ATLANTIS PRESS

Journal of Epidemiology and Global Health

ISSN (Online): 2210-6014 **ISSN (Print): 2210-6006**
Journal Home Page: https://www.atlantis-press.com/journals/jegh

An overview of mortality & predictors of small-cell and non-small cell lung cancer among Saudi patients

Hatim I. Alghamdi, Ali F. Alshehri, Ghada N. Farhat

To cite this article: Hatim I. Alghamdi, Ali F. Alshehri, Ghada N. Farhat (2018) An overview of mortality & predictors of small-cell and non-small cell lung cancer among Saudi patients, Journal of Epidemiology and Global Health 7:Suppl. 1, S1–S6, DOI: https://doi.org/10.1016/j.jegh.2017.09.004

To link to this article: https://doi.org/10.1016/j.jegh.2017.09.004

Published online: 16 April 2019

Journal of Epidemiology and Global Health 7 (2018) S1–S6

Contents lists available at ScienceDirect

Journal of Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/jegh

An overview of mortality & predictors of small-cell and non-small cell lung cancer among Saudi patients

Hatim I. Alghamdi [a,*], Ali F. Alshehri [a], Ghada N. Farhat [b]

[a] Ministry of Health, Saudi Arabia
[b] Emory University, Rollins School of Public Health, Hubert Department of Global Health, USA

ARTICLE INFO

Article history:
Received 19 June 2017
Received in revised form 6 September 2017
Accepted 18 September 2017
Available online 28 September 2017

ABSTRACT

Lung cancer ranks as the top cancer worldwide in terms of incidence and constitutes a major health problem. About 90% of lung cancer cases are diagnosed at advance stage where treatment is not available. Despite evidence that lung cancer screening improves survival, guidelines for lung cancer screening are still a subject for debate. In Saudi Arabia, only 14% of lung cancers are diagnosed at early stage and researches on survival and its predictors are lacking. This overview analysis was conducted on predictors of lung cancer mortality according to the two major cancer types, small-cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs) in Saudi Arabia. A secondary data analysis was performed on small-cell lung cancers (SCLCs) and Non-small cell lung cancers (NSCLCs) registered in the Saudi Cancer Registry (SCR) for the period 2009–2013 to estimate predictors of mortality for both lung cancer types. A total of 404 cases (197 SCLC and 207 NSCLC) were included in the analysis, all Saudi nationals. A total of 213 (52.75%) deaths occurred among lung cancer patients, 108 (54.82%) among SCLCs and 105 (50.72%) among NCSLCs. Three quarter of patients are diagnosis with advance stage for both SCLC & NSCLC. Univariate analysis revealed higher mean age at diagnosis in dead patients compared to alive patients for SCLCs ($p = 0.04$); but not NSCLCs, a lower mortality for NSCLCs diagnosed in 2013 ($p = 0.025$) and a significant difference in stage of tumor ($p = 0.006$) and ($p = 0.035$) for both SCLC and NSCLC respectively. In multiple logistic regression, stage of tumor was a strong predictor of mortality, where distant metastasis increased morality by 6-fold (OR = 5.87, 95% CI: 2.01 – 17.19) in SCLC and by 3-fold (OR = 3.29, 95% CI: 1.22 – 8.85) in NSCLC, compared to localized tumors. Those with NSCLC who were diagnosed in 2013 were less likely to die by 64% compared to NSCLC diagnosed in 2009 (OR = 0.36, 95% CI: 0.14 – 0.93). Age, sex, topography and laterality were not associated with mortality for both types of lung cancer. We observed that the stage of the tumor is the strongest predictor of mortality for both SCLCs and NSCLs. This confirms the impact of diagnostic stage on survival. However, establishing Saudi-specific lung cancer screening guidelines will require further research on the benefits and harms of screening modalities in the Saudi population.

Contents

1. Introduction . . . S2
2. Methods . . . S2
   2.1. Study design . . . S2
   2.2. Setting and data source . . . S2
   2.3. Study variables . . . S2
   2.4. Data management . . . S2
   2.5. Statistical analysis . . . S2
3. Results . . . S2

Peer review under responsibility of Ministry of Health, Saudi Arabia.
* Corresponding author at: Baha – building No. 6800, Unit 2, Baha 65711-3508, Saudi Arabia.
E-mail address: Hatimalghamdi077@gmail.com (H.I. Alghamdi).

https://doi.org/10.1016/j.jegh.2017.09.004
2210-6006/

3.1. Demographic and tumor characteristics for overall cases, SCLC and NSCLC S2
3.2. Lung cancer mortality, for SCLC S3
3.3. Lung cancer mortality, for NSCLC S3
4. Discussion S3
Acknowledgements S5
References S5

1. Introduction

Lung cancer is the most commonly diagnosed cancer in the world. According to GLOBACAN, 1.8 million cases of lung cancer were registered during 2012, making up 13% of all cancer deaths [1].

Lung cancer incidence shows a growing trend globally given that in 2002 the number of registered cases was 1.35 million cases which increased to 1.6 million cases by 2008 [2]. This change in incidence contributed to changes in exposure to risk factors, especially smoking, as well as increased lifespan and population size [2,3].

Mortality rate of lung cancer is relatively close to incidence rate, that, global mortality-to-incidence ratio being 0.88 for males and 0.84 for females [3,4]. Lung cancer was responsible for 2.3% of total deaths worldwide during 2004 and ranked as the 8th leading cause of death [5,6].

Saudi Arabia has low incidence rate of lung cancer compared to global incidence. In 2013, age standardized ratio (ASR) was 5.5 per 100,000 for males and 1.8 per 100,000 for females [7]. In contrast, the average global ASR during 2008 was 33.8 per 100,000 for males and 13.5 for females [8]. But, a growing population in Saudi Arabia, along with an expected increase in elderly population size by sevenfold, accompanied by high smoking prevalence; which is gradually increasing by 1.5% for males and 2.0% for females, are all factors that can potentially result in more incidence of lung cancer in Saudi Arabia [9–12].

Lung cancers staging globally shows that only 15% of cases are diagnosed at an early stage [8]. Saudi Arabia falls within the global range, with only 14% of cases diagnosed early with localized tumors [7]. However, in developed countries this percentage is higher. In Canada for example, 20–30% of cases are diagnosed at an early stage [13].

Annual lung cancer screening has been recommended since 2012 by several health organizations and expert panels, which showed a significant decrease in lung cancer mortality by 20.0% (95% CI: 6.8–26.7) (P = 0.004) [14]. However, screening implications are still subject to discussion [15].

Currently, Saudi Arabia does not have national screening guidelines for lung cancer. Developing country-specific screening guidelines requires a strong research base on lung cancer mortality to offer more evidence for decision makers about the value of instituting and implementing national screening guidelines.

The existing gap in detailed knowledge on lung cancer mortality in Saudi Arabia needs to be offset to provide information-for-action for the development of Saudi-customized screening and management guidelines for this malignancy. Hence, main purpose of this paper is focused on the predictors of mortality among lung cancer patients, both small-cell and non-small cell, in Saudi Arabia for the period of 2009–2013.

2. Methods

2.1. Study design

A secondary data analysis was performed on lung cancer cases reported to the (SCR) during the period of 2009–2013 after their permission to use and disseminate the data. Determination of IRB was reviewed by Emory university.

2.2. Setting and data source

Data was requested and readily available from the SCR, as part of their objective is to support dissemination and utilization of registered data.

2.3. Study variables

Data obtained by the SCR includes information on patients demographic data (sex, age, nationality), date of diagnosis, tumor characteristics (topography, morphology, behavior, grade, extension [SEER stage], and laterality), date of last contact (via telephone) and mortality indicators (status and cause of death) [7,16].

2.4. Data management

The dataset included 452 registered cases of lung cancer during 2009–2013, all of which were of Saudi nationality. Diagnoses were restricted to NSCLC and SCLC types of lung cancers. We exclude 48 cases; observations without a valid vital status (N = 1) were excluded as well as unknown cause of death (N = 1) or non-reported data on cancer extension (N = 47; 23 dead and 24 alive). Therefore, the final dataset included 404 observations with a total exclusion of 48 observations.

2.5. Statistical analysis

The distribution of variables was examined by conducting a univariate analysis stratified by SCLC and NSCLC to find differences at each variable within vital status.

To estimate predictors of mortality among lung cancer patients, logistic regression was performed with stratification by histological type. A dichotomous mortality indicator variable was regressed on age, sex, topography, extension, laterality and year of diagnosis. Odd ratios (OR) and 95% confidence intervals (95% CI) were calculated for each predictor. Tumor grade was not included in this study's model due to the large number of missing data (N = 272) and due to the lack of a widely-accepted grading system for lung cancer that is used consistently by all health facilities [17,18]. Tumor behavior variable also was not included in the model due to collinearity, where all observations are recorded as malignant behavior. The level of statistical significance was set at 0.05. Stata (version SE64, Stata Corporation, College Station, TX) was used for analysis.

3. Results

3.1. Demographic and tumor characteristics for overall cases, SCLC and NSCLC

A total of 404 lung cancer cases were diagnosed during the period 2009–2013 and included in the final analysis. SCLC composed 48.8% (N = 197) of the cases, out of which 108 (54.8%) did

not survive; and NSCLC composed 51.2% of observations (N = 207), out of which 105 (50.7%) did not survive. Out of a total of 404 cases, there were 337 (83.4) cases in males and 67 (16.6%) in females. The overall median age of lung cancer diagnosis was 63.3 year (SD 12.46 years). The median age of diagnosis was 63.7 years (SD 12.4 years) in males and 61.02 (SD12.37) in females (p = 0.10). majority of patient are diagnosed at advance stage, 74.1% of SCLC and 76.8% of NSCLC has diagnosed with metastasis stage [Table 1].

In univariate analysis, SCLC cases showed a statistically significant difference in mean age between those who are alive and those dead (p = 0.0386), however, in NSCLC, age showed no significant difference between alive and dead (p = 0.3833). For year of diagnoses there was no statistically significant difference between alive and dead at SCLC (p = 0.433), but it showed a statistically significant difference for NSCLCs (p = 0.025). Stage of tumor showed a significant difference for both, SCLC (p = 0.006) and NSCLC (p = 0.035) [Table 1].

3.2. Lung cancer mortality, for SCLC

Using multiple logistic regression analysis for SCLC, extension was found to be the strongest predictor of mortality. Having regional extension by both direct extension and lymph node increase the odd of mortality by 6-fold compared to having localized disease (OR = 6.08, 95% CI: 1.05–35.18), and having distance metastasis increased the odds of mortality by 5-fold compared to having localized disease (OR = 5.87, 95% CI: 2.01–17.19).

None of the other variables were found to be statistically significantly associated with mortality in SCLC, including age (OR = 1.02, 95% CI 1.00–1.03) gender (OR = 2.30, 95% CI: 0.90–5.89) and year of diagnosis [Table 2]

3.3. Lung cancer mortality, for NSCLC

Multiple regression model for NSCLC showed a statistically significant increase in mortality among cases with distance metastasis compared to those with local disease (OR = 3.29, 95% CI: 1.22–8.85). However, in contrast to SCLC, regional extension by both direct and lymph node extension did not significantly increase the odds of mortality. Besides that, year of diagnosis in cases showed a decrease in the odds of mortality for those diagnosed in 2013 compared to those diagnosed in 2009 (OR = 0.36, 95% CI: 0.14–0.93).

None of the other variables were found to be statistically significantly associated with mortality in NSCLC, including age (OR = 1.01, 95% CI 0.99–1.04) gender (OR = 1.26, 95% CI: 0.59–2.69) [Table 3].

4. Discussion

In this secondary data analysis, the overall mortality rate of lung cancer among Saudi national patients in the period 2009–2013 for both SCLC and NSCLC was 52.75% (54.82% in SCLC and 50.72% in NSCLC). Mortality was strongly predicted by tumor extension. In SCLC, regional extension by both direct and lymph node extension increase mortality by 6-folds compared to localized tumor and distance metastasis/systematic increase mortality by 5-fold compared to localized tumor. In NSCLC, distance metastasis/systematic disease increased mortality by 3-fold compared to localized tumor.

The lung cancer survival rate shows a difference by histological type, with NSCLC having a better prognosis compared to SCLC [19]. However, the staging of a tumor is the strongest determinant factor of lung cancer survival. Chansky et al. conducted a retrospective study on 9137 patients and observed a strong correlation between Tumor, Node, Metastasis (TNM) stage and survival, where the median survival for patients at stage IIIA was 19 months, compared to 95 months for patients at stage IA [20]. Our study, confirms the strong effect of disease stage on mortality for both NSCLC and SCLC.

Several efforts have tried to develop an accurate prediction model for lung cancer prognosis by adding further factors to tumor staging, although, tumor staging is still the major mortality predictor [25]. Other factors that showed a prognostic effect independent of disease stage include performance status (PS), age and gender [26,27]. Additionally, several genetic biomarkers associated with lung cancer were found to have a prognostic effect [28–31]. Other factors like obesity [32] and smoking history [33] were also found to impact survival in lung cancer. Hence, to achieve higher prediction accuracy, a more complex approach that integrates individual, pathological markers and genetics factors is needed [34]. Our study did not allow for a full investigation of important prognostic factors because of the limited nature of data collected within cancer registries.

Analysis of mortality by year of diagnosis showed significantly lower odds for those diagnosed in 2013 compared to 2009 for NSCLC but not for SCLC. It is unclear whether any significant improvements were introduced in clinical management of lung cancer during 2013 [64]. However, the observed drop in mortality in 2013 and the reason why it applied to NSCLCs but not SCLCs requires further investigation.

The overall mean age of diagnosis for both SCLC and NSCLC was 63.27 years (SD = 12.46), which is 6.73 years younger than the average age at diagnosis in the United States. Additionally, the age range in our study overlapped with the age range of lung cancer screening (55–74 years) used in the NLST. The NLST age range was determined by the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial's 2012 prediction model ($PLCO_{m2012}$) which determined that the 55–74 year age range as an inclusion criterion in the trial [21]. It is worth to note that the screening recommendations of the USPTF recommended an age range for screening of 55–80 years. For Saudi Arabia, it is not clearly evident whether screening beyond the range of 55–74 years could be an advantage or not, especially when viewing this issue from the angle of premature mortality impact of lung cancer, and by taking into consideration the expected age difference between the US and Saudi Arabia.

Various studies revealed that the effect of cigarette smoking on lung cancer varies by histological types, where cigarette smoking and early initiation of smoking show a stronger association with SCLC compared to NSCLC [22,23]. In the US, the proportion of SCLC was tracked over from 1973 to 2002 and showed a gradual decrease from 17.26% in 1986 to 12.95% in 2002; this decrease in SCLC proportion is potentially a result of strengthened in tobacco control policies during the 1980s [24]. However, the histological distribution of lung cancer in Saudi Arabia supports this association. Our study showed that SCLC constituted 50% of lung cancer cases among males and 37% among females. This could be explained, in part, by differences in smoking prevalence rates between men and women in Saudi Arabia, where the age-standardized smoking prevalence rate among males during 2013 was 26.8%, compared to 3% among women [12].

A main limitation of this study is the unavailability of time-to-event data which prevented the use of survival analysis methods and the ascertainment of an accurate estimate of survival rates for each cancer type. Another limitation is the restricted data on predictors. For a better characterization of lung cancer mortality, a prediction model that integrates pathological variables, biological markers, genetics and patient physical status is needed [68]. The lack of such factors is assumed to have a residual confounding role in the results. Lastly, the study population is restricted to Saudi nationals and it include only the registered cases in SCR as the

Table 1
Characteristics of lung cancer patients stratified by histological type.

		SCLC N = 197				NSCLCN = 207			
		Alive 89 (45.18%)	Dead108 (54.82%)	Total	P-value	Alive102 (49.28%)	Dead105 (50.72%)	Total	P-value
Age at diagnosis, mean (SD)		62.39 (SD 13.26)	66.04 (SD 11.30)	64.39(SD 12.33)	0.04 *	61.42 (SD 12.09)	62.94(SD 12.94)	62.19(SD 12.52)	0.3833*
Sex	Male	73 (42.69%)	98 (57.31%)	171 (86.80%)	0.07**	79 (77.45%)	87 (82.86%)	166 (80.19%)	0.329**
	Female	16 (61.54%)	10 (38.46%)	26 (13.20%)		23 (22.55%)	18 (17.14%)	41 (19.81%)	
Year of diagnosis	2009	16 (17.98%)	21 (19.44%)	37 (18.78%)	0.433 **	29 (28.43%)	30 (28.57%)	59 (28.5%)	0.025**
	2010	19 (21.35%)	28 (25.93%)	47 (23.86%)		22 (21.57%)	22 (20.95%)	44 (21.26%)	
	2011	17 (19.10%)	19 (17.59%)	36 (18.27%)		9 (8.82%)	22 (20.95%)	31 (14.98%)	
	2012	14 (15.73%)	23 (21.30%)	37 (18.78%)		17 (16.67%)	20 (19.05%)	37 (17.87%)	
	2013	23 (25.84%)	17 (15.74%)	47 (20.30%)		25 (24.51%)	11 (10.48%)	36 (17.39%)	
Topography	Main Bronchus	7 (7.87%)	12 (11.11%)	19 (9.64%)	0.597***	6 (5.88%)	4 (3.81%)	10 (4.83%)	0.851***
	Upper lobe	24 (26.97%)	27 (25%)	51 (25.89%)		33 (32.35%)	34 (32.38%)	67 (32.37%)	
	Middle lobe	4 (4.49%)	5 (4.63%)	9 (4.57%)		3 (2.94%)	6 (5.71%)	9 (4.35%)	
	Lower lobe	19 (21.35%)	14 (12.96%)	33 (16.75%)		21 (20.59%)	20 (19.05%)	41 (19.81%)	
	Overlapped lesion	3 (3.37%)	7 (6.48%)	10 (5.08%)		5 (4.90%)	3 (2.86%)	8 (3.86%)	
	Not otherwise specified	32 (35.96%)	43 (39.81%)	75 (38.07%)		34 (33.33)	38 (36.19%)	72 (34.78%)	
	Carcinoma Of other ill-defined sites	0	0	0		0	0	0	
Stage	Localized	16 (17.98%)	6 (5.56%)	22 (11.17)		16 (15.69%)	7 (6.67%)	23 (11.11%)	
	Regional by direct extension	7 (7.87%)	2 (1.85%)	9 (4.54%)		7 (6.86%)	3 (2.86%)	10 (4.83%)	
	Regional by lymph node	6 (6.74%)	4 (3.7%)	10 (5.08%)		7 (6.86%)	2 (1.9%)	9 (4.35%)	
	Regional by both direct extension and lymph node	4 (4.49%)	5 (4.63%)	9 (4.57%)		2 (1.96%)	2 (1.9%)	4 (1.93%)	
	Regional-NOS	0	1 (0.93%)	1 (0.51%)		1 (0.98%)	1 (0.95%)	2 (0.97%)	
	Distance metastasis/Systematic disease	56 (62.92)	90 (83.33%	146 (74.11)		69 (67.65%)	90 (85.71%)	159 (76.81%)	
Laterality	Not paired	1 (1.12%)	1 (0.93%)	2 (1.02%)	0.876 ***	0	0	0	0.453***
	Right origin	44 (49.44%)	51 (47.22%)	95 (48.22%)		57 (55.88%)	64 (60.95%)	121 (58.45%)	
	Left origin	32 (35.96%)	35 (32.41%)	67 (34.01%)		34 (33.33%)	32 (30.48%)	66 (31.88%)	
	Only one side involved (right or left) unspecified	0	0	0		6 (5.88%)	2 (1.90%)	8 (3.86%)	
	Bilateral (side of origin unknown or single primary)	2 (2.25%)	4(3.70%)	6 (3.05%)		5 (4.90%)	7 (6.67%)	12 (5.80%)	
	Midline origin	0	0	0		0	0	0	
	paired no information concerning laterality	10 (11.24%)	17 (15.74%)	27 (13.71%)		0	0	0	

* T-test ** Chi-square test *** Fisher's exact test.

Table 2
Mortality Predictors among SCLC.

Mortality	Odd Ratio	95% Confidence interval	P-Value
Age	1.02	1.00–1.05	0.10
Sex			
Female (Ref.)	1		
Male	2.30	0.90–5.89	0.08
Extention			
Localized (ref.)	1		
Regional by direct extension	0.84	0.12–5.82	0.86
Regional by lymph node	1.62	0.29–9.13	0.58
Regional by both direct extension and lymph node	6.08	1.05–35.18	0.04
Regional nos	–	–	- *
Distance Metastasis/systematic disease	5.87	2.01–17.19	0.00
Topographgy			
Main bronchus (ref.)	1		
Upper lobe	0.41	0.11–1.61	0.20
Middle lobe	0.67	0.09–5.32	0.71
Lower lobe	0.29	0.07–1.23	0.09
Overlapped lesion	0.56	0.08–3.76	0.55
Not otherwise specified	0.41	0.11–1.52	0.18
Laterality			
Left (ref.)			
Not paired	0.18	0.01–4.12	0.28
Right origin	0.86	0.42–1.75	0.68
Bilateral (side of origin unknown or single primary)	2.20	0.32–15.24	0.43
Paired no information concerning laterality	1.48	0.51–4.31	0.47
Year of diagnosis			
2009 (ref.)	1.00		
2010	1.29	0.48–3.44	0.61
2011	0.83	0.30–2.30	0.71
2012	1.59	0.57–4.50	0.38
2013	0.54	0.20–1.48	0.23

*Estimates for this category could not be obtained because count = 1 for SCLC.

Table 3
Mortality Predictors among NSCLC.

Mortality	Odd ratio	95% confidence interval	P-value
Age	1.01	0.99–1.04	0.31
Sex			
Female (ref.)			
Male	1.26	0.59–2.69	0.56
Extension			
Localized (ref.)	1		
Regional by direct extension	0.77	0.14–4.16	0.76
Regional by lymph node	0.81	0.12–5.22	0.82
Regional by both direct extension and lymph node	2.15	0.22–20.70	0.51
Regional nos	1.26	0.06–27.56	0.88
Distance metastasis/systematic disease	3.29	1.22–8.85	0.02
Topography			
Main bronchus (ref.)	1		
Upper lobe	1.67	0.38–7.29	0.50
Middle lobe	2.67	0.34–21.08	0.35
Lower lobe	1.42	0.31–6.58	0.65
Overlapped lesion	1.45	0.17–12.25	0.73
Not otherwise specified	2.23	0.50–10.01	0.30
Laterality			
Left (ref.)	1.00		
Not paired	1 (empty)		
Right origin	1.04	0.54–2.03	0.90
Bilateral (side of origin unknown or single primary)	0.25	0.04–1.51	0.13
Paired no information concerning laterality	0.84	0.20–3.55	0.81
Year of diagnosis			
2009 (ref.)	1.00		
2010	0.96	0.41–2.23	0.92
2011	2.14	0.77–5.95	0.14
2012	1.10	0.45–2.67	0.83
2013	0.36	0.14–0.93	0.04

completeness and accuracy of SCR's data are questionable, and the results may not be generalizable to other populations.

A major strength of our study is the use of data from the SCR, which is a population-based registry with nation-wide coverage of diagnosed cancers that uses standardized methods for data collection.

As a conclusion, this study showed a strong effect of disease stage on mortality, especially in SCLC. It also showed that, majority of lung cancer patients in Saudi Arabia are diagnosed at an advanced stage. For establishment of a Saudi-specific lung cancer screening guidelines, further research on economic analysis, cost-effectiveness, safety, and complication will be required to make a final recommendation on lung cancer screening.

Acknowledgements

We acknowledge with gratitude the efforts of the Saudi Cancer Registry who provided us with the data to conduct this research. We also thank Ms. Yasmin Zaki who provided editing support for the manuscript.

References

[1] Torre LA et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87–108.
[2] Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3(8):819–31.
[3] Gibson GJ et al. Respiratory health and disease in Europe: the new European Lung White Book. Eur Respir J 2013;42(3):559–63.
[4] Müller-Hermelink HK., et al.. Pathology & genetics, tumours of the lung, pleura, thymus and heart. World Health Organization Classification of Tumors, IARC Press, Lyon, France, 2004: pp. 146–147.
[5] Mathers CD, T Boerma, DM Fat. Global and regional causes of death. British medical bulletin, 2009: p. ldp028.
[6] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLOS med 2006;3(11):e442.
[7] Saudi Cancer Registry, Cancer Incidence Report. Saudi Health Council, 2013.
[8] Ridge CA, McErlean AM, Ginsberg MS, Epidemiology of lung cancer. in Seminars in interventional radiology. 2013, Thieme Medical Publishers.
[9] Roudi F, Population trends and challenges in the Middle East and North Africa. 2001.
[10] Mourshed MV, Hediger, Lambert T, Gulf cooperation council health care: challenges and opportunities. Global competitiveness reports, 2006.
[11] Ng M et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA 2014;311(2):183–92.
[12] World Health Organization, WHO report on the global tobacco epidemic, 2015: Raising taxes on tobacco. 2015.
[13] M Ellis P, Vandermeer R, Delays in the diagnosis of lung cancer, Journal of thoracic disease, 2011. 3(3): pp. 183–188.
[14] Moyer VA. Screening for lung cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160(5):330–8.
[15] Kathuria H et al. Updates and controversies in the rapidly evolving field of lung cancer screening, early detection, and chemoprevention. Cancers 2014;6(2):1157–79.
[16] Saudi Cancer Registry, Cancer Incidence Report. 2010.
[17] Travis WD, Brambilla E, Geisinger KR. Histological grading in lung cancer: one system for all or separate systems for each histological type? Eur Respir J 2016;47(3):720–3.
[18] Travis WD et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10(9):1243–60.
[19] Campobasso O et al. Survival rates of lung cancer according to histological type. Br J Cancer 1974;29(3):240.
[20] Chansky K et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. J Thorac Oncol 2009;4(7):792–801.
[21] Tammemägi MC et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368(8):728–36.
[22] Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer 2001;31(2):139–48.
[23] Khuder SA et al. Effect of cigarette smoking on major histological types of lung cancer in men. Lung Cancer 1998;22(1):15–21.
[24] Govindan R et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24(28):4539–44.
[25] Putila J, Remick SC, Guo NL. Combining clinical, pathological, and demographic factors refines prognosis of lung cancer: a population-based study. PLoS One 2011;6(2):e17493.

[26] Sculier J-P, et al.. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. Journal of Thoracic Oncology, 2008. 3(5): pp. 457–466.
[27] Office for National Statistics, Cancer survival in England: adults diagnosed in 2009 to 2013, followed up to 2014, 2015.
[28] Kandioler D et al. Growing clinical evidence for the interaction of the p53 genotype and response to induction chemotherapy in advanced non–small cell lung cancer. J Thorac Cardiovasc Surgery 2008;135(5):1036–41.
[29] Esteller M et al. Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. Cancer Res 1999;59(1):67–70.
[30] Tong J et al. Expression of p16 in non-small cell lung cancer and its prognostic significance: a meta-analysis of published literatures. Lung Cancer 2011;74 (2):155–63.
[31] Rosell R et al. K-ras genotypes and prognosis in non-small-cell lung cancer. Ann Oncol 1995;6(suppl 3):S15–20.
[32] Lam VK et al. Obesity is associated with long-term improved survival in definitively treated locally advanced non-small cell lung cancer (NSCLC). Lung Cancer 2017;104:52–7.
[33] Ou S-HI, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. J Thorac Oncol 2009;4 (1):37–43.
[34] Alyson L Mahar CC, Lisa M McShane, Susan Halabi, Hisao Asamura, Ramon Rami-Porta, Patti A Groome, Refining prognosis in lung cancer: a report on the quality and relevance of clinical prognostic tools. Journal of Thoracic Oncology, 2015. 10(11): pp. 1576–1589.