

Timeliness of In-Hospital Journey of Suspected Lung Cancer Patients: From First Presentation-to-Start of Therapy

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Abstract

Aim: Assess timeliness of lung cancer management, causes for delays, and whether length of delays affected the prognosis.

Method: A retrospective study of patients diagnosed with lung cancer between January 2012 - September 2014.

Results: The median (range) delay in CT scan from first presentation to health care setting, "CT scan-to-first diagnostic procedure," "first diagnostic procedure to confirmed diagnosis," "confirmed diagnosis-to-start of treatment" was 13 (1-399), 7 (1-490), 3 (1-176), and 35 (1-150) days respectively. The median length of the journey from "CT scan-to-start of treatment," and "first presentation to healthcare-to-start of treatment" was 56 (6-192), and 74 (2-438) days respectively. Thirty six percent waited more than 2 months to start definitive treatment from the time of their CT scan. Less-timely care correlated with those who underwent transthoracic needle aspiration, elderly males, and had non-small cell carcinoma. It also correlated with better survival 272 (18-965) vs. 97 (2-1615) days ($p=0.01$) due to more number of early stage lung cancer in this group (43.1% vs. 27.1%, $p=0.05$). Common causes of less-timely care were misdiagnosis of cancer as TB, failure of first diagnostic procedure to provide diagnosis, delay in patient's decisions regarding initiation of therapy, and development of inter-current illness while waiting for therapy.

Conclusions: Delay in the management of early stage lung cancer patients was seen. CT guided biopsy (transthoracic needle aspiration), advanced age, male gender, and NSCLC were the predictors of delay. Limited (twice weekly) availability of CT guided biopsy, misdiagnosis as TB, delayed patients' decision, and development of inter-current illness were the main causes of delay. Correlation between less timely care and better survival, attributable to the early stage indicates risk for progression of the disease and merits measures for more efficient resource allocation.

Keywords: Timeliness; Bronchoscopy; Cancer (lung); Tuberculosis

Introduction

Journey of the suspected lung cancer patients in the hospital is made up of four sequential stages. The timeliness of each stage depends on the timeliness of the output of the stage prior to it. These stages are: 1) first presentation to healthcare facility for clinical & radiographic features of lung cancer-to-first computed tomography (CT) scan or pulmonary specialist consult; 2) CT scan-to-diagnostic procedure; 3) diagnostic procedure-to-confirmation of diagnosis, and 4) confirmation of diagnosis-to-start of treatment.

It is intuitively conceivable that minimizing delay in these stages will translate into quicker diagnosis, early initiation of treatment, and better outcomes. Correspondingly several guidelines have been established setting target intervals for maximum wait in each stage. Based on the recommendations of Swedish Lung Cancer Study Group, most patients with suspected lung cancer should complete the diagnostic test by 4 weeks of consulting the chest physician [1]. This should be followed by initiation of therapy within 2 weeks [1]. The guidelines from UK recommend initiation of radical radiotherapy within 2 weeks of requesting it [2]. Similar time frame have been proposed by the guidelines from Canada [3]. In general, the maximum wait time permissible between first presentation to healthcare facility for clinical & radiographic features of lung cancer and start of treatment is 60 days [4,5].

However, the reports on the impact of the timeliness of care on prognosis in the published literature provides conflicting results. In

systematic review by Olson et al, no association between timeliness and outcome was seen in 8 studies [6-13]. Some studies showed inverse relationship between survival and delay in diagnosis and treatment [14-16], and some studies paradoxically showed favourable relationship between delay and survival [17-21].

We did this study to assess timeliness of lung cancer management, and causes for delays. We also evaluated whether length of delays were acceptable, and examined their relationship with prognosis.

Methods

This is retrospective evaluation of lung cancer patients who were managed by our pulmonary department between January 2012 and September 2014. Data was collected on demographics, Computed Tomography (CT) findings, type of diagnostic technique employed, pathological result, number of procedure required to reach conclusive diagnosis, and time from first presentation to healthcare facility for clinical & radiographic features of lung cancer-to-first CT scan, CT scan-to-diagnostic procedure, diagnostic procedure-to-confirmation of diagnosis, and confirmation of diagnosis-to-start of treatment. Approval from Institutional board review was obtained.

Definitions

Timely care

Patient were considered to have received timely care if the duration between their CT scan and start date of treatment (chemotherapy,

radiotherapy, surgery or tyrosine kinase inhibitors) was 60 days or less [4,5].

Less timely care

Patient were considered to have received less-timely care if the duration between their CT scan and start date of treatment (chemotherapy, radiotherapy, surgery or tyrosine kinase inhibitors) was more than 60 days.

Data analysis

We used software (SPSS, version 17; SPSS, Chicago, Ill) for all statistical analyses. The results were compared using a Wilcoxon two-sample test or Fisher exact test. P values were two sided and considered indicative of a significant difference if less than .05.

Results

Out of 202 patients, 82 (41%) had adenocarcinoma, 29 (14%) squamous cell carcinoma, 13 (6%) small cell lung cancer (SCLC), 11 (5.4%) non-small cell cancer, and 67 (33%) had other sub-types. Forty three were treated with chemotherapy, 44 with radiotherapy (RT), 21 with surgery, 32 with tyrosine kinase inhibitors (TKI), 1 with laser therapy, 5 patients were treated at another hospital, 5 defaulted, 10 declined, 6 died before treatment, 1 patients was undecided, and 34 received best supportive care, [Table 1].

Timeliness of care

The median (range) length of the journey from “1st presentation to healthcare-to-start of treatment” was 74 (2-438) days.

1st presentation-to-CT scan: The median length of time between 1st presentation-to-CT scan for all patients was 13 (1-399) days. Fifteen (20.5%) of patients waited more than 2 weeks for CT scan from the time of 1st presentation with features of lung cancer. After developing lung cancer related symptoms, patients who first presented to Emergency Department (ED) had shorter delay of 2 (1-232) days in having the CT scan performed as inpatient during their hospitalization, versus those who presented to General Practitioner (GP), poly-clinic, or non-respiratory physician clinic of 5 (1-595) days (p=0.02). Those referred to respiratory specialist and managed either as suspected lung cancer (n=30), or as suspected smear negative tuberculosis (n=24) had significantly longer delay in performing the CT scan of 6 (2-201), and 28 (2-438) vs. 2 (1-595) days for those referred to ED (p=0.003) respectively. Patient initially managed as smear negative tuberculosis had longest delay in this stage [Table 2].

CT scan-to-first diagnostic procedure: The median length of time between CT scan-to-first diagnostic procedures was 7 (1-490) days. Sixty seven (34.5%) had delay of more than 2 weeks between “CT scan-to-first diagnostic procedure.” Main reasons were patient refusal and missed radiographic opacity.

First diagnostic procedure-to-diagnosis: The median length of time between 1st diagnostic procedure (thoracentesis, pleural biopsy, bronchoscopy, percutaneous biopsy, or others)-to-confirmation of diagnosis in 181 patients was 3 (1-176) days. Two hundred and forty one procedures (1.19 per patient) were done in 202 patients. Twenty four (13%) had a delay of more than 2 weeks in this stage. Main reason for delay was need for multiple procedures to establish the diagnosis due to non-diagnostic first procedure. Forty six (22.7%) patients had a mean delay of 13 days between “first diagnostic procedure-to-diagnosis” due to need for 2 or more procedures compared to 2 days in those requiring single procedure (p= 0.004).

Diagnosis-to-start of treatment: The median length of diagnosis-to-start of treatment time in our cohort was 35 (1-150) days. Sixty eight

	CT scan-to-start of treatment time			
	Total N=202	≤60 days N=151	>60 days N=51	P value
Demographics				
Age	68 (31-93)	67 (31-93)	68 (42-89)	0.63
Male	141 (69.8)	105 (69.5)	36 (70.5)	1.0
Age <40	4 (1.9)	4 (2.6)	0	0.33
Age <50	17 (8.4)	15 (9.9)	2 (3.9)	0.24
Age <60	48 (23.7)	39 (25.8)	9 (17.6)	0.26
Age >70	87 (43)	64 (42.3)	23 (45)	0.74
Age >80	20 (10)	15 (9.9)	5 (9.8)	1.0
Race				
Chinese	173 (85.6)	128 (84.7)	45 (88.8)	0.64
Malay	14 (6.9)	12 (7.9)	2 (3.9)	0.52
Indian	10 (4.9)	7 (4.6)	3 (5.8)	0.71
Others	5 (2.4)	4 (2.6)	1 (1.9)	1.0
Diagnostic Procedure				
TTNA	35 (17.3)	15 (9.9)	20 (39.2)	0.0001
Bronchoscopy	123 (60.8)	93 (61.5)	30 (58.8)	0.74
Pleural tap	25 (12.3)	25 (16.5)	0	0.0008
Histology				
Adenocarcinoma	82 (40.5)	60 (39.7)	22 (43.1)	0.74
Squamous cell carcinoma	29 (14.3)	20 (13.2)	9 (17.6)	0.48
Small cell carcinoma	13 (6.4)	13 (8.6)	0	0.041
Non-small cell carcinoma	11 (5.4)	9 (5.9)	2 (3.9)	0.73
Others & unknown	67 (33.1)	--	--	
Stage				
I	20 (9.9)	13 (8.6)	7 (13.7)	0.288
II	19 (9.4)	11 (7.2)	8 (15.6)	0.09
III	24 (11.8)	17 (11.2)	7 (13.7)	0.622
IV	137 (67.8)	108 (71.5)	29 (56.8)	0.058
Metastasis to brain	37 (18.3)	30 (19.8)	7 (13.7)	0.40
Metastasis to liver	28 (13.8)	21 (13.9)	7 (13.7)	1.00
Metastasis to adrenal	32 (15.8)	26 (17.2)	6 (11.7)	0.50
Metastasis to pleura	80 (39.6)	66 (43.7)	14 (27)	0.047
Metastasis to bone	66 (32.6)	51 (33.7)	15 (29.4)	0.60
ECOG				
1	168 (83.1)	123 (81.4)	45 (88.2)	0.386
2	28 (13.8)	22 (14.5)	6 (11.7)	0.815
3	4 (1.9)	4 (2.6)	0	0.574

Data presented as number (%) or mean (±SD)

TTNA: Transthoracic needle aspiration; **ECOG:** Eastern Cooperative Group.

Table 1: General characteristics of patients with subgroup analysis of timely CT scan-to-start of treatment time (≤60 days) and less-timely CT scan-to-start of treatment time (>60 days) groups (n=202).

(48.9%) patients had a delay of mean of more than 1 month. Longest delay of more than 6 weeks occurred in nearly a third (40/139, 29%) of patients in this stage. Main reasons were awaiting patient’s decision, development of inter-current illness, waiting for staging, lung tumour board, surgery, and mutation analysis result.

RAND Corporation targets a maximum interval of 8 weeks from chest x-ray or CT scan of the chest showing mass or nodule and its surgical resection [22]. The mean length of CT scan-to-treatment interval was 56 (6-192) days. Fifty (36%) waited more than 2 months to start definitive treatment from the time of their CT scan, [Figure 1]. The reasons for the delay in each stage are presented in Table 3.

	1 st Visit to ED - CT scan (n=20)	1 st Visit to GP/OPS/Non-respiratory physician- CT scan (n=53)	GP/OPS/Non-respiratory physician triaged patients to ED - CT scan (n=23)	GP/OPS/Non-Resp physician triaged patients to respiratory physician – CT scan (n=30)	GP/OPS/Non-Resp physician triaged patient to TBCU – CT scan (n=24)
	A	B	C	D	E
1 st visit –to-CT scan Days Median (range)	2 (1-232)	5 (1-595)	2 (1-595)	6 (2-201)	28 (2-438)
P Value		A & B <i>p</i> =0.02		C & D <i>p</i> =0.007	C & E <i>p</i> =0.003

Data presented as number (%) or mean (±SD)

ED: Emergency department; CT: Computed tomography; GP: general practitioner; OPS: poly clinic; TBCU: TB control unit.

Table 2: Timeliness of the first presentation-to-CT scan stage

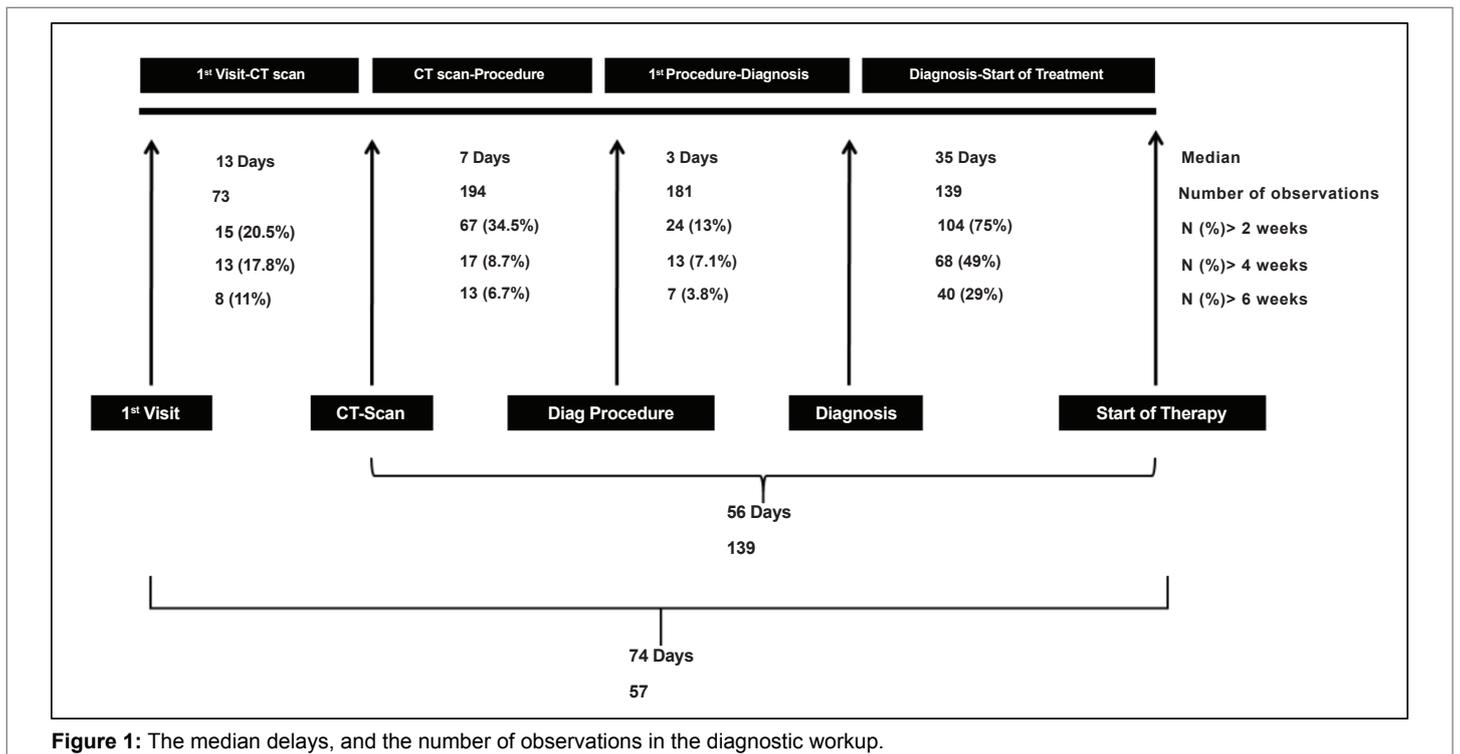


Figure 1: The median delays, and the number of observations in the diagnostic workup.

Predictors of timely care

Factors associated with less-timely care in univariate analysis were lack of pleural effusion, Transthoracic Needle Aspiration (TTNA), sub-type other than small cell carcinoma, curative surgery, radiotherapy, greater number of diagnostic procedures, and initial treatment as smear negative tuberculosis. Multivariate analysis revealed TTNA, sub-type other than small cell carcinoma, advanced age, and male gender as factors associated with less-timely care.

Timeliness of care and prognosis

Median survival was 122 (2-1615) days. Mortality showed negative correlation with the timeliness. Despite prompt care, patients in timely group had a shorter survival 97 (2-1615) days vs. less-timely group 272 (18-965) days (*p*=0.01) due to greater proportion of advanced stage lung cancer patients in the timely group. Survival was greatest and significantly higher in patients who underwent resection (early stage) versus those who did not (late stage) with 459 (286-927) vs. 117 (2-1615) days, *p*= 0.0005 respectively, [Table 4].

Discussion

The results of this study indicate that a third of patients were delayed

beyond the recommended time targets in each stage. Longest delay affecting most number of patients was seen between confirmation of diagnosis-to-start of treatment. However, as the delay occurred more frequently in patients with early stage cancer, it was not associated with poorer prognosis. This indicated patients pre-determined to have poor prognosis by virtue of their advanced stage were being treated more expeditiously for an unavailing benefit than those who could gain more in-terms of survival from such expediency.

In the pre-diagnosis stage, upon their first presentation to primary physician, some patients were suspected to have TB instead of cancer. These patients had a greater delay in performing the CT scan as compared to those referred to respiratory physician or ED. This may have been due to regional prevalence of TB and inappropriate attribution of the radiograph changes to smear negative TB. Fifty to 80% of patients with pulmonary TB have positive sputum smears [23]. The remaining smear negative patients in high prevalence countries often mislead clinicians to diagnose lung cancer as TB due to clinical and radiological similarities of pulmonary TB with lung cancer [24]. Main reasons for this error is the delay in investigating the opacities detected on chest radiograph by CT scan or Fibre Optic Bronchoscopy (FOB) [24]. Lack of utilization of these tests in developing countries is attributed to their high cost and limited availability limited to urban areas and tertiary care centres. Hence, in the

Reasons	Number of patients affected by stage of the journey			
	1 st Visit-to-CT scan	CT-to-Procedure	Procedure-to-Diagnosis	Diagnosis-to-Treatment
Therapeutic trial of TB treatment	8	–	–	–
Multiple diagnostic procedures	–	–	46	–
Patient refusal of investigation	–	1	–	–
Patient delayed treatment	–	–	–	10
Development of inter-current illness	–	–	–	6
Waiting for staging scans	–	–	–	4
Waiting for surgery	–	–	–	4
Uncertain primary	–	–	–	2
Unavailability of ICU beds for post-surgery monitoring- postponement of surgery	–	–	–	2
Waiting for MDM decisions	–	–	–	1
Waiting for mutation analysis result	–	–	–	1
Missed diagnosis	–	1	–	–

Table 3: Reasons for long delay in the 4 stages of the journey of lung cancer

	Total N=202	CT scan-to-start of treatment time		P value
		≤60 days N=151	>60 days N=51	
CT – Diagnostic procedure time	7 (1-490)	6 (1-490)	18 (1-184)	0.0004
Diagnostic procedure – confirmation of diagnosis time, days	3 (1-176)	3 (1-176)	3 (1-73)	0.08
Confirmation of diagnosis – Start of 1 st treatment, days	35 (1-150)	35 (1-56)	54 (1-150)	0.00007
CT scan – start of treatment, days	56 (6-192)	48 (6-60)	88 (61-192)	0.00005
Number of procedures	241	167	72	0.01
Number of procedures per patient	1.28	1.10	1.46	0.01
Patients with stage IV lung cancer	137 (67.8)	108 (71.5)	29 (56.8)	0.05
Therapy				
Radiotherapy	43 (21.2)	26 (17.2)	17 (33.3)	0.01
Chemotherapy	41 (20.2)	28 (18.5)	13 (25.4)	0.30
Surgery	17 (8.4)	6 (3.9)	11 (21.5)	0.0008
Tyrosine kinase inhibitor	32 (15.8)	24 (15.8)	8 (15.6)	1.0
Survival in those who died, days	122 (2-1615)	97 (2-1615)	272 (18-965)	0.01

Data presented as number (%) or mean (±SD)

Table 4: Subgroup analysis of timely (CT scan-to-start of treatment time of ≤ 60 days) and less-timely care (CT scan-to-start of treatment time of >60 days), by stage of cancer, therapy, and survival. Less-timely care correlated with early stage cancer, radiotherapy, surgical resection, and better survival.

high TB prevalence areas, therapeutic trial of TB treatment is an acceptable practice. However, therapeutic trial of TB treatment should be limited to a certain period, beyond which the diagnosis of TB must be reconsidered for poor or no response. A prospective case series of 107 patients of cutaneous TB indicated that if patient does not respond to 5 weeks of TB treatment, the diagnosis of TB should be reviewed [25]. Whether this can be extrapolated to pulmonary TB remains to be established.

Another common reason for the delay in the “pre-diagnosis” stage (diagnostic procedure-to-confirmation of diagnosis) was failure of single procedure to yield the diagnosis. These findings are similar to existing literature. Need for multiple diagnostic tests and consultations has been reported as common causes of delay by other investigators [5, 26]. British Thoracic Society recommends that the results of bronchoscopy or any other similar diagnostic test, including the histological or cytological result, should be available within 2 weeks of a decision to do it [27]. This seems feasible as this time interval in our cohort was 2 days for those who needed only single procedure and 13 days for those who needed more than 2 procedures.

In the post-diagnosis stage, delay of average more than 1 month was seen in diagnosis-to-start of treatment in half of the patients. The Swedish Lung Cancer Study group recommends that treatment should be started within 2 weeks after completion of diagnostic tests [1]. In the UK it is advocated that radical radiotherapy should start within 2 weeks after it is requested [2]. In Canada the recommended waiting time from completion

of diagnostic tests to surgery should not exceed 2 weeks [3]. The NHS National Cancer Plan and RAND Corporation target a maximum interval of 4 weeks and 6 weeks respectively from diagnosis to treatment. The implication of this delay is that time observed for lung tumours to double their volume ranges from 4 to 56 weeks, with a median time of 17 weeks [28,29]. Although only a third (50 patients) had CT scan-to-treatment time of more than 8 weeks, 12 patients in our cohort had the CT scan-to-treatment time of more than 120 days (16 weeks). It seems likely that delay of 16 weeks, which approximate to one tumour volume-doubling time for Non-small Cell Carcinoma (NSCLC) in these patients would have made some tumours inoperable.

The most common reason for delay in the “post-diagnosis” stage was patient taking time to decide about their treatment, followed by development of inter-current illness, and waiting for completion of staging, treatment decisions from Multi-Disciplinary Meetings (MDM), and surgery. Waiting time for surgery, and reluctance to undergo invasive procedures has also been reported as common causes of delay by other investigators [26]. However, proportion of patients taking time to decide to start therapy was higher in our cohort than previously described and could be due to cultural differences or cost considerations, but requires further study.

Bronchoscopy, TTNA, and thoracentesis were most commonly performed diagnostic procedures. Undergoing TTNA as the first diagnostic procedure was associated with longer CT scan-to-treatment

time. This may reflect difficulty in obtaining timely slot for TTNA as compared to bronchoscopy and was attributable to *batch processing*. TTNA is done by limited number of radiologists and it is only done twice a week at our centre whereas bronchoscopies are done daily. Batch processing is known to cause waiting behind the date of processing and behaves like a constraint in the flow of a process [30]. Principles of *lean thinking* propose efficient use of staff, resources, and technology to provide the highest level of service and involve five steps to improve a selected process: *value, the value stream, flow, pull, and perfection*. The goal of “flow” component of these five steps is to eliminate the use of batching and queuing within a process to ensure that a process is continuously worked on until it is complete.

NSCLC patients experienced longer delay. Small cell carcinoma by virtue of its aggressive nature on the one hand, and chemo-responsiveness on the other is known to receive prompt treatment by creating a sense of urgency. Similar shorter delay has been reported in small cell carcinoma group by other investigators although they did not specify the reasons [26].

The reason for correlation between male gender and longer CT scan-to-treatment interval could be due to more number of males and longer CT scan-to-treatment interval in the patients treated with non-TKI therapy versus more females ($p=0.05$) and shorter CT scan-to-treatment interval ($p=0.01$) in TKI group. The shorter delay in TKI group can be attributed to ease of initiation of oral therapy, lack of delay associated with staging work-up, lung function tests, and resource intensive therapies such as chemotherapy and radiotherapy.

Advanced age has been shown to be associated with less-timely care [31]. Advanced age makes decision making difficult due to associated co-morbidities and risk-benefit profile swaying more toward risks than benefits. Such patients themselves often take longer time to decide if they want to undergo therapy that entails side effects, and even when they do, they often require relatively more preoperative tests, consults or preparation for the operating room.

Mortality showed negative correlation with the timeliness, being higher in the timely care group, and lower in the less timely group. This was attributable to stage of the disease, reflecting patients with advanced disease receiving prompt treatment. However, it also indicates that patient with limited disease those who have the highest chance of better survival if treated promptly paradoxically waited longer than those with advanced disease in whom prompt treatment is unlikely to offer much benefit. Surgically treated patients had a longer CT scan-to-treatment time than those treated non-surgically mostly due to delay in “post-diagnosis” period. This reflects the extra time needed to refer patients to thoracic surgery units where additional treatment considerations are made like staging scans. This raises the question about the efficiency of resource allocation and reflects the area of weakness amenable to improvement.

Various approaches have been evaluated to improve timeliness of care in lung cancer such as MDM, nurse-led care coordination, telemedicine and a “two-stop” diagnostic process whereby patients receive CT, and diagnostic procedure at the initial visit followed by formulation of a treatment plan in a multidisciplinary meeting within 3 days [32-39]. Out of these the “two-stop” diagnostic process described by Laroche et al and Murray et al has been shown to be significantly effective in reducing diagnostic delay [35,38].

Our findings enable us to formulate the following recommendations for timely care: 1) Since CT scan is more accurate than a chest radiograph, the best and cost effective way to reduce miss-diagnosis of lung cancer as TB will be to perform CT scan on all patients diagnosed as smear negative TB, and having risk factors for lung carcinoma such as significant smoking history in males, non-smoking Asian females, upper lobe involvement,

and self or family history of cancer. Upper lobe involvement alone should not be considered as the hallmark of TB as commonly thought, because the physiologic disparities in the perfusion-ventilation ratio, lymphatic flow, metabolism, and mechanics, all of which result from the influence of gravity across the various parts of the lung have been recognized as important factors determining the upper lobe predominance of several pulmonary diseases [40]. 2) Matching the first diagnostic procedure closely to the radiographic features may help to reduce the number of procedure needed and hence time taken to confirm the diagnosis. For example, performing trans bronchial lung biopsy for bronchus sign, endobronchial ultrasound guided transbronchial needle aspiration for mediastinal lymph node and central masses. 3) In our institution MDM is held every fortnightly, and on occasions, staging work-up is not completed by the time of MDM. Conducting MDM on a weekly basis, with special emphasis on stage IIIA cases along with attempt to complete the diagnostic, staging, and operability work up where necessary prior to the meeting so that the management decisions can be finalised during the meeting. 4) Exploring the reasons why patients take a long time to decide before embarking on therapy even after knowing they have lung cancer also demands attention. Focus group discussions may help to unravel the reasons for such delays.

In conclusion, longer delay in the management of early stage lung cancer patients was seen indicating bias toward delivering expeditious treatment to symptomatic (by virtue of advanced stage) versus asymptomatic patients. This implies that those with inherent chance of cure (early stage) had to wait longer, with risk for progression of their disease. Undergoing CT guided biopsy (transthoracic needle aspiration) to establish diagnosis, advanced age, male gender, and NSCLC were the predictors of delay. Limited (twice weekly) availability of CT guided biopsy (transthoracic needle aspiration), failure of first diagnostic procedure to provide diagnosis, misdiagnosis of lung cancer as TB, delayed patients’ decision, and development of inter-current illness were the main causes of delay. Delay did not correlate with poor survival due to greater proportion of early stage cancer in the delayed group suggesting need for more efficient resource allocation.

Conflict of Interest Statement: A.V., A.C., A.L., D.Y.H.T., S.K.G., A.C.K., B.H., D.B.A.A., Y.W.L., and J.A. have no potential conflicts of interest to report.

Summary at a Glance

We performed a retrospective study to elucidate predictors and causes of delay in the management of lung cancer. CT guided biopsy (transthoracic needle aspiration), advanced age, male gender, and NSCLC were the predictors of delay. Limited (twice weekly) availability of CT guided biopsy, misdiagnosis of lung cancer as TB, delayed patients’ decision, and inter-current illness were the main causes of delay.

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