive pulmonary disease and acute respiratory failure. Chest 1982; 82:568-71
6. Braun, SR, Dixon, RM, Keirn NL, Luby, M, Anderegg, A, Shrago, ES. Predictive clinical value of nutritional assessment factors in COPD. Chest 1984; 85 :353-71
7. Askanazio, J, Weissman, C, Rosenbaum, SH, Hyman, AI, Milic-Emili, J, Kinney, JM. Nutrition and the respiratory system. Crit Care Med 1982; 10:163-72.
8. Barrocas, A, Tretola, R, Alonson, A Jr. Nutrition and the critically ill pulmonary patient. Respir Care 1983; 28: 50-61.
9. Efthimiou, J, Fleming, J, Gomes, C, Spiro, SG. The effect of supplementary oral nutrition in poorly nourished patients with

chronic obstructive pulmonary disease. Am Rev Respir Dis 1988; 137: 1075-82.
10. Bestall, JC, Paul, EA, Garrod, R, Gamham, R, Jones, PW, Wedzicha, JA. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54:581-6.
11. Lewis MI, Belman MJ, Dorr-Uyemura L. Nutritional supplementation in ambulatory patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1987: 135:1062-8.

Sustained-Release Bupropion Hydrochloride (SR) for the Treatment of Nicotine Dependence as an Aid to Smoking Cessation among Filipinos

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Objective: The purpose of this study was to evaluate the efficacy and safety of bupropion hydrochloride (SR) among Filipinos as an aid to smoking cessation and to determine factors that may promote smoking abstinence among Filipinos.
Design: This was a non-randomized, prospective, open-labeled trial.
Setting: The Pulmonary Medicine Section of the Philippine General Hospital, Manila, Philippines.
Main Outcome Measures: Urine cotinine-confirmed or true smoking abstinence, psychological well-being, safety, and predictors of abstinence
Results: A 57% urine cotinine-confirmed abstinence rate was noted at eight weeks among the Filipino smokers who underwent a smoking cessation program and utilized bupropion hydrochloride (SR) as an aid to smoking cessation. Predictors of smoking abstinence were educational attainment, age at smoking onset, presence of smoker(s) in the home, and baseline carbon monoxide levels. There was no difference between abstainers and the non-abstainers regarding safety and psychological well-being. There were no serious adverse events.
Conclusion: Bupropion hydrochloride (SR) is effective and safe as an aid to smoking cessation among Filipinos. *Phil Journal of Chest Diseases. Vol 13 No 1 pp: 57-64*

Keywords: nicotine dependence, smoking cessation, bupropion hydrochloride

Introduction

The Philippines is the 15th biggest consumer of cigarettes in the world and the largest consumer among the Association of Southeast Asian Nations.[1] Smoking is very prevalent in the Philippines with 45.6% among Filipinos having a history of smoking and 47% being passive smokers.[2] Fifty-six percent of adult Filipino men and 12% of adult Filipino women smoke. In 2003 the prevalence of current smokers increased from 32.7% in 1999 to 34.8%.[3]

Smoking causes at least 40 different chronic diseases. In 1999 alone, approximately 252,640 Filipinos suffered from lung cancer, chronic obstructive pulmonary disease, coronary artery disease and cerebrovascular disease as a direct consequence of smoking. During that same period, healthcare costs, productivity losses secondary to disease and death due to these illnesses cost the Philippines more than 46 billion pesos.[3]

Smoking cessation therefore should be a major health care goal for the Philippines. Several guidelines cirltJ reviews on the different smoking cessation techniques have shown variable efficacy and it is the consensus of most experts that concomitant use of pharmacologic treatment for nicotine dependence significantly increases the chance of success.[4,5]

One of the newer non-nicotine drugs shown to be efficacious as an aid to smoking cessation is bupropion hydrochloride. Bupropion hydrochloride is an aminoketone compound originally developed as an antidepressant (Wellbutrin). As an antidepressant, bupropion is thought to act primarily via a noradrenergic mechanism, but also has some dopaminergic activity.

Results from clinical studies have documented that bupropion is relatively free of anticholinergic, sedative, cardiovascular, and sexual side effects. Although infrequent, the most common adverse experiences are

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headache, dry mouth, nausea, dizziness, insomnia and constipation.[6]

Bupropion is associated with seizures. In a study of subjects with depressive disorders, the incidence was 0.1% at a maximum dose of 300 mg per day of slow-release bupropion hydrochloride (SR).[7] In previously reported smoking cessation trials, which excluded subjects with a predisposition to seizures, no seizures were reported for any of the subjects included.[8]

The results of two placebo-controlled clinical trials on slow-release (SR) bupropion hydrochloride demonstrated both the safety and efficacy of bupropion as an aid to smoking cessation in subjects who were motivated to quit.[9,10]

Because of the well-documented proof of its efficacy, slow-release bupropion hydrochloride was approved for marketing in the US by the Food and Drug Administration (FDA) in 1997 as an aid to smoking cessation under the trade name *Zyban.*

It is therefore the aim of this study to evaluate the efficacy and safety of bupropion hydrochloride as an aid to smoking cessation among the Filipino population. It must be noted that, despite the high prevalence of smoking in the Philippines, there are no available pharmacologic drugs at the time this study was conducted; whether direct nicotine replacement systems or not, to aid Filipino smokers who wish to stop smoking.

We also wanted to assess the rate of successful smoking cessation in response to bupropion treatment among Filipino smokers in the Philippines. The effect of bupropion hydrochloride (SR) on the psychological well being of Filipino patients was also determined. And finally, we wanted to discover factors that may promote smoking abstinence among Filipinos when treated with bupropion.

Methodology

Subjects This randomized, double-blind, placebo-controlled study of relapse prevention was performed at the Philippine General Hospital and was approved by the Research Implementation and Development Office (RIDO). Recruitment was done by advertisement, word of mouth and doctors' referrals. A total of 106 volunteers were evaluated of whom 84 met the study criteria.

Subjects were eligible for inclusion if they were at least 21 years of age, had smoked an average of 10 cigarettes or more per day for the past year for a period greater than three months, were motivated to stop smoking, and were generally in good health. Exclusion criteria included a predisposition to seizures or family history of seizures, a history or current diagnosis of bulimia or anorexia nervosa, was currently using other pharmacologic treatments for smoking cessation (nicotine gum, nicotine patch, etc.) or tobacco products other than cigarettes (e.g. pipes, cigars, snuff, chewing tobacco), a history of severe head trauma, was currently on psychotropic medications, with other unstable concurrent medical or psychiatric illnesses that in the investigator's opinion interfered with therapy (e.g. unstable diabetes, angina pectoris, renal dysfunction, or alcoholism, non-nicotine substance abuse, severely immunosuppressed condition), was positive on urine drug screen for methamphetamine use, females of child-bearing potential, had no telephone or mobile phone access, had no ready access to the study site or currently included in other study trials.

Study Procedure. At the base-line visit subjects received bupropion hydrochloride (SR) 150 mg tablets which they took once daily during the first 3 days and then twice daily for the remainder of the 8-week study period. Subjects set a target quitting date for smoking (or "target quit date" after one week of medication (usually the eighth day). They returned weekly during the first 4 weeks of treatment and then at 6 and 8 weeks for follow-up. At the baseline physical examination, each subject received a brief, personalized message to stop smoking from the physician and the *Zyban* Advantage Plan manual.

We obtained data on smoking history and administered several questionnaires on the first visit: the Fagerstrom Tolerance Questionnaire, the Center for Epidemiologic Studies Depression Scale (CESD), the Spielberger Trait Anxiety Inventory for Adults (ST AI), and the Minnesota Withdrawal Scale (MWQ).

Each week we collected the subjects' daily diaries and recorded concomitant medication use, adverse events, vital signs, and the carbon monoxide (CO) content of expired air. Exhaled CO concentration was measured using the EC50 *Smokerlyser* (Bedfont Instruments; Kent, UK). Prior to the start of the study, the analyzer was calibrated with a mixture of 50 ppm CO in air. The subjects were asked to exhale completely, inhale fully and then hold their breath for 15 seconds. They were then asked to exhale slowly into the *Smokerlyser* and were encouraged to exhale fully in order to sample alveolar air. The *Smokerlyser* measures breath CO levels in parts per million (ppm)

based on the conversion of CO to carbon dioxide (CO_2) over a catalytically active electrode. Carbon monoxide level in expired air of 10 ppm or below commonly indicates abstention from smoking for the immediate past few hours.[11] Carbon monoxide level, in this study, was utilized as an immediate biological feedback to the subject to reinforce his/her effort to abstain from smoking.

Brief individual counseling (approximately 10 to 15 minutes) was provided by a study assistant at each visit.

At the end of 8 weeks urine cotinine determination was done using the *Immunalysis* Cotinine Direct Elisa Kit. If the absorbance of the sample was equal to or less than the average absorbance of the laboratory positive reference standard, the sample was labeled POSITIVE. If the average sample absorbance was greater than the average absorbance of the laboratory positive reference standard, the sample was called NEGATIVE.

Several questionnaires were again administered during each subsequent visit, the CESD, MWQ and the Spielberger State Anxiety Inventory.

Patients were withdrawn from the study for severe allergic reactions or any adverse reaction deemed sufficiently serious to require discontinuation of therapy such as death, life threatening events, hospitalization, development of a persistent or significant disability or incapacity or the occurrence of a significant medical event. Subjects who failed to attend at least two clinic visits were considered withdrawals.

Study endpoints. Confirmed smoking abstinence was defined as a self-report of continuous abstinence confirmed by a negative urine cotinine test. The subjects' self-report of continuous abstinence was defined as no cigarettes smoked from quit day until the end of the study. At the end of 8 weeks, smoking abstinence was verified by a negative urine cotinine result level.

Respiratory CO level, determined at each clinic visit, was correlated with the confirmed smoking abstinence rate of the population.

The safety of bupropion hydrochloride (SR) was evaluated by assessing the mean arterial blood pressure, weight and adverse events at each clinic visit.

Psychological well-being was assessed using several questionnaires. The eight-item Fagerstrom Tolerance Questionnaire is a widely used measure of nicotine dependence in adults (Fagerstrom 1978) with a score ranging from 0 to 11; a score of 6 or greater indicates higher levels of dependence. The Center for Epidemiologic Studies Depression Scale (CESD, Radloff, 1977) is a self-report scale which is an amalgamation of previously devised depressive inventories. The scale includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. The response values are 4-point Likert scales with the final score spanning from 0 to 60. People with a final score of 16 or higher are typically identified as a depressive "case." The State-Trait Anxiety Inventory (STAI, Spielberger, 1983) is an instrument for measuring anxiety in adults. It differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The STAI has 40 questions with a range of four possible responses to each. The Minnesota Nicotine Withdrawal Questionnaire (MWQ, Hughes and Hatsukami 1986) assesses self-report ratings of eight nicotine withdrawal symptoms on a scale from 0 to 4. This measure has been shown to be valid and sensitive to withdrawal effects in smokers.

The baseline characteristics and smoking features of the population were analyzed to determine which may be factors that correlated with smoking abstinence.

Statistical Analysis. 1. Sample size. With the assumption of the power of the study (1-,8) at 0.8, α at 0.05, and an estimated quit rate of 10% for smokers with no pharmacologic intervention and 40% with bupropion as the active intervention,[10] the estimated sample size needed for significance was 80.

Subjects who dropped out or withdrew were included in the analysis as treatment failures.

2. Success in smoking abstinence. Confirmed smoking abstinence was computed as a percentage. Patient's self-reported abstinence was analyzed for significance using the *t-test*. Abstinence determined by exhaled CO levels < 10ppm were also analyzed by *t-test*.

3. Safety. Changes in mean arterial blood pressure and weight from baseline were computed as percentage change from baseline.

The number of minor and serious adverse events was also computed as percentage of the total number of subjects.

It is acknowledged that this study does not have a control arm. The accompanying behavioral interventions also varied from simple clinicians advice

Table 1 Demographic characteristics of the study population (n=84)

Age	39.9 ± 13.1
Sex	
Male	76 (60.5)
Female	8 (9.5)
Civil Status	
Married	53 (63.1)
Single	27 (32.1)
Divorced/widowed	4 (4.8)
Educational Attainment	
College/Vocational	38 (45.2)
High school/Grade school	46 (54.8)
Employment	
Full time	36 (42.9)
Part time	16 (19.0)
Not employed	32 (38.1)
Baseline Laboratory Results	
FBS (mg/L)	90.1 ± 21.8
Creatinine (mg/dl)	1.0 ± 0.4
ECG	
Normal	77 (92.8)
Sinus bradycardia	6 (7.2)
Presence of psychiatric diagnoses	
Depression disorder	2 (2.4)
Anxiety disorder	1 (1.2)
Alcohol abuse	6 (7.1)
Others (somatoform)	31 (36.9)
Absence of psychiatric disorder	45 (53.6)
Smoking Characteristics	
Age of onset	17.5 ± 6.0
Age at regular smoking	18.1 ± 6.7
Duration of smoking	21.8 ± 12.4
Number of pack years	21.7 ± 17.9
Current no. of sticks smoked per day	
Past week	17.1 ± 9.6
Past year	16.7 ± 11.7
First year of smoking	8.7 ± 11.1
Number of Quit attempts	1.8 ± 1.9
CESD (Score at baseline)	11.6 ± 5.7
Spielberger T (Score at baseline)	39.6 ± 7.5
Fagerstrom (Score at baseline)	
Very low dependence (0-2)	0
Low dependence (3-4)	9 (10.7)
Moderate dependence (5)	15 (17.9)
High dependence (6-7)	34 (40.5)
Very high dependence (8-10)	26 (30.9)
Current smoking exposure	
At home	36 (43.4)
At work	57 (68.7)
Among friends	81 (97.6)
Motivation level	9.3 ± 1.2
Confidence level	8.9 ± 1.5
Baseline CO Level (ppm)	36.9 ± 21.3

to formal smoking cessation programs. Another limitation to the study is that the investigators who monitored the response of the subjects to the pharmacologic intervention were most often the ones who also supervised the behavioral intervention on the subjects.

4. Psychological well-being. The t-test was used for two-group comparisons and ANOVA 1 for multiple group comparisons.

5. Factors promoting abstinence. The different demographic features and smoking characteristics of the subjects were analyzed using *t-test*, *chi-square,* and logistic regression formulae to determine which were associated with a better abstinence rate.

The *Stata 8.0* program was used for the descriptive date, while the ANOVA repeated measures test used the SPSS.

Results

Baseline Profile. The baseline characteristics of the subjects are presented in *Table I.*

Smoking Cessation Rate by Week. The self-reported abstinence rate after 8 weeks and exhaled carbon monoxide levels are shown in *Figure 1*. Seventy-one subjects reported that they were still smoking after the first week, 30 after the second week, 19 by the third, seven by the fourth, one by the sixth and four by the end of the study. Sixty-three subjects had carbon monoxide levels above 10 ppm by the end of the first week, 47 by the second, 38 by the third and the fourth, 42 by the sixth. Forty-two subjects still had CO levels above 10 ppm at the end of the study. Urine cotinine was negative in 48 of the subjects after 8 weeks. Two subjects had CO levels below 10 ppm before commencement of the study though they claimed to be active smokers.

Predictors. By the end of the 8 weeks, 48 subjects were able to maintain smoking cessation while 36 could not abstain. Educational attainment, age at smoking onset, having a smoker at home and baseline CO level were shown to be predictors of smoking cessation failure. The higher the educational attainment, the more likely the subject was able to maintain abstinence ($p < 0.1$, O.R. 3.17 (95% CI: 1.097882 – 9.157408). If there was also a smoker at home, the less likely the subject would be able to abstain ($p < 0.05$, O.R. 0.28 (95% CI: 0.950023 – 1.00226). The higher the baseline CO level, the less likely the subject would be able to abstain ($p < 0.05$). Finally, subjects starting smoking at a later age were

Table II Predictors of Smoking Abstinence

Factors	Abstinent	Non-abstinent	p-value	Odds Ratio	95% CI
Educational Attainment					
College/Vocational	26 (54.2)	12 (33.3)	*p < 0.05*	3.170766	1.097882 – 9.157408
High School/Grade School	22 (45.8)	24 (66.7)			
Smokers at Home					
Yes	18 (37)	22 (61)	*p < 0.05*	0.277431	0.0988362 – 0.7787425
No	30 (63)	14 (39)			
Age of Onset	19.6 ± 7.8	16.1 ± 4.0	*p < 0.05*		
Baseline CO Level	32.8 ± 19.5	42.9 ± 22.7	*P < 0.10*		

Table III. Adverse Events (in %)

Adverse Event	Abstainers (n=48)	Non-abstainer (n=36)	Total (n=84)
Dry mouth	54	44	50
Insomnia	27	39	32
Headache	8	11	10
Nausea	6	11	8
Restlessness	6	8	7
Tremors	6	3	5
Constipation	4	3	4
Anorexia	4	3	4
Rashes	2	6	4
Vomiting	0	3	1
Weight loss	0	0	0
Seizure	0	0	0

more likely to be able to maintain their abstinence ($p < 0.05$).

Psychological Well Being. The Fagerstrom scores of the subjects showed that 80% of the subjects had a high to very high dependence on nicotine at the start of the study (*Table 1*).

The mean CESD score of the participants at baseline was 11.6, 11.16 for the confirmed abstainers (n=43) and 12.43 for non-abstainers (n=23). At the end of 8 weeks, the mean score was 8.0, 7.37 for the abstainers and 9.14 for the non-abstainers (*Figure 2*).

The mean Spielberger State score of the participants at baseline was 33.9, 33.06 for the confirmed abstainers (n=43) and 35.5 for non-abstainers (n=23). At the end of 8 weeks the mean score was 30.2, 29.79 for the abstainers and 30.87 for the non-abstainers (*Figure 3*).

The mean Withdrawal score of the participants at baseline was 6.8, 6.13 for the confirmed abstainers (n=43) and 8.04 for non-abstainers (n=23). At the end

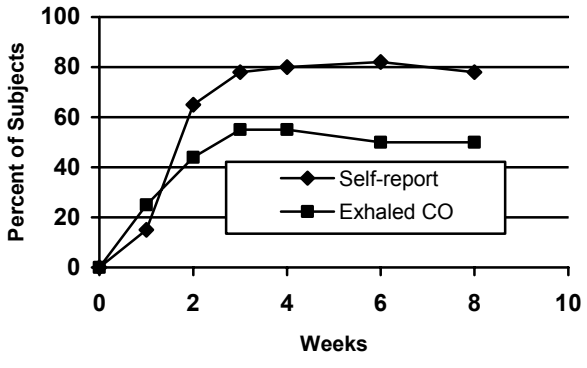

Figure 1 Comparison of smoking abstinence by self-report (*p<0.001*) and exhaled CO level (*p<0.001*) after 8 weeks

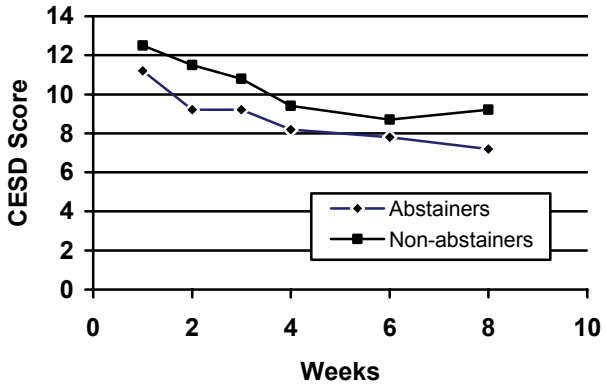

Figure 2 Comparison of CESD Scores Between confirmed abstainers and Non-abstainers at the end of 8 weeks

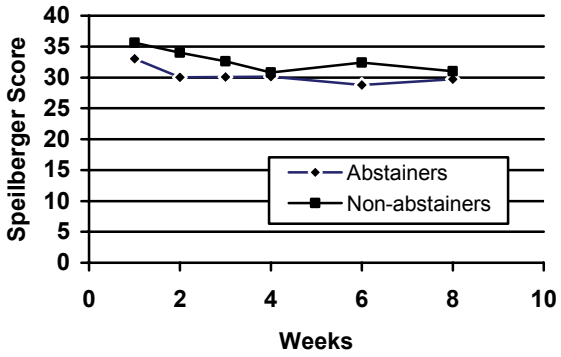

Figure 3. Comparison of Spielberger State Anxiety Scores between confirmed abstainers and Non-abstainers at the end of 8 weeks.

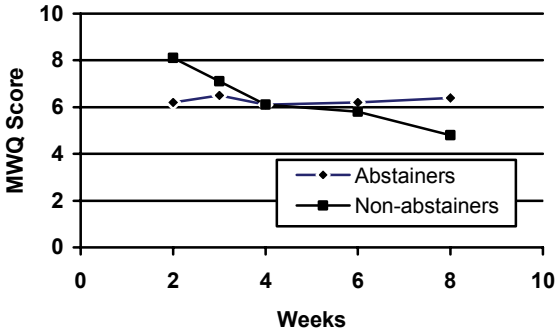

Figure 4. Comparison of MWQ Scores between confirmed abstainers and Non-abstainers at the end of 8 weeks

of the study, the mean score was 5.34, 4.76 for the abstainers and 6.34 for the non-abstainers (*Figure 4*).

The adverse events are listed in *Table III*. The most common adverse event reported was dry mouth with 50% of the subjects experiencing this event. Insomnia was the next most common with 32%. In decreasing order of frequency, the other adverse events reported were headache, nausea, restlessness, tremors, constipation, anorexia, rashes and vomiting. There was no significant adverse event between groups ($p > 0.05$).

Weight Change. The mean change in weight from the start of medication (baseline) for the 84 subjects is shown in *Figure 5*. The abstinent subjects had a mean weight of 63.37 kg and gained a mean of 1.61 kg at the end of the study. Those who continued to smoke had a mean weight of 62.81 kg and lost a mean of 0.02 kg.

Blood Pressure. The mean change in mean arterial blood pressure (MAP) from the start of medication to the end of 8 weeks is shown in *Figure 6*. The mean of the MAP of the abstinent subjects was 103.5 at baseline and decreased by 0.69 kg at the end of the study. The mean of the MAP of the subjects who continued to smoke was 101.8 at the beginning of the study and decreased by 4.17 kg after 8 weeks. There was a decreasing trend for both groups.

Discussion

We found that bupropion is effective in promoting smoking abstinence at 8 weeks. The finding of a 57% true abstinence rate in Filipinos as confirmed by urine cotinine is consistent with the results of earlier studies on Caucasian subjects.[9,10] In a study done at the Singapore General Hospital,[11] smoking abstinence was reported to be 36%. After 6 and 12 months, the abstinence rate was 38 and 36%, respectively. Abstinence in the Singapore study was determined by self-report and confirmed by exhaled carbon monoxide with a cut-off value of 6 ppm.

The excessively high abstinence rate noted on self-report may be caused by several factors including a reticence by the subjects to report non-abstinence due to shame and social stigma. The increase in social unacceptability of smoking may in itself result in underreporting of smoking status.[1]

Breath CO may be influenced by a patient's smoking style.[12] If the subject smoked a considerable time prior to taking the exhaled CO test, it could conceivably yield results of less than 10 ppm since the reported half life of alveolar CO is only 150 minutes.[13] This could explain the low CO level of the two subjects at the beginning of the study.

The inconsistency of the urine cotinine with the exhaled carbon monoxide results again may be due to several factors. Underlying airway inflammation and oxidative stress may falsely elevate CO levels.[12] Environmental pollution as well as second hand smoke may also be contributing factors. Other factors that may affect CO levels are type and location of home and occupation, cooking and heating appliances, and mode of transportation.[14]

There is no value for the cut-off level for breath CO that is universally agreed upon. Sato et al proposed a 10 ppm cut off for breath carbon

monoxide.[12] The American Thoracic Society Statement

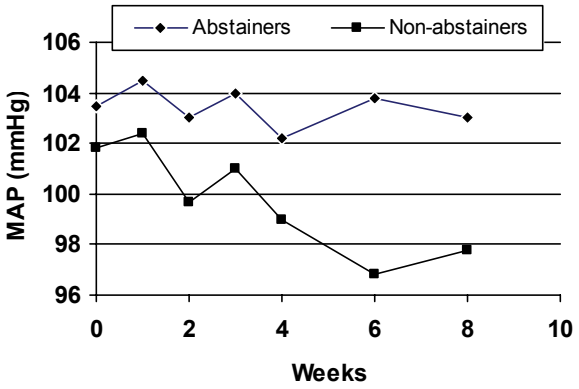

Figure 6 Mean arterial pressure among Subjects

time, this was not found to be statistically significant.

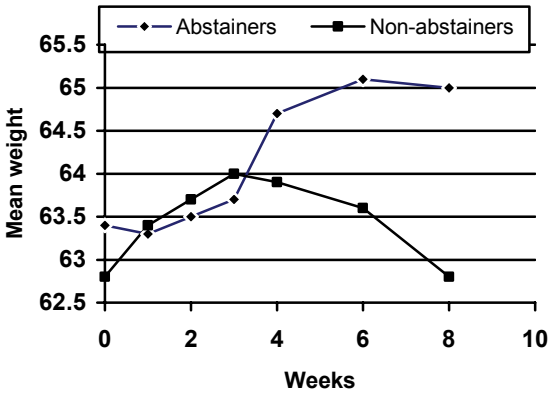

Figure 5 Mean weight of Subjects

of 2001 recommended that 6 ppm was the optimal cut off level[14] from the previous cut-off of 8. Deveci et al proposed a cut off value of 6.5ppm.[15]

Considering the numerous factors that may affect breath carbon monoxide levels, it may be prudent to determine cut-off levels for each location it is to be used. In this particular study, a higher cut-off level may be more appropriate.

Due to these inaccuracies, we recommend serum or urine cotinine over self-reporting or exhaled carbon monoxide as the standard for determining true smoking abstinence.

Some of the predictors of smoking abstinence we noted were also found in a similar study done at Columbia University.[16] Significant predictors in that study were ethnicity, age, confidence in ability to stop smoking, living with a smoker, times quit and educational attainment. Predictors found in both studies were educational attainment and living with a smoker. In another unpublished study at PGH,[17] age at enrollment was also found to be a predictor of abstinence consistent with the Columbia study. Other predictors noted in this study were age at onset of smoking and number of pack years. Aubin et al found treatment, motivation to quit, Fagerstrom score and current smoking-related diseases to be predictors of abstinence in a large multicentre study.[18] These predictors may help in tailoring smoking abstinence programs for the particular needs of the individual smoker.

There was no significant difference between abstainers and non-abstainers with regard to psychological well being. Though there was a trend for decreasing CESD scores among both groups with None of the subjects could be identified as depressive cases with CESD scores of 16 or greater. The mean Spielberger Trait score of the participants was higher, 67 percentile, than the mean of the subjects of the same age group that Spielberger studied suggesting a higher anxiety trait for these particular patients.[19] The mean Spielberger State scores of the subjects at the start of the study was comparable to the mean of Spielberger, 53 percentile. The scores decreased to the 35 percentile suggesting lower anxiety states at the end of the study.[19] The mean CESD, STAI, and MWQ scores of abstainers were lower than non-abstainers but again these were not statistically significant. All scores were within the normal ranges and no treatment effect was noted.

Previous research has shown that bupropion therapy can reduce weight gain after smoking cessation.[9] Though there was a small weight gain in the abstinent group and minimal weight loss in the non-abstinent group, these changes in weight were not statistically significant. The weight gained by the abstinent subjects was consistent with that reported by Hurt and lower than the typical weight gain of 3 to 4 kg in successful smoking cessation.

There were no serious adverse events noted during the eight week period. No treatment effect on blood pressure was noted in either group. Though the non-abstinent group had a bigger decrease in mean arterial pressure, changes in blood pressure among subjects and groups was not statistically significant. Seizures, which have been reported with bupropion, did not occur. There were significantly more episodes of dry mouth with the abstainers than the non-abstainers.

Summary

We found bupropion hydrochloride (SR) to be effective as an aid to smoking cessation at 8 weeks in Filipinos. The true abstinence rate was 57%. It was safe with no serious or life threatening adverse events. There were insignificant changes in weight and mean arterial pressure. Though there was a trend for decreasing scores, especially with depression, there was no significant treatment effect on psychological well-being. Age at onset of smoking, educational attainment, having another smoker in the house and baseline exhaled carbon monoxide levels were found to be predictors of smoking abstinence success.

Acknowledgements

Jorel A. Manalo and Maria Luz L. Dayrit compiled the database. Emiliano Sevilleja did the statistical analysis.

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Ethics Approval

This study was approved by the ethics committee of the Research Implementation and Development Office (RIDO).

References

1. Alechnowicz K, Chapman S. The Philippine tobacco industry: "the strongest tobacco lobby in Asia", Tobacco Control 2004; I3 (SupplII): ii71-ii78.
2. Dans, Fernandez, Fajutrao, et al. A Monograph on Cigarette Smoking in tne Philippines. 1999. (unpublished)
3. Dans, A, Fernandez, L et al. National Nutrition and Health Survey 2003 - 2004
4. Raw, McNeill, West. Smoking Cessation Guidelines for Health Professionals. Thorax 1998; 53(Supplement 5}:S1-S18.
5. Mahmarian, J. Nicotine replacement therapy: what are the options today? Journal of Respiratory Diseases 1998; 19 (August supplement}:S13-19.
6. Ascher, Cole, Collin. Buproprion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395-401.
7. Aubin, HJ. Tolerability and safety of sustained-release bupropion in the management of smoking cessation. Drugs. 2002;62 Suppl2:45-52
8. Johnson, Lineberry, Acher et al. A 102-center prospective study of seizure in association with buproprion. J Clin Psychiatry 1991 ;52:450-6.
9. Hurt, Sachs, Glover, et sl. A comparison of sustained-release buproprion and placebo for smoking cessation. N Engl J Med 1997 Oct; 337(17}:1195-202.
10. Jorenby, Leischow, Nides, et al. A controlled trial of sustained-release buproprion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999 Mar; 340(9}:685-91.
11. Zow, HC et al. Smoking Cessation program: the Singapore General Hospital Experience.
12. Singapore Med J 2004 Vol 45(9):430-434
13. Sato, S. et al. Optimal Cutoff Level of Br-eath Carbon Monoxide for Assessing Smoking Status in Patients with Asthma and COPD. Chest 2003; 124:1749-1754
14. Russell, M. et al. Comparison of effect on tobacco consumption and carbon monoxide absorption of changing to high and low nicotine cigarettes. BMJ 1973; 4:512-516
15. Kharitonov, S. et al. Exhaled markers of Pulmonary disease. Am J Respir Crit Care Med 2001; 163:1693-1722
16. Deveci, Deveci et al. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respiratory Medicine (2004) 98,551-556
17. Covey, Let al. ongoing study at Columbia University, NY, USA
18. Tipones, R, Fernandez L et al. ongoing study Philippine General Hospital, Manila Philippines
19. Aubin, HJ. Predictors of successful outcome during Zyban LP treatment in smokers. Ppreliminary results of a French multicenter study. Poster presentation, Fourth European Conference of the Society for Research on Nicotine and Tobacco, Spain 2002
20. Spielberger, C. Stait-Trait Anxiety Inventory For Adults. 1993
21. Hutchinson, D. The trial investigator's GCP handbook: a practical guide to ICH requirements. Brookwood Medical Publications 1997

The Spectrum and Frequency of Causes, Complications and Outcome of Specific Therapy of Chronic Cough among Filipino Adults

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Background: Chronic cough can be simultaneously due to more than one condition. Several studies have shown that chronic cough may be due to a single cause from 38 - 82% of the time and to multiple causes from 18 to 62% of the time. The most common causes of chronic cough in non-smokers in all age group are postnasal drip syndrome (PNDS), bronchial asthma and gastroesophageal reflux disease (GERD). Few studies have investigated the cause of chronic cough using the anatomic diagnostic protocol in the Asian population. In our local setting, there is only one study available.

Study Objectives: This study investigated the spectrum and frequency of causes of chronic cough and the laboratory examinations employed, and assessed the outcome of specific therapy among Filipino adults.

Materials and Methods: Consecutive unselected adult patients, at least 18 years of age, who consulted at or were referred to the pulmonary clinics of a university teaching hospital (Philippine General Hospital, Manila) and the outpatient pay clinics of four pulmonary consultants between January 2003 and December 2004 were included in the study. Cough of at least three weeks' duration should be the sole or major reason for consultation or referral. Patients with immunocompromised states were excluded. An ambispective study design was employed.

Results: 287 subjects were entered into the study. Ninety one percent (n = 262) consulted at the private clinics of the study pulmonologists. Nine percent (n = 25) consulted at the PGH charity outpatient clinics. Seventeen percent (n = 50) were lost to follow up. The mean duration of cough was 22.2 ± 55.64 weeks. The causes of cough were determined in 236 out of237 (99.5%) evaluated patients. Asthma (33.3%), postnasal drip syndrome (30.4%), pulmonary tuberculosis (20.3%), post infectious cough (15.2%) and COPD/chronic bronchitis (10.1%) were the most common etiologies. GERD was found in only 3.8% of patients. A single diagnosis was found to explain cough in the majority of patients (67.5%). Treatment was judged successful in 63% of patients whose cough resolved completely in 3.20 ± 2.38 weeks and in 32.5% of patients who reported significant improvement in 3.9 ± 2.59 weeks. The overall treatment failure rate was 4.6%. Treatment failure was found to be related to non-compliance of the patients, significant lung structural abnormalities that cannot be expected to reverse and terminal illness rather than to the failure of the evaluation and management process. The outcome of treatment was not influenced by the overall compliance rate (RR= 0.99; 95% CI: 0.94, 1.06) and the use of empiric drug treatment (RR= 0.99; 95% CI: 0.93, 1.06). Some laboratory tests recommended by the protocol were not locally available, including bronchoprovocation test and 24-hour esophageal pH monitoring.

Conclusions: The most common causes of chronic cough among Filipinos are asthma, postnasal drip syndrome and pulmonary tuberculosis. A single diagnosis was found to explain cough in 67% of patients. Successful treatment was achieved in 95% of the patients. The laboratories most commonly requested were chest X-rays, spirometry and sputum AFB smears. *Phil Journal of Chest Diseases. Vol 13 No.1 pp: 65-77*

Keywords: Cough, asthma, COPD

3. 1.

Introduction

Cough remains the most common reason for patients to seek medical attention probably because it can manifest with profound dysfunction in their usual daily activities. It has been proven that after treatment of chronic cough, there is resolution of the patients' deterioration in quality of life.[1] Cough can be caused by a multiplicity of disorders. Estimating the duration of cough is the first step in narrowing the list of possible diagnosis. This will help us in the proper management of cough. The American College of Chest Physicians (ACCP) categorized cough into: acute, lasting for less than three weeks; or chronic, lasting for three weeks or more.[2] The European

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Respiratory Society (ERS), on the other hand, defined chronic cough of more than eight weeks duration.[3]

Worldwide, the exact prevalence has proved difficult to estimate since the results of questionnaire surveys were clearly influenced by the population studied and the questions posed.[4] Nevertheless, it is estimated that chronic cough is reported by 3 to 40% of the population.[5-7] In the local setting, the prevalence of patients consulting for chronic cough is not precisely known. An informal survey among 15 pulmonologists practicing in different regions of the country revealed an estimate of a high proportion of patients consulting their clinics for chronic cough (that is cough persisting for at least three weeks), accounting for about 39% of their out-patient load per year. A survey utilizing the ATS standardized questionnaire on respiratory symptoms, conducted at a rural Filipino community (Barangay Banca-Banca, Victoria, Laguna) and involving a random sample of 723 residents aged 15 years and over, revealed that 10% of the respondents reported chronic cough.[13] This is likely an underestimation of its true prevalence since the authors employed a stricter definition of chronic cough, as one which lasted for at least 12 weeks for at least two consecutive years that is, the internationally accepted definition of chronic bronchitis, which is but one cause of chronic cough. Another study was conducted at an urban community (San Andres Bukid, Paco, Manila) involving 1160 respondents and utilizing the same questionnaire showed that as many as 24.6% of the adults had chronic cough.[14] In 2002, another urban community survey was conducted in Metro Manila, Cebu and Davao and involved 1964 adults aged 20 to 44 years. The study revealed that 13% and 1.8% had cough that persisted for more than two weeks and for more than three months, respectively, in the past year.[14]

Chronic cough can be simultaneously due to more than one condition. Several studies have shown that chronic cough may be due to a single cause from 38-82% of the time and to multiple causes from 18 to 62% of the time. In 42% of the time, chronic cough is due to three diseases. The most common causes of chronic cough in non smokers in all age groups for which patient seek medical attention are postnasal drip syndrome (PNDS), bronchial asthma and gastroesophageal reflux disease (GERD). In non-smokers not taking ACE inhibitor drugs who have normal chest radiographs, chronic cough is likely due to PNDS, bronchial asthma and/or GERD approximately 100% of the time.[8-11] In another study, chronic cough was found to be due to three or more diseases among 26% of their subjects.[11,12]

Few studies have investigated the cause of chronic cough using the anatomic diagnostic protocol in the Asian population. In 2003, Nadri found that in tropical countries such as India, the most common causes of chronic cough were different from those reported in the western literature; Loeffler's syndrome was among their top three causes and 5% of patients were confirmed to have pulmonary tuberculosis.[16] Another study was done among 122 adult Thais, wherein the author was successful in identifying the cause of chronic cough (persisting for at least three weeks) in 96% of the patients. Cough was due to a single cause in 81% and the most common causes were postnasal drip syndrome (45%), bronchial asthma (26%), and both (13%). In contrast to western studies, gastroesophageal reflux disease was seen in only two patients (1.6%). A significant deviation of this study from the anatomic diagnostic protocol proposed by Irwin, et. a1. is the failure of the authors to include chest radiography in the diagnostic work up.[17]

In our local setting, there is only one study available. This was conducted by Balgos et al in 1993 at a tertiary referral center (Philippine General Hospital) involving a small sample size (n=21). The author utilized a stricter definition of chronic cough as one that lasted for eight weeks or more and the subjects included were patients with normal chest radiographs. The cause of cough was identified in all cases and was found to be due to bronchial asthma in nine patients, postnasal drip in three. Specific therapy was successful in 89%.[18] Because of this limited data in our country, we investigated a larger sample size to provide more accurate data on the spectrum and frequency of causes of chronic cough and the laboratory examinations employed, and to provide an assessment of the outcome of specific therapy among Filipino adults. Specifically, we determined the prevalence of causes of chronic cough, the laboratory modalities employed in establishing the diagnosis of chronic cough, and we determined the outcome of treatment directed at the specific cause(s) of chronic cough.

Materials and Methods

Study Population. Consecutive, unselected adult patients, at least 18 years of age, who consulted at or were referred to the pulmonary clinics of a university teaching hospital (Philippine General Hospital) and the outpatient pay clinics of four pulmonary consultants

between January 2003 and December 2004 were included in the study. Cough of at least three weeks' duration should be the sole or major reason for consultation or referral. Patients with immunocompromised states such as the presence of known active malignancy, recent or ongoing chemotherapy and/or radiotherapy, suspected or diagnosed human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), chronic intake of systemic steroids, and previously diagnosed with end-stage diseases including patients with chronic renal failure undergoing dialysis, those with uncontrolled diabetes or patients with chronic liver failure were excluded.

Study Design. The study design is ambispective; that is, data on the characteristics of cough, prior consults, treatment and expenses incurred were collected retrospectively or were available from records and then the cohort was followed up, taking into consideration the diagnostic modalities done, response and compliance to treatment and expenses subsequently incurred.

Study Procedure. Figure 1 provides an outline of the general conduct of the study.

1. *Initial Assessment*. At entry (First Visit), a medical history was taken and physical examination was performed by the fellow- or consultant-in-charge. General data was obtained including age, sex, complete address and contact numbers, marital status, occupation and history of smoking. The initial evaluation also included questions on the duration, frequency, timing, character, and any recent worsening of cough; presence (viscosity, color and quantity) or absence of phlegm production; any concomitant or associated complaints, e.g., dyspnea, chest pain or tightness, nasal symptoms, postnasal drip, throat complaints, epigastric pain and constitutional symptoms; history of an upper respiratory tract infection (URTI) or flu-like symptoms prior to or at the onset of cough; suspected or identifiable environmental irritants; intake of angiotensin converting enzyme inhibitor (ACEI) drugs or other anti-hypertensive medications: known medical illness, including asthma and other lung diseases, allergic rhinitis, gastroduodenal pathologies, atopy, hypertension and cardiac illnesses, or any other co-morbidities; and a list of current medications. The patients were also probed in greater detail about the prior management of cough from its onset and up to the first visit, including previous medical consults, diagnostic studies and their results; intake of self-medicated and/or doctor-prescribed drugs for the cough, noting down the dose, dosing interval, duration of intake and the effect of therapy; and, any procedure undertaken to resolve the cough. When the physician-in-charge failed to record any of the previous information, attempts were made to ask the patient at a later time, during subsequent clinic follow ups, updates by telephone or via home visits. Whenever possible, previous medical records of patients from other clinics were retrieved or their prior doctors contacted to verify their given information.

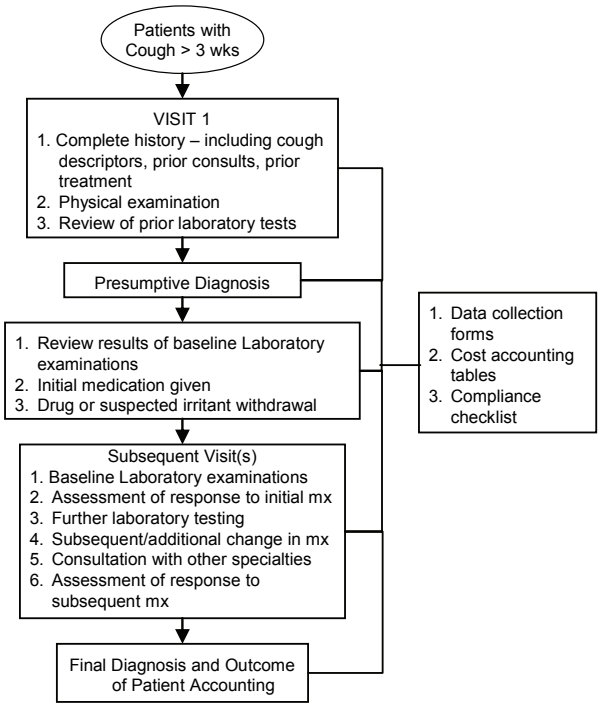

Figure 1. Study flow chart

After the initial evaluation, Presumptive Pre-Treatment Diagnoses (primary and differential diagnoses) made by the physician-in-charge were recorded. The laboratory examination(s) and all the medication(s) he/she prescribed or withdrew on the first visit were likewise noted.

2. *Subsequent Follow-up(s).* Subsequent follow up information was obtained including the results of any laboratory examination(s) that were ordered at the first visit and in any of the subsequent visits; self-reported compliance, development of adverse events and response to initial management any change or addition of medications for the cough; noting down the drug, dose, dosing interval, self-reported compliance, actual duration of intake and the effect of therapy; withdrawal of medications; total number of pulmonary visits related to the current cough; and, referrals to other physicians or specialists, including the number of visits. The sequence by which the laboratory

Table I. Characteristics of Patients Studied

Characteristics	Completed No. ([%)	Lost to Follow-up No. (%)	Total No. (%)	p-value
Actual No. of Patients	237 (82.6)	50 (17.4)	287 (100.0)	
Females	147 (62.8)	27 (54.0)	174 (61.3)	0.242
Age, years, mean (SD)	50.18 (18.69)	48.92 (17.76)	49.97 (18.51)	0.664
Ever smoked	57 (25.0)	19 (44.2)	76 (28.2)	0.010
Current smokers	15 (6.6)	8 (18.6)	23 (8.5)	0.016
History of atopy	35 (15.1)	5 (12.2)	40 (14.7)	0.629
History of prior lung disease	55 (23.7)	13 (28.9)	68 (24.5)	0.529
With co-morbidities	74 (31.5)	14 (8)	88 (31.1)	0.751
Hypertension	38 (16.2)	9 (10)	47 (16.6)	0.661
Diabetes	12 (5.1)	5 (4)	17 (6.0)	0.141

Table II. Cough Description

Description	Completed No. (%)[a]	Lost to Follow-up No. (%)[a]	Total No. (%)[a]	Chi-square value
Duration of cough, weeks, Mean (SD)	21.2 (52.06)	26.8 (70.64)	4.0 (55.64)	0.521[c]
Duration of cough, weeks, Mode (SD)	4.0 (52.06)	8.0 (70.64)	16	
Productive cough	139 (63.8)	16 (59.2)	155 (63.3)	0.647
Nocturnal cough	62 (31.2)	7 (46.7)	69 (32.2) 32.2	0.169[b]
Most common associated complaints				
Dyspnea	95 (40.8)	16 (37.2)	111 (40.2)	0.662
Chest pain	55 (23.7)	10 (23.3)	65 (23.6)	0.949
Nasal symptoms	57 (24.5)	6 (13.6)	63 (22.8)	0.116
Post-nasal drip	42 (18.4)	3 (7.5)	45 (16.8)	0.088
Throat complaints	101 (44.1)	13 (31.7)	114 (42.2)	0.139
Epigastric pain	9 (3.9)	2 (4.4)	11 (4.0)	0.558[b]
Constitutional symptoms	94 (40.2)	20 (41.7)	114 (40.4)	0.847
Recent worsening of cough	65 (27.5)	11 (23.4)	76 (26.9)	0.559
History of URTI prior to onset of Cough	47 (20.0)	7 (14.6)	54 (19.1)	0.384

Table III. Etiologies of Chronic Cough for Patients with Laboratory Determination

Final Diagnosis	Evaluable[b] No. (%)	Lost to Follow-up)[c] No. (%)	Total No. (%)	p-value
Total Patients	236 (99.6)	29 (58.0)	265 (92.3)	0.001d
Cough Variant Asthma	79 (33.3)	6 (12.0)	85 (29.6)	0.003
PNDS	72 (30.4)	6 (12.0)	78 (27.2)	0.008
GERD	9 (3.8)	1 (2.0)	10 (3.5)	0.455[d]
Bronchiectasis	16 (6.8)	1 (2.0)	17 (5.9)	0.169[d]
COPD/Chronic Bronchitis	24 (10.1)	3 (6.0)	27 (9.4)	0.271[d]
ACEI-induced Cough	9 (3.8)	2 (4.0)	11 (3.8)	0.600[d]
PTB	48 (20.3)	8 (16.0)	56 (19.5)	0.490
Pulmonary Malignancy	7 (3.0)	5 (10.0)	12 (4.2)	0.040[d]
CHF	2 (0.8)	0 (0.0)	2 (0.7)	0.681[d]
Post-Infectious Cough	36 (15.2)	0 (0.0)	36 (12.5)	0.003[d]
Pneumonia	12 (5.1)	1 (2.0)	13 (4.5)	0.304[d]
Others	4 (1.7)	1 (2.0)	5 (1.7)	0.619[d]

examinations were ordered and the medications prescribed was likewise recorded. The type, number

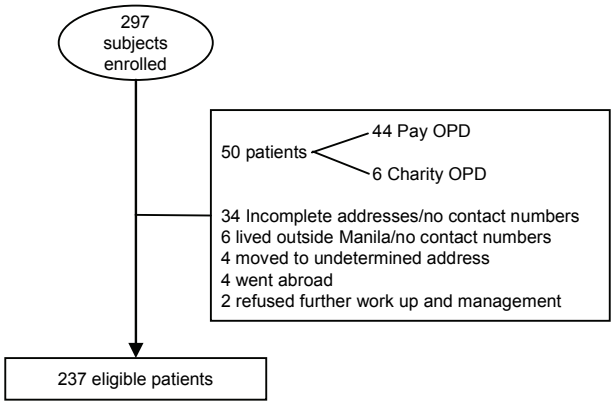

Figure 2 Patient accounting

and prioritization of laboratory examinations ordered and the medications prescribed for any given patient were at the discretion of the attending physician; no attempt was made to influence his/her decision. Likewise, scheduling of follow-up visits was determined by the physician and the patient. If a patient, out of his own volition, decided to consult other physicians, the former was interviewed on the diagnosis provided by the latter, results of laboratory examinations that were ordered or carried out, and details on the medications prescribed. Whenever possible, these physicians were likewise contacted.

3. *Final Outcome*. The final diagnosis of chronic cough was determined by taking into consideration the results of the historical information, physical findings, laboratory examinations and the response to specific therapy directed at the identified etiology. Even if the findings from the first three criteria already highly suggested an etiologic diagnosis but information on the latter was not available, the final outcome (up to two months from the first visit) was still labeled as unknown. The final diagnosis of the cough is a reflection of the consensus assessment of at least two pulmonologists who independently assessed the data collection forms of each patient. The response of the patient to therapy was graded as: Complete Resolution of cough (complete disappearance of cough); Significant Improvement (cough still present but there was a notable decrease in frequency and severity and it was no longer disturbing or distressing); Minimal Improvement (some decrease in frequency and severity but cough was persistently disturbing or distressing); Absence of Improvement (same character as pre-treatment descriptors); and, Worsening

Table IV Primary Presumptive Diagnoses of Patients Lost to Follow-Up

Presumptive Diagnosis	No. (%)
Cough Variant Asthma	12 (24.0)
Post-Nasal Drip Syndrome	9 (18.0)
GERD	1 (2.0)
COPD/Chronic Bronchitis	3 (6.0)
ACE I-induced Cough	1 (2.0)
PTB III	15 (30.0)
Congestive Heart Failure	3 (6.0)
Post-Infectious Cough	4 (8.0)
Pneumonia	1 (2.0)
Chronic Tonsillitis	1 (2.0)

Table V. Combinations of Final Etiologies

Combinations	No. (%)
Two-diagnoses	
ACEI-induced cough, Congestive Heart Failure	1 (1.4)
ACEI-induced cough, Bronchiectasis	4 (5.7)
Asthma, GERD	1 (1.4)
Asthma, PNDS	28 (40.0)
Asthma, Pneumonia	3 (4.3)
Astl1ma, Post-infectious Cough	2 (2.9)
Asthma, PTB	4 (5.7)
Asthma, Fungus ball	1 (1.4)
Bronchiectasis, ACEI-induced cough	1 (1.4)
Bronchiectasis, PTB	3 (4.3)
COPD, Pneumonia	2 (2.9)
COPD, PTB	1 (1.4)
COPD, Pulmonary Malignancy	2 (2.9)
GERD,COPD	1 (1.4)
PNDS, ACEI-induced Cough	1 (1.4)
PNDS, Bronchiectasis	2 (2.9)
PNDS, COPD	1 (1.4)
PNDS, GERD	2 (2.9)
PNDS, Post-infectious Cough	3 (4.3)
PNDS, PTB	1 (1.4)
PTB, Pneumonia	4 (5.7)
PTB, Post-infectious Cough	1 (1.4)
PTB, Pulmonary abscess	1 (1.4)
Three diagnoses	
Asthma, PNDS, ACEI-induced cough	1 (16.7)
Asthma, PNDS, GERD	2 (33.3)
COPD, ACEI-induced Cough, Congestive Heart Failure	1 (16.7)
PNDS, Bronchiectasis, Pneumonia	I (16.7)
Bronchiectasis, COPD, PTB	1 (16.7)

Table VI. Etiologies of Chronic Cough among Patients with Normal and Near-Normal Chest Radiographs

Final Diagnosis	Normal No. (%)	Near-Normal No. (%)	Total No. (%)
Patients with Definitive Final Diagnosis	53 (98.1)	8 (100.0)	61 (98.4)
Cough Variant Asthma	21 (38.9)	3 (37.5)	24 (38.7)
Post-Nasal Drip Syndrome	21 (38.9)	3 (37.5)	24 (38.7)
Post-Infectious Cough	12 (22.2)	1 (12.5)	13 (21.0)
COPD/Chronic Bronchitis	4 (7.4)	2 (25.0)	6 (9.7)
GERD	5 (9.3)	0	5 (8.1)
ACEI-induced Cough	3 (5.6)	0	3 (4.8)
Bronchiectasis	0	1 (12.5)	1 (1.6)
PTB V or III	2 (3.7)	0	2 (3.2)
Pneumonia	2 (3.7)	0	2 (3.2)

Table VII. Final Diagnosis among Patients with a History of Prior Lung Disease

Characteristics	No. (%)"
Asthma	13 (23.6)
PNDS	10 (18.2)
GERD	1 (1.8)
Bronchiectasis	15 (27.3)
COPD	14 (25.5)
ACEI-Induced Cough	2 (3.6)
PTB	17 (30.9)
Pulmonary Malignancy	1 (1.8)
Congestive Heart Failure	1 (1.8)
Post-Infectious Cough	3 (5.5)
Pneumonia	6 (10.9)

(aggravation of cough compared to pre-treatment descriptors). The first two categories defined Treatment Success whereas the latter three categories were considered together as Treatment Failure. For patients whose cough completely resolved or significantly improved, the number of weeks needed to achieve the desired result was likewise determined. The response to therapy was a purely subjective assessment as graded by the patient. If the patient failed to follow up before an outcome could be definitively assessed, he/she was contacted by phone or via home visit. For this study the final outcome/response to management was determined up to two months from the initial visit, during which time a note was made of the follow up status of each patient. Every attempt was made to contact all the patients entered into the study. Patients who were completely lost to follow up because of the absence of or wrong information on their contact telephone or mobile phone numbers, non-disclosure or provision of fictitious addresses, change of address or residence in areas outside of Manila were identified.

Operational Definition. 1. *Presumptive Pre-Treatment Diagnostic Criteria* - The following Criteria are established by the ACCP Consensus Panel in making a specific diagnosis for the known etiologies of cough. A comprehensive review of these conditions can be found in the report.[2] The following is a summary for the more common etiologies of chronic cough:

Table VIII. Etiologies of Chronic Cough among Patients with Abnormal Chest Radiographs

Etiologies	Completed No. (%)	Lost to Follow-up) No. (%)	Total No. (%)	Fishers Exact Test p-value
Cough Variant Asthma	13 (25.5)	1 (1.11)	14 (23.3)	0.322
Post-Nasal Drip Syndrome	11 (21.6)	0	11 (18.3)	0.139
Bronchiectasis	10 (19.6)	0	10 (16.7)	0.169
COPD/Chronic Bronchitis	7 (13.7)	1 (1.11)	8 (13.3)	0.656
ACEI-induced Cough	2 (3.9)	1 (1.11)	3 (5.0)	0.391
PTB	22 (43.1)	4 (44.4)	26 (43.3)	0.610
Pulmonary Malignancy	1 (2.0)	2 (22.2)	3 (5.0)	0.056
Post-Infectious Cough	1 (2.0)	0	1 (1.7)	0.850
Pneumonia	8 (15.7)	0	8 (13.3)	0.249
Others	1 (2.0)	0	1 (1.7)	0.850

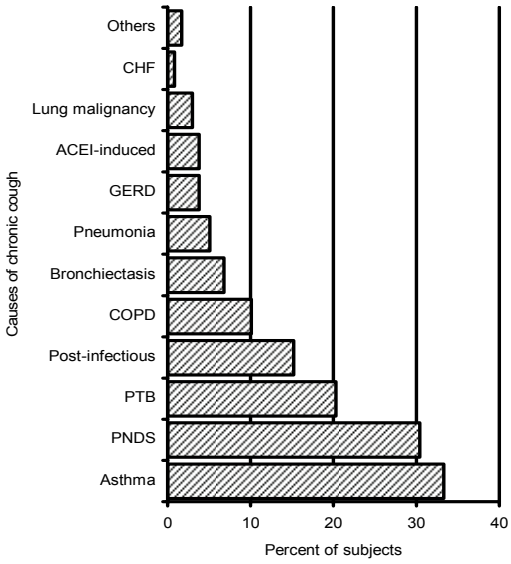

Figure 3 Frequency distribution of the causes of chronic cough among the evaluable patients

a. Postnasal drip syndrome (PNDS) is considered when:

(1) Patients describe tile sensation of having something drip down into their throats, nasal discharge, and/or the need to frequently clear their throats, and/or

(2) Physical examination of the nasopharynges and oropharynges reveals mucoid or mucopurulent secretions and/or a cobblestone appearance of the mucosa; and,

(3) Rhinosinusitis is considered a potential cause of PNDS when sinus radiographs demonstrate more than 6 mm of mucosal thickening, air-fluid levels, or opacification of any sinus.

b. Bronchial Asthma is considered when:

(1) Patient complains of episodic wheezing, shortness of breath plus cough, and are heard to wheeze, or

(2) Reversible airflow obstruction is demonstrated

Table IX Frequency of diagnosis according to cough and radiologic descriptors.

Descriptor	N	Asthma No. (%)	PNDS No. (%)	GERD No. (%)	PTB No. (%)	COPD No. (%)	Post-infectious cough No. (%)	Others No. (%)
Cough character								
Paroxysmal	12	14 (45.2)	2 (7.4)	0	1 (3.7)	1 (8.3)	4 (14.8)	0
Throat clearing	17	1 (3.2)	5 (18.5)	0	2 (7.4)	0	6 (22.2)	3 (25.0)
Intermittent	72	19 (61.3)	17 (63.0)	1 (100)	18 (66.7)	8 (66.7)	5 (18.5)	4 (33.3)
Continuous	19	2 (6.5)	3 (11.1)	0	2 (7.4)	1 (8.3)	8 (29.6)	3 (25.0)
Variable/No distinguishing characteristics	17	5 (16.1)	0	0	4 (14.8)	2 (16.7)	4 (14.8)	2 (16.7)
Cough timing								
Mostly occurring during the day	23	3 (9.7)	6 (21.4)	0	5 (19.2)	3 (27.3)	5 (19.2)	1 (7.7)
Mostly occurring or distinct worsening in the evening	10	8 (25.8)	5 (17.9)	0	4 (15.4)	0	3 (11.5)	0
Mostly occurring during meqls or post-prandial	1	0	1 (3.6)	0	0	0	0	0
Variable – no particular timing, occurring anytime	74	14 (45.2)	14 (50.0)	1 (100)	16 (61.5)	7 (63.6)	12 (46.2)	10 (76.9)
With cough upon awakening	12	5 (16.1)	1 (3.6)	0	1 (3.8)	0	4 (15.4)	1 (7.7)
No episodes of cough upon wakening	6	1 (3.2)	1 (3.6)	0	0	1 (9.1)	2 (7.7)	1 (7.7)
Cough complication								
Hemoptysis	13	2 (6.5)	0	0	7 (24.1)	1 (7.1)	2 (6.9)	1 (5.9)
No complications	137	29 (93.5)	28 (100)	2 (100)	22 (75.9)	13 (92.9)	27 (93.1)	16 (94.1)
Chest x-ray								
Normal	37	8 (72.7)	10 (71.4)		1 (6.3)	2 (22.2)	10 (100)	4 (44.4)
Near normal	6	2 (18.2)	2 (14.3)		0	2 (22.2)	0	0

Table X Frequency of diagnosis according to characteristics of phlegm production.

Descriptor	N	Asthma No. (%)	PNDS No. (%)	GERD No. (%)	PTB No. (%)	COPD No. (%)	Post-infectious cough No. (%)	Others No. (%)
Viscosity of Phlegm **Production**								
Productive of loose/serous/watery phlegm and easy to expectorate	54	10 (32.3)	10 (33.3)	0	15 (51.7)	8 (72.7)	5 (17.2)	6 (40.0)
Productive of thick/mucoid phlegm and hard to expectorate	36	6 (19.4)	10 (33.3)	1 (33.3)	6 (20.7)	0	8 (27.6)	5 (33.3)
Variable	15	4 (12.9)	3 (10.0)	0	4 (13.8)	2 (18.2)	2 (6.9)	0
Non-productive	43	11 (35.5)	7 (23.3)	2 (66.7	4 (13.8)	1 (9.1)	14 (48.3)	4 (26.7)
Color of Phlegm Production								
Mainly/mostly white	60	10 (33.3)	15 (50.0)	1 (33.3)	13 (43.3)	11 (84.6)	5 (17.2)	5 (31.3)
Yellow/green at the outset	25	5 (16.7)	4 (13.3)	0	6 (20.0)	0	8 (27.6)	2 (12.5)
Initially white then recently turned yellow/green	12	3.3 (1)	2 (6.7)	0	4 (13.3)	1 (7.7)	1 (3.4)	3 (18.8)
Variable	10	3 (10.0)	1 (3.3)	0	3 (10.0)	0	1 (3.4)	2 (12.5)
Non-productive	8	11 (36.7)	8 (26.7)	2 (66.7)	4 (13.3)	1 (7.7)	14 (48.3)	4 (25.0)
Quantity of Phlegm Production								
Minimal - average < 2 tbsp/day	66	14 (46.7)	13 (48.1)	1 (50.0)	16 (64.0)	4 (40.0)	14 (48.3)	4 (33.3)
Moderate - average 2-4 tbsp/day	12	2 (6.7)	3 (11.1)	0	2 (8.0)	2 (20.0)	2 (6.9)	1 (8.3)
Copius - average> 4 tbsp/ day	6	1 (3.3)	1 (3.7)	0	0	1 (10.0)	1 (3.4)	2 (16.7)
Val'iable	10	1 (3.3)	2 (7.4)	0	3 (12.0)	2 (20.0)	0	2 (16.7)
No phlegm	41	12 (40.0)	8 (29.6)	1 (50.0)	4 (16.0)	1 (10.0)	12 (41.4)	3 (25.0)
Throat Complaints								
Throat itchiness/scratchiness	58	12 (36.4)	16 (61.5)	1 (33.3)	7 (22.6)	1 (7.1)	17 (56.7)	4 (23.5)
Throat soreness/pain	3	0	1 (3.8)	0	1 (3.2)	0	1 (3.3)	0
Sensation of phlegm stuck in the throat	1	1 (3.0)	0	0	0	0	0	0

by spirometry (FEV_1 increased at least 12% + absolute 200 ml increase from baseline after inhalation of two puffs of a short-acting bronchodilator, even in the absence of wheeze), or

(3) A bronchoprovocation test is positive in the presence of normal routine spirometry and absence of wheeze, or

(4) Diurnal peak flow variability is at least 20%, in the presence of normal routine spirometry and absence of wheeze.

(5) The diagnosis of asthma is not made in any patient who experiences an obvious respiratory tract infection within two months prior to examination.

c. Gastroesophageal reflux disease (GERD) is considered when:

(1) Patients complain of heartburn and a sour taste in their mouths, or

(2) Upper gastrointestinal contrast roentgenograms demonstrate reflux of barium, or

(3) 24-hour pH esophageal monitoring is abnormal, in the absence of upper gastrointestinal complaints.

d. Chronic Bronchitis is considered when:

(1) Cough and phtlegm production are present on most days over a period of at least three months and for more than two consecutive years in a patient in whom other causes of chronic cough have been excluded, and,

(2) The patient is known to smoke cigarettes or is

Table XI Description of prior management of cough

Characteristics	Completed No. (%)	Lost to Follow-up No. (%)	Total No. (%)	Chi- square p-value
Patients who sought prior medical consult	165 (71.1)	29 (80.6)	194 (72.4)	0.239
Patients who had prior self-medication	112 (50.5)	7 (30.4)	119 (48.6)	0.068
Number of doctors consulted, mean(SD)	1.4 (0.66)	1.4 (0.85)	1.4 (0.69)	0.865°
Types of doctors consulted				
Family Med/GP	64 (42.1)	11 (61.1)	75 (44.1)	0.125
Cardiologist	11 (7.2)	1 (5.6)	12 (7.1)	0.630[b]
ENT	12 (7.9)	5 (27.8)	17 (10.0)	0.021[b]
Pulmolologist	37 (24.3)	2 (11.1)	39 (22.9)	0.168[b]
IM	26 (17.1)	2 (11.1)	28 (16.5)	0.400[b]
ER doctor	13 (8.6)	3 (16.7)	16 (9.4)	0.230[b]
Others	15 (9.9)	0	15 (8.8)	O.I73[b]
Patients with prior laboratory examination	129 (54.4)	24 (48.0)	153 (53.3)	0.407

exposed to industrial dust or fumes, and,

(3) Spirometry reveals airflow obstruction without bronchodilator reversibility.

e. Bronchiectasis is considered when:

(1) Cough with productive phlegm which is thick, tenacious and difficult to expectorate and becomes frankly purulent during an exacerbation; and

(2) Chest radiographic changes are suggestive (e.g., crowded markings, increase in size and loss of definition of segmental markings; and/or,

(3) High resolution CT scan of the chest confirms the diagnosis.

f. Postinfectious Cough is considered when:

(1) Cough occurs only after a respiratory tract infection; and,

(2) A patient has normal chest radiograph; and

(3) Other diagnoses have been excluded.

2. Post-treatment/Final Diagnostic Criteria - According to the ACCP consensus panel report, the final diagnosis of the cause of cough requires fulfillment of the presumptive diagnostic criteria and having cough disappear or substantially improve as a complaint within two to four weeks of specific therapy directed at the identified cause. The following is a summary of the recommended treatment for the more common etiologies of chronic cough:

a. Cough due to PNDS

Specific therapy for postnasal drip syndrome depended upon the etiology. Allergic, perennial nonallergic, postinfectious, environmental irritant, and vasomotor rhinitis are treated predominantly with intranasal steroid, an antihistaminic decongestant preparation (dexbrompheniramine maleate plus d-isoephedrine) and, when feasible, avoidance of environmental precipitating factor(s). Vasomotor rhinitis that failed to respond to the above measures is treated with intranasal ipratropium bromide. Sinusitis is treated with a combination of antibiotic, decongestant nasal spray (oxymetazoline hydrochloride) and dexbrompheniramine maleate plus d-isoephedrine.

Table XII Etiologies of Chronic Cough of Patients with Treatment Failure

Diagnosis	No.*
Bronchiectasis	3
Bronchogenic cancer	3
COPD/Chronic Bronchitis	2
Post-Nasal Drip Syndrome	2
Cavitary/ MDR PTB	1
PTB with cicatrisation atelectasis and cor pulmonale	1
Metastatic carcinoma	1
Psychogenic Cough	1
Asthma	1
Unknown Diagnosis	1

* Two patients had two etiologies

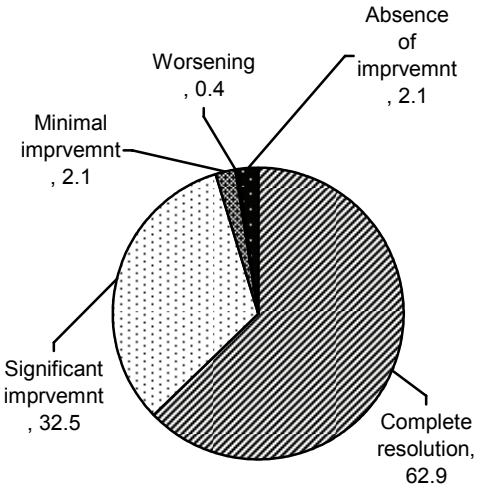

Figure 5 Response to treatment

b. Cough due to Bronchial Asthma

Asthma is treated with oral or inhaled steroids, and inhaled or oral bronchodilators.

c. Cough due to GERD

GERD is treated with a high protein, low fat, antireflux diet, eating three meals a day, not eating or drinking for 2 to 3 hours prior to lying down except for taking medications, head of bed elevation, and a proton pump inhibitor for at least eight weeks.

d. Cough due to Chronic Bronchitis

Chronic bronchitis is treated initially with cessation of smoking or the elimination of the irritant from the environment and inhaled anticholinergic drugs.

e. Cough due to Bronchiectasis

Bronchiectasis is treated with antibiotics, chest physiotherapy and postural drainage, and theophylline and/or beta-agonists.

f. Postinfectious Cough

Patients whose cough is protracted or persistently troublesome can be treated with a trial of a brief course

Table XIII Outcome of Treatment by Overall Compliance Rate among Evaluable Patients with Chronic Cough

Compliance	Treatment		RR (95% CI)	p-value
	Success No. (%)	Failure No. (%)		
> 80%	159 (95.2)	8 (4.8)	0.99 (0.94, 1.06)	0.583[a]
< 80%	67 (95.7)	3 (4.3)		

[a] Fisher's Exact Test

Table XIV Comparison of treatment response between empiric therapy and laboratory aided therapy among Evaluable patients with chronic cough

Compliance	Treatment		RR (95% CI)	p-value
	Success No. (%)	Failure No. (%)		
Confirmatory laboratory testing done prior to drug therapy	66 (95.7)	3 (4.3)	0.99 (0.93, 1.06)	0.566[a]
Empiric drug therapy	152 (95)	8 (5.0)		

[a] Fisher's Exact Test

of oral corticosteroid. An inhaled corticosteroid can be tried if tolerated and the cough is not severe. Ipratropium has also been shown to attenuate postinfectious cough. Antitussives can be added on occasions. Macrolide antibiotics are given for presumed mycoplasmal or chlamydial infections. In the case of presumed pertussis, treatment with a macrolide or trimethoprim/sulfamethoxazole is indicated.

Statistical Analysis. Data collection forms were developed and pre-tested. Data encoding was accomplished using *Epi Info* version 6.04. Statistical analyses were performed using *Epi Info* version 6.04 and *Stata 7*. Descriptive statistics such as frequencies, means (± SD), modes, medians, ranges, and percentile ranks were obtained. Differences between groups were compared with *Student t test* for 2-group analyses and *ANOVA* for > 2-group analyses of continuous variables, and *chi square* analysis, for categorical variables. Risk ratios and their 95% confidence intervals were measured to predict clinical outcome and to test associations. All tests were performed at a level of significance $p = 0.05$.

Sample Size Calculation. Assuming compliance to the ACCP Anatomic Diagnostic Protocol is achieved in only 10% of patients and using the formula:

N = [P(1-P)/ CI2] x f(I - £)

where: N = number of patients with chronic cough to be studied

P = expected compliance rate

f(1 - £) = square of the upper ½ £ point of the standard normal distribution at 95% CI = 3.84

CI = width of the interval

Thus:

N = [10 (100-10)/25] x 3.84 = 139

Considering further a sampling design clustering effect of patients (to a specific physician) of 1.5 and multiplying this to the estimated sample size, the required number of subjects is 209. Finally, to cover for an estimated lost to follow up rate of 20%, the final minimum sample size should be 251.

Results

Two hundred eighty seven subjects were entered into the study. Ninety one percent (n = 262) consulted at the private clinics of the study pulmonologists. Nine percent (n = 25) consulted at the PGH charity out patient clinics. Seventeen percent (n = 50) were lost to follow up. Twelve percent (n = 6) of these patients were charity patients. Thus, 24% of charity and 17% of pay chronic coughers dropped out from the study.

Of all the patients who were lost to follow up, 34 gave incomplete/wrong addresses and no/incorrect contact phone numbers; six lived outside of Manila and had no/incorrect contact phone numbers; four moved to an undetermined address; four went abroad; and two claimed to have minimal response to the initial management and later preferred to take herbal medications, refusing further work up and treatment

In all, 237 subjects were able to undergo evaluation for the study.

Baseline Characteristics. The baseline characteristics of all the patients entered into the study is shown in *Table I.* The patients who were evaluated were comparable to those who were lost to follow up, except for a higher rate of smokers among the latter. Majority (61.3%) of the patients were females, with mean age of 50 years. A quarter of the patients had a history of prior lung disease, usually tuberculosis while about a third of patients had other co-morbidities, the most common being hypertension and diabetes.

Table XV Outcome of treatment by non-specific cough therapy initiation among evaluable patients with chronic cough

Compliance	Treatment		RR (95% CI)	*p*-value
	Success No. (%)	Failure No. (%)		
Withheld at the outset	132 (95.7)	6 (4.3)	0.99 (0.94, 1.05)	0.513[a]
Not withheld at the outset	94 (94.9)	5 (5.1)		

[a] Fisher's exact test

Table XVI Outcome of treatment by the frequency of final etiologies among evaluable patients with chronic cough

Final Diagnosis	Treatment		RR (95% CI)	*p* Value
	Success No. (%)	Failure No. (%)		
1 diagnosis only	153 (95.6)	7 (4.4)	1.00 (0.94, 1.05)	0.591[a]
2-3 diagnoses	73 (96.1)	3 (3.9)		

[a] Fisher's exact test

Table XVII Summary of clinic attendance

Specialists Seen	Completed No. (&)	Lost to Follow-up No. (%)	Total No. (%)	Fisher's Exact *p* value
Number of pulmonary visits; mean ± SD	2.1 ± 0.93)	1.5 ±0.71	2.0 ± 0.93	< 0.001
Specialists seen/ referred to				
EENT	18 (7.6)	0	18 (6.5)	0.063
GI	2 (0.8)	0	2 (0.7)	0.742
Cardiologist	4 (1.7)	0	4 (1.5)	0.549

The mean duration of cough was 22.2 ± 55.64 weeks. Similarly, there was no difference in the cough characteristics between patients who were evaluated and those who were lost to follow up. (*Table II*)

The longest duration was 10 years, declared by two patients. More than 40% of subjects (41% of all subjects and 43% of the evaluated subjects) consulted for cough lasting for three to four weeks. Sixty-three percent of patients reported productive cough and about a third complained of nocturnal cough. Dyspnea, throat complaints and constitutional symptoms were common. Almost 30% of the patients noted worsening cough prior to consultation. Two out of ten patients reported symptoms consistent with an upper respiratory tract infection prior to or at the onset of cough.

Identification of Causes of Chronic Cough. The causes of chronic cough were definitely identified in 236 patients. The final diagnosis could not be ascertained in one of the evaluated patients, a 73 year old female, who consulted twice for a 4 week-long cough. She had hypertension and diabetes. Her chest radiograph and peak flow were normal and physical examination was unremarkable. Her course was followed up to six weeks from the first visit. She presented with symptoms suggestive of GERD and was given an empiric one-month trial with a proton pump inhibitor and a gastrokinetic agent, with little success. Paranasal and sinus radiographs showed septal deviation and congested nasal turbinates; she was advised to start a nasal steroid and an anti-leukotriene, still with little improvement; angiotensin-receptor blocker-induced cough was also entertained and she was advised to shift to another anti-hypertensive but failed to do so. The patient subsequently consulted another physician and went home to the province. Her subsequent course could not be ascertained.

As can be gleaned from *Figure 3* and *Table III*, the most frequent causes of chronic cough in the Filipino adult consulting a pulmonary specialist clinic are asthma (33.3%), postnasal drip syndrome (30.4%), pulmonary tuberculosis (20.3%), postinfectious cough (15.2%) and COPD/chronic bronchitis (10.1%). GERD was found to be uncommon, identified in only 3.8% of patients. These data apply only to patients whose response to therapy could be determined.

Table III further displays the results for the patients who were lost to follow up and had available historical, physical and laboratory information; these were compared with the data of the subjects who were evaluated. There were significantly more patients found to have asthma and PNDS among patients who were evaluated, compared to the drop-outs. The proportion of patients with pulmonary malignancy was greater among the latter. Nevertheless, if these patients were included in the total analysis, asthma, PNDS, PTB and postinfectious cough are still the most common etiologies.

The primary presumptive diagnosis for the 50 patients who were lost to follow up is seen in *Table IV*. It is noteworthy that in 15 patients, the primary diagnosis considered was PTB.

A single diagnosis was found to explain cough in the majority of patients (67.5%). Two concomitant etiologies were identified in a third of patients; asthma and postnasal drip syndrome were the most common

Table XVIII Laboratory investigations performed and proportion of abnormal results

Investigation	Completed			Lost to Follow-up			Total		
	No. Ordered	No. Done (% of ordered)	% Abnormal	No. Ordered	No. Done (% of ordered)	% Abnormal	No. Ordered	No. Done	% Abnormal
Chest x-ray	127	113 (89)	45.1	18	15 (83)	60	145	128	46.9
PNS series	49	36 (73)	86.1	6	4 (67)	50	55	40	82.5
PEF determination	42	42 (100)	347.8 + 118.4[a]	0	0	NA	42	42	60.0
Spirometry	65	48 (74)	66.7	9	4 (44)	50	74	52	65.4
Chest CT Scan	17	14 (82)	78.6	6	3 (50)	100	23	17	82.4
Sputum AFB	49	38 (78)	21.1	13	5 (38)	60	62	43	25.6
Screening CT of sinuses	6	1 (17)	100	0	NA	NA	6	1	100

combination. Three concomitant etiologies were seen in only 2.5% of patients (see *Figure 4* and *Table V*).

Table VI shows the identified etiologies among patients with normal and near normal chest radiographs.

In the great majority of these patients, the cause is due to one of three disorders: asthma, postnasal drip syndrome or postinfectious cough.

On the other hand, among patients with a history of prior lung disease, the most common etiologies are PTB, bronchiectasis and COPD, as seen in *Table VII*.

In contrast to *Table VI*, *Table VIII* shows the most common causes of chronic cough among patients with abnorma1 chest radiographs. PTB was the identified etiology in almost half of the patients who were evaluated and those who were lost to follow up. Still, asthma and postnasal drip syndrome were common in either group. Bronchiectasis and pneumonia were also in the top five etiologies in the evaluated group with abnormal chest radiographs.

Tables IX and *X* display the proportion of causes according to cough and radiologic descriptors among patients with a single diagnosis of the chronic cough.

Prior Management. Table XI describes the management of cough prior to consultation with the subject pulmonologists.

Over 70% of patients had consulted previously with at least one medical doctor, most frequently with a general or family physician. Half of the patients admitted that they resorted to self-medication while 23% of patients had already seen a pulmonologist. Half of the patients had laboratory examinations done prior to the first visit.

Response to Treatment. Figure 5 shows the response to therapy among the patients whose outcome of the cough can be determined. Treatment was judged successful in 95.4% of the subjects. In 63%, cough resolved completely in 3.20 ± 2.38 weeks. Significant improvement of the cough was reported in 32% of patients in 3.9 ± 2.59 weeks, although cough was still present but no longer disturbing two months from the first visit.

Eight (2.1%) of the subjects reported minimal improvement, while cough worsened in 0.4% (n=2) and persisted in 2.1% (n=4), for an over-all treatment failure rate of 4.6%

Among the eight patients with minimal improvement were the two patients who refused further work up and treatment and were lost to follow up, as described previously. Another patient was the 73 year old female with unknown diagnosis, also described previously. Three patients had significant bronchiectasis (one, post pneumonic; two, post-tuberculous) apparent in the chest radiograph or chest CT scan; two of these patients were charity patients who were poorly compliant to the prescribed medications because of financial constraints. One patient, also a charity patient, had cavitary PTB and was being worked up for MDR TB; compliance with medications was erratic because of financial limitations. The last patient, also a charity patient, was assessed to suffer from PTB III with significant cicatrization atelectasis of the left lung and cor pulmonale; he was undergoing DOTS TB treatment.

Two patients reported worsening of cough. One patient was assessed to have asthma and postnasal drip syndrome was also suspected. She developed chest tightness after taking a few doses of the prescribed fixed combination steroid-betaz agonist inhaler. She stopped the medication and did not follow up after one visit. She claimed improvement with self-medication with *lagundi* and expectorants, although the cough

would still recur intermittently. One patient also had worsening dyspnea; he was diagnosed to have COPD and pulmonary malignancy with brain metastases.

Absence of improvement was noted in four patients. One patient seen at the charity clinic had bronchogenic cancer with liver metastases and refused further treatment. One pay patient also had bronchogenic cancer. Another patient had metastatic pulmonary nodules due to bladder carcinoma. Psychogenic cough was suspected in the fourth patient.

Table XII shows a summary of the etiologies of the chronic cough of patients with treatment failure.

Further analyses were executed to determine if the outcome of treatment was affected by the number of final etiologies, the degree of compliance of the physicians to the ACCP algorithm, their use of empiric drug therapy or prescription of nonspecific cough medications. As shown in Table 13, the success or failure of response to therapy was not influenced by the overall compliance rate (RR= 0.99 [95% CI: 0.94, 1.06]).

Moreover, it is interesting to note that there was no difference in the outcome of treatment whether drug therapy was initiated empirically or confirmatory laboratory tests were performed beforehand. (RR= 0.99; 95% CI: 0.93, 1.06), as seen in *Table XIV*.

Similarly, there was no difference in the outcome of treatment whether nonspecific cough therapy was withheld or not at the outset (RR= 0.99; 95% CI: 0.94, 1.05), as viewed in *Table XV*.

Finally, as shown in *Table XVI*, the success or failure of response to therapy was not influenced by the number of final diagnoses (RR= 1.00; 95% CI: 0.94, 1.05).

Follow-up Visits. The mean number of visits to the pulmonary out-patient clinics ""IS 2.1± 0.93. Significantly fc\\"cJ visits were made by patients who were lost to follow up. The most frequent referrals were to ENT specialists. These data can be reviewed from *Table XVII*.

Laboratory Examinations. Table XVIII provides a summary of the laboratory investigations ordered and actually performed and the proportion of abnormal results. The most common radiologic abnormalities seen were linear or reticular infiltrates, non specific pleural changes and cardiomegaly. The most common abnormality seen on spirometry was "small airways abnormality" or the note of sagging in the terminal portion of the flow-volume loop. The abnormal paranasal sinus radiographs detected congestion of nasal turbinates, nasal septal deviation and sinusitis. Only one patient had a sinus CT scan done after the first visit and this revealed polysinusitis and the presence of maxillary sinus retention cyst.

It is noteworthy that not all laboratory investigations ordered by the physicians were actually carried out by the patients. A disturbing result is that less than half of patients who were suspected to have PTB and were subsequently lost of follow up were found to have actually performed sputum AFB studies.

Discussion

The etiologies of chronic cough were definitely identified in the great majority of patients. The most frequent causes among Filipino immunocompetent adults were similar to those reported elsewhere; namely, asthma (33.3%) and postnasal drip syndrome (30.4%). The similarity ends there. The third most frequent disease noted in this study was PTB (20.3%) and not GERD; in fact, GERD was considered in a minority of patients (3.8%). Postinfectious cough was also common in our population, likely because the duration of cough chosen for this study was eight weeks (15.2%). Among patients with a normal or near-normal chest radiograph, the etiologies that should be considered are asthma (38.7%), PNDS (38.7%) and postinfectious cough (21.0%). Among patients with an abnormal chest radiograph, PTB was the most common etiology (43.3%), although asthma and PNDS were also frequently seen (23.3% and 18.3 %, respectively).

The treatment success rate of 95% and the mean time to improvement or resolution of less than 4 weeks observed in this study is similar to the reports of the other studies that have been described previously. The treatment failure rate was small (4.6%) and can be ascribed to non-compliance, significant lung structural abnormalities that cannot be expected to reverse and terminal illness, rather than to failure of evaluation and management procedure.

It is interesting to note that the outcome of treatment was not significantly influenced by the degree of compliance of the physicians to the ACCP recommendations (RR 0.99, 95% CI 0.94, 1.06, *p* value 0.583). This is likely due to the success of empiric therapy. Other results that were not significant statistically include the following: outcome of treatment whether drug therapy was initiated empirically or confirmatory laboratory tests (RR= 0.99; 95% CI: 0.93, 1.06, *p* value 0.566), outcome of

treatment whether nonspecific cough therapy was withheld or not at the outset. (RR= 0.99; 95% CI: 0.94, 1.05, *p* value 0.513), and success or failure of response to therapy was not influenced by the number of final diagnoses (RR= 1.00; 95% CI: 0.94, 1.05, *p* value 0.591).

Conclusion

The use of the ACCP algorithm resulted in the identification of the causes of chronic cough in all but one patient. The most common causes are asthma, postnasal drip syndrome and pulmonary tuberculosis. Gastroesophageal reflux disease was uncommon in this patient population. A single diagnosis was found to explain cough in 67% of patients. Successful treatment was achieved in 95% of the patients. Treatment failure was found to be related to non-compliance of the patients, significant lung structural abnormalities that cannot be expected to reverse, and terminal illness, rather than to the failure of the evaluation and management process. The outcome of treatment was not influenced by the frequency of final etiologies, the degree of compliance of the physicians to the ACCP algorithm or the use of empiric drug therapy. The laboratories most commonly requested were Chest X rays, Spirometry and Sputum AFB smears. This is in parallel with the three most common causes of cough in the study.

References

1. French CL, Irwin RS, Curley FJ, Krikorian Cl Impact of chronic cough on quality of life. Arch Intern Med 158(15): 1657-61, 1998.
2. Irwin RS. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest 114 Supplement: 133S-81S, 1998
3. Morice AH, Fontana GA, Sovijarvi ARA, et. al. ERS Task Force: The diagnosis and management of chronic cough. Elir Repir J 24: 481-92, 2004.
4. Morice AH, Kaste1ik JA. Cough 1: Chronic cough in adults. Thorax 58: 901-7, 2003.
5. Di Pede C, Viegi G, Quackenboss JJ, et.al. Respiratory symptoms and risk factors in an Arizona population sample of Anglo and Mexican-American whites. Chest 99: 916-22, 1991.
6. Cullinan P. Persistent cough and sputum: prevalence and clinical characteristics in south east England. Respir Med 86: 143-9, 1992.
7. Loundon RG, Brown LC. Cough frequency in patients with respiratory disease. Am Rev Respir Dis 96: 1137-43, 1967.
8. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 123: 413-7, 1981.
9. Irwin RS, Curley FJ, et. al. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation and outcome of specific therapy. Am Rev Respir Dis 141: 640-7, 1990.
10. Mello CJ, Irwin RS, et. aI. The predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 156: 997-1003, 1996.
11. Smyrnios Na, Irwin RS, Curley Fl Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes and key components of the diagnostic evaluation and outcome of specific therapy. Chest 108: 991-7, 1995.
12. Palombini BC, Villanova CA, Araujo E, et. al. A pathogenic triad in chronic cough, asthma, postnasal drip syndrome and gastroesophageal disease. Chest 116: 279-84, 1999.
13. Roa C, Salonga R, et. al. The prevalence of general pulmonary symptoms in a rural Philippine community. Phil J Int Med 27: 367-76, 1989.
14. Roa C, Dantes R. et. a1. A prevalence survey of general pulmonary symptoms and acute and chronic lung diseases in an urban Philippine community. Phil J Int Med 29: 309:21, 1991.
15. Roa C, David-Wang AS, Tuazon J, et. al. The National Epidemiology Survey (NAES) Phase 1: Urban Focus. Report submitted to the World Health Organization and Department of Health, January 2004.
16. Nadri FR. Evaluation of chronic cough in a tertiary care center in tropics. Chest 124(4): 136S, 2003
17. Wongtim S., Mogmeud S, et. al. The role of methacholine inhalation challenge in adult patients presenting with chronic cough. Asian Pac J Allergy Immllnol15(1): 9-14, 1999
18. Balgos AA, Reyes-Pingol RR, et. al. Chronic persistent cough: local experience in diagnosis using the anatomic and diagnostic protocol, spectrum and frequency of causes and outcome of specific treatment. Phil J Chest Dis 1(1): 6-11,1993.