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Association Between Patient Characteristics and Histopathological Features of Lung Cancer At RSUP Dr. Mohammad Hoesin Palembang

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ABSTRACT

Introduction. Lung cancer is the uncontrolled growth of malignant cells by the body in lung tissue and is caused by genetic mutations and changes in protein synthesis in normal cells. Histopathological features of lung cancer include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and other types. Early detection, as well as prevention, needs to be done in high-risk communities with the aim of reducing the number of events. This study aims to determine the relationship between sociodemographic factors and histopathological features of lung cancer. **Methods.** This study is an analytic observational study with a cross-sectional design. The research sample is in the form of secondary data from the Department of Anatomical Pathology and Medical Record Installation for 2019-2021. The research was conducted at Dr. Mohammad Hoesin Palembang. The sampling technique was carried out by total sampling. **Results.** Most of the respondents were in the age group >45 years (84.1%), male (78.3%), had no history of smoking (60.9%), the predominant main complaint was shortness of breath (63, 8%), the most common histopathological picture is adenocarcinoma. There was no significant relationship between age (p=0.998), gender (p=0.736), smoking history (p=0.572) and histopathological features of lung cancer patients. **Conclusion.** There was no significant relationship between age, sex and smoking status on the histopathological features of lung cancer.

1. Introduction

Lung cancer is the uncontrolled growth of malignant cells by the body in lung tissue and is caused by genetic mutations and changes in protein synthesis in normal cells.[1,2] The incidence and mortality of lung cancer reaches 13% of all cancer diagnoses. [3] Lung cancer is the second most common cancer most frequently diagnosed after breast cancer with a prevalence of 11.4% and is one of the main causes of mortality with a total of 1.8 million deaths (18%).[4] Globally, it is estimated that more than two million new cases and 1.7 million deaths due to cancer lung cancer in 2018. The highest mortality rates and incidence of lung cancer are usually in high-income countries, particularly the United States and European countries. In America in 2017 new cases reached 222,500 (116,990 men and 105,510 women). In 2018 the number of new cases increased to 234,030 (83,550 men and 70,500 women), as well as 154,050 deaths.[3,5]

The 2020 World Health Organization noted that the total cases of lung cancer in Indonesia ranked third highest (8.8%) after breast cancer (16.6%) and cervical cancer (9.2%).[6] The characteristics of lung cancer incidence are influenced by male sex, smokers, with histopathological type of adenocarcinoma. Patients with lung cancer in Indonesia are generally under the age of 40.[7]

Lung cancer incidence and mortality are closely related to smoking patterns. Adenocarcinoma is the most common histopathological subtype found in both men and women. Squamous cell lung cancer is the second most common subtype, comprising 20% of primary lung neoplasms. Small cell lung cancer is generally associated with a history of smoking and causes paraneoplastic syndromes.[8] The risk of lung cancer is based on factors such as age, number, duration of smoking, and environmental exposure. As many as 55 substances in cigarette smoke have been considered carcinogenic by the International Agency for Research on Cancer, including polycyclic aromatic hydrocarbons. Activation of these substances leads to the formation of DNA and gene methylation, alteration of DNA sequences, amplification or deletion of DNA segments,

as well as chromosomal abnormalities. The relative risk of lung cancer in smokers varies (10-30 times), based on the number of cigarettes consumed. The UK's Health Improvement Network shows that women who smoke heavily (>20 cigarettes daily) have a greater chance of developing lung cancer than men even though their smoking history is comparable.[8]

Histopathological distribution of lung cell cancer based on smoking history shows that squamous cell carcinoma and small cell carcinoma are more closely related to smoking than other histopathological types. Squamous cell carcinoma mostly occurs in men, while adenocarcinoma occurs in women.[9] Guarga et al in 2021 also reported that all histopathological types are related to smoking. The strongest idea is squamous cell carcinoma and small cell carcinoma, while the weakest idea is adenocarcinoma. Filters, tar cigarettes, and nicotine can increase inhalation and lead to a more peripheral distribution of tobacco smoke in the lungs.[10,11]

Age is one of the main risk factors for lung cancer. The results of a lung cancer study at Sanglah Hospital in Denpasar 2017-2018 stated that most sufferers were from the age group of 46-55 years (31.5%). Most of the sexes were men (61.4%). [12] A study by Albasri in 2019 reported adenocarcinoma shows a male predominance with a ratio of 2.9:1 (male: female) and an average age of 60.7 ± 14.8. Squamous cell carcinoma was mostly found in men with a ratio of 4.8:1 and the mean age of the patients was 64.7 ± 15.1. Small cell carcinoma is the rarest type, accounting for 16.7% of cases where the average age of the patient is 57 years.[13]

Poor survival rates are related to the diagnosis of lung cancer that has entered an advanced stage. This delay makes survival beyond a few years highly unlikely. Early detection as well as prevention need to be carried out in high-risk communities with the aim of reducing the number of events, ensuring the identification of early-stage malignancies, and reducing mortality.[14] These goals can be achieved by collecting information data about the characteristics of patients and their relationship with the histopathological features of lung cancer. Data and information regarding the growth, spread, and treatment of lung cancer are still very limited. Therefore, researchers are interested in carrying out studies at RSUP Dr. Mohammad Hoesin as the referral health center for the city of Palembang to add and strengthen available data related to patient characteristics and their relationship with the histopathological picture of lung cancer. Thus, government and agency targets regarding early detection and prevention by health workers can be more effective for people at high risk of developing lung cancer. This study aims to determine and analyze the relationship between patient characteristics and histopathological features of lung cancer in RSUP Dr. Mohammad Hoesin Palembang in 2019-2021.

2. Methods

This study design is cross-sectional. Data were obtained from the KSM Department of Anatomical Pathology and Medical Record Installation of RSUP Dr. Mohammad Hoesin. Samples in this study are lung cancer patients at RSUP Dr. Mohammad Hoesin from January 2019 to December 2021 who had anatomical pathology data and complete medical records, including age, sex, smoking history, chief complaint, tumor location, stage, and histopathological features were included in this study.

Samples were taken using a total sampling technique. The data that has been collected is then recorded according to the variables to be studied. There are two variables in this study, namely the histopathological description of lung cancer patients at Dr. Mohammad Hoesin in 2019-2021 as the dependent variable and age, gender, and smoking history of lung cancer patients at Dr. Mohammad Hoesin 2019-2021 as the independent variable. The data obtained will then be processed and analyzed using the SPSS.

3. Results

Table 1 shows that most patients were in the age group >45 years, namely 58 people (84.1%) with an average age of 46-55 years and 11 other people were in the age group ≤45 years (15.9%). The majority of patients were male, namely 54 people (78.3%). Most of the respondents did not have a history of smoking, totaling 42 patients (60.9%). Meanwhile, 27 other patients (39.1%) had a positive history of smoking. The distribution of patients based on their chief complaint showed shortness of breath was the most dominant complaint with 44 people (63.8%). Table 2 shows that most of the patients had histopathological features of adenocarcinoma, namely 36 patients (52.2%).

Table 3 shows that the majority of lung cancer patients had a histopathological picture of adenocarcinoma, namely 36 patients (52.2%) with 6 respondents (8.7%) being in the age group ≤ 45 years and 30 other respondents (43.5%) are in the age group >45 years. The association between age and histopathological features of lung cancer patients had a p-value of 0.998, which means that there was no significant association between age and histopathological features of lung cancer patients.

Table 4 shows that the majority of male patients had a histopathological picture of adenocarcinoma, namely in 24 patients (34.8%), 18 patients had a histopathological picture of squamous cell carcinoma (26.1%), 7 patients had a histopathological picture of small cell carcinoma (10.1%) and 5 other patients (7.2%) had other types of histopathology.

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Table 1. Characteristics of study patients

Characteristics	n	%
Age		
≤45 years	11	15.9
>45 years	58	84.1
Sex		
Male	54	78.3
Female	15	21.7
Smoking history		
Smoker	27	39.1
Non-smoker	42	60.9
Chief complaint		
Shortness of breath	44	63.8
Coughing	14	20.3
Chest pain	11	15.9
Total	69	100.0

Table 2. Histopathological features of lung cancer in study patients

Histopathological feature	n	%
Squamous Cell Carcinoma (SCC)	20	29.0
Adenocarcinoma (AC)	36	52.2
Small Cell Carcinoma	7	10.1
Other types	6	8.7
Total	69	100.0

Table 3. Association between age and histopathological features of lung cancer

Age (yrs)	Histopathological features				p
	SCC n (%)	AC n (%)	Sm n (%)	Other n (%)	
≤ 45	2 (2.9)	6 (8.7)	1 (1.4)	2 (2.9)	0.998
>45	18 (26.1)	30 (43.5)	6 (8.7)	4 (5.8)	
Total	**20 (29.0)**	**36 (52.2)**	**7 (10.1)**	**6 (8.7)**	

*SCC: squamous cell carcinoma, AC: adenocarcinoma, Sm: small cell carcinoma

Table 4. Association between sex and histopathological features of lung cancer

Sex	Histopathological features				p
	SCC n (%)	AC n (%)	Sm n (%)	Other n (%)	
Male	18 (26.1)	24 (34.8)	7 (10.1)	5 (7.2)	0.736
Female	2 (2.9)	12 (17.4)	0 (0.0)	1 (1.4)	
Total	**20 (29.0)**	**36 (52.2)**	**7 (10.1)**	**6 (8.7)**	

*SCC: squamous cell carcinoma, AC: adenocarcinoma, Sm: small cell carcinoma

Table 5. Association between smoking history and histopathological features of lung cancer

Smoking	Histopathological features				p
	SCC n (%)	AC n (%)	Sm n (%)	Other n (%)	
Smoker	11 (15.9)	9 (13.0)	4 (5.8)	3 (4.3)	0.572
Non-smoker	9 (13.0)	27 (39.1)	3 (4.3)	3 (4.3)	
Total	**20 (29.0)**	**36 (52.2)**	**7 (10.1)**	**6 (8.7)**	

*SCC: squamous cell carcinoma, AC: adenocarcinoma, Sm: small cell carcinoma

In female patients, the most common histopathological appearance was adenocarcinoma in 12 patients (17.4%), 2 patients had squamous cell carcinoma histopathology (2.9%), and 1 patient (1.4%) had other types of histopathology. The association between sex and histopathological features of lung cancer patients in this study had a Kolmogorov-Smirnov test p-value of 0.736, which means that there was no significant association between sex and histopathological features of lung cancer patients.

Table 5 shows that the majority of patients with a positive smoking history had a histopathological picture of squamous cell carcinoma, namely in 11 patients (15.9%), 9 patients had a histopathological picture of adenocarcinoma (13%), 4 patients had a histopathological picture of small cell carcinoma (5.8). %), and 3 other patients (4.3%) had other types of histopathology. Patients who did not have a history of smoking, the most common histopathological picture was adenocarcinoma in 27 patients (39.1%), 9 patients (13.0%) had squamous cell carcinoma histopathology, 3 patients (4.3%) had small cell histopathology carcinoma, and 3 other patients (4.3%) had other types of histopathology. The relationship between smoking history and histopathological features of lung cancer patients in this study had a Kolmogorov-Smirnov test p-value of 0.572, which means that there was no significant relationship between smoking history and histopathological features of lung cancer patients.

4. Discussion

The dominant age distribution of lung cancer patients in this study was the age group >45 years, namely 58 people (84.1%) (average age 46-55 years) with a minimum age of 18 years and a maximum of 79 years. Lung cancer is a cancer that is often experienced in individuals with older ages. The incidence rate increases markedly around the ages of 45-49 and peaks in the 85-89 age group for men and in the 80-84 age group for women. Various publications have reported that the incidence of lung cancer shows a correlation with age and the highest incidence rates are found in the elderly. The United Kingdom Cancer Research portal reports that between 2013 and 2015, >40% of lung cancer cases were diagnosed in the age group ≥75 years. Age-specific incidence rates began to increase in the age group of 45–49 years, with the highest rates being found in the age group 85–89 years in men and 80–84 years in women. The highest incidence of lung cancer in men was 585.9 per 100,000 people aged 85–89 years, while the highest incidence in women was 365.8 per 100,000 people aged 75–79 years.[15,16]

Aging involves changes in physiological function and an increased risk of various diseases. The respiratory system undergoes a number of structural, physiological and immunological changes with age. As a result of this decrease in physiological function, substances that play a role in the pathogenesis of lung cancer can accumulate and can increase the risk of lung cancer in the elderly.[17] Increasing age is associated with higher somatic mutations (single nucleotide variants and small insertions/deletions). In most cancer types, with an estimated increase of 0.077 mutations per megabase per year. Spontaneous deamination of the 5-methylcytosine to thymine transition (C>T), often cited as a signature mutation dominates the increasing mutational burden associated with aging. In addition, signs of DNA damage are more likely to be found in older individuals. In addition to somatic mutations, somatic copy number (SCNA) changes also increase with age-related changes in the occurrence of certain types of cancer. Recent genome-wide association (GWA) studies have been able to identify several genetic polymorphisms underlying lung cancer risk by utilizing up to one million nucleotide polymorphism markers (SNP) to identify common genetic variations. The main susceptibility at the three loci identified were in the 15q25, 5p15 and 6p21 regions. The tumor mutation burden (total number of somatic mutations) increases with age. Tumor-specific genomic EGFR changes differ depending on age. Although mutations of exon 21 L858R are more common in the older population, deletions of exon 19 are more common in younger patients. KRAS mutations are common in NSCLC (20–40%), tend to be associated with poorer clinical outcomes and are more common in the older population, although the reported age differences are inconsistent.[16,17,18] However, this variation in mutation frequency may be largely explained by differences in study populations, as KRAS mutations are commonly present in lung cancer survivors who smoke and those with non-squamous NSCLC. The presence of BRAF mutations, which can be targeted by BRAF inhibitors, is rare and does not clearly differ by age, although BRAF-specific mutation V600E may be more common in the elderly.[19,20,21]

The most common histopathological feature of male lung cancer patients in this study was squamous cell carcinoma, while the most histopathological feature in women was adenocarcinoma. The results of this study showed that there was no significant relationship between gender and histopathological features of lung cancer patients. The results of this study are in accordance with previous reports which show that adenocarcinoma in women is one of the most common histopathological types of lung cancer with an age distribution in each country, namely in Denmark (age 55-64 years), Germany (age 30-64

years), New Zealand (30-64 years) and the Netherlands (30-34 years and 50-64 years).[20,22,23,24]

Currently, adenocarcinoma is the most common subtype, in both men and women. In women, up to 80% of lung cancers are adenocarcinomas, compared to only 60% in men, which are attributable to differences in smoking habits. Cancer in people who have never smoked is also more common in women. The likelihood of predominantly lepidic adenocarcinoma (former bronchoalveolar carcinoma; cancer cells spread along alveolar walls) increases 2-4-fold in women. The 5-year survival rate of all lung cancer stages is 19.7% in men and 27.8% in women (2014–2018), regardless of stage, age, or histological subtype. This difference cannot be explained by the fact that women generally have a longer life expectancy. This may be in part explained by earlier diagnosis of lung cancer in women, different histopathology, fewer comorbidities, better response to chemotherapy (but possibly at a higher cost of toxicity), and better prognosis in non-smokers.[24,25,26]

In this study, male patients were more likely than female patients to be diagnosed at stage 3-4. Differences in the percentage of males versus females diagnosed with stage 3–4 was negatively correlated with an increase in female smoking with squamous cell carcinoma and did not correlate with rates of cancer in females, or differences between male and female cancers. While the total incidence of lung cancer is similar between men and women, there are differences in the incidence of certain types of lung cancer between the sexes, with men having a higher incidence of small cell carcinoma and squamous cell carcinoma, and women having a higher rate of adenocarcinoma. [27,28] Adenocarcinoma generally occurs on the outside of the lung, which makes it more difficult to diagnose in its early stages. Despite these gender-based differences, in recent decades, all forms of lung cancer have increased among women. While the majority were possibly due to increased smoking among women, the higher incidence rates of lung cancer among women are more than would be expected from increased smoking prevalence alone.[28,29]

The high rate of adenocarcinoma in non-smokers suggests a possible etiologic factor other than smoking.[30,31] Factors that have been considered include gender-specific genetic alterations, second-hand smoke, age at nicotine addiction (women start smoking at a later age), differential metabolism of nicotine in women, occupational exposure, diet, and chronic obstructive pulmonary disease. Female lung cell lines show higher CYP1A1 basal mRNA expression and also an increase in CYP1 enzyme activity upon exposure to benzo(α)-pyrene compared to those from males and there are differences in the rate of formation of DNA adducts in adenocarcinoma cell lines derived from females. There is a positive correlation between estrogen, smoking, and adenocarcinoma with respect to lung cancer development.[30,32,33]

5. Conclusion

The majority of lung cancer patients were >45 years old (58 people, 84.1%) with an average age of 46-55 years. Lung cancer was often found in males, as many as 54 people (78.3%) and patients who did not have a history of smoking, as many as 42 people (60.9%). The most common chief complaint in patients with lung cancer was shortness of breath, found in 44 people (63.8%). The most common histopathological picture found in lung cancer patients was adenocarcinoma, which was 36 people (52.2%). There was no significant relationship between age, sex, and smoking history with histopathological features of lung cancer.

6. References

1. Nasional KPK. Kanker paru. Pedoman Nasional Pelayanan Kedokteran. 2017;59.
2. Inamura K. Lung cancer: understanding its molecular pathology and the 2015 WHO classification. Front Oncol 2017; 7:7.
3. American Cancer Society. Lung cancer statistics: how common is lung cancer. American Cancer Society [Internet]. 2020 Feb 14 [cited 2022 Jun 17]. Available from: https://www.cancer.org/cancer/lu ng-cancer/about/key- statistics.html
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021 May;71(3):209–49.
5. American Cancer Society. Cancer facts and figures 2017. Genes Dev 2017;21(20):2525–38.
6. Andriani D. Ini jenis kanker yang paling banyak diderita masyarakat indonesia. Lifestyle.bisnis.com [Internet]. 2020 Jan [cited 2022 Jun 17]. Available from: https://databoks.katadata.co.id/da tapublish/2021/06/29/ini-jenis- kanker-yang-paling-banyak- diderita-penduduk-indonesia%0A
7. Purnamawati P, Tandrian C, Sumbayak EM, Kertadjaja W. Tinjauan pustaka: analisis kejadian kanker paru primer di Indonesia pada tahun 2014-2019. J Kedokt Meditek 2021 Jun;27(2):164–72.
8. Barta JA, Powell CA, Wisnivesky JP. Global

epidemiology of lung cancer. Ann Glob Heal 2019; 85(1):1–16.
9. Zhong YJ, Wen YF, Wong HM, Yin G, Lin R, Yang SY. Trends and patterns of disparities in burden of lung cancer in the United States 1974-2015. Front Oncol 2019 May;9:404.
10. Tsukazan MTR, Vigo Á, Silva VD da, Barrios CH, Rios J de O, Pinto JA de F. Lung cancer: changes in histology, gender, and age over the last 30 years in Brazil. J Bras Pneumol 2017 Sep;43(5):363–7.
11. Guarga L, Ameijide A, Marcos- Gragera R, Carulla M, Delgadillo J, Borràs JM, et al. Trends in lung cancer incidence by age, sex and histology from 2012 to 2025 in Catalonia (Spain). Sci Rep 2021 Dec;11(1):23274.
12. Pradnyaandara IBMA, Saputra H, Dewi IGASM, Sumadi IWJ. Karakteristik pasien karsinoma paru dirsup sanglah denpasar tahun 2017-2018. JMU J Med Udayana 2020;9(11):81–2.
13. Albasri AM. A histopathological analysis of lung cancers: An 11- year retrospective study from Al-Madinah Al-Munawwarah, Saudi Arabia. Saudi Med J 2019 May;40(5):503–6.
14. Babar L, Modi P, Anjum F. Lung cancer screening. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan 19 [cited 2022 Jun 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537283/
15. U.S. Department of Health and Human, Services National Institutes of Health, National Cancer Institute. Anatomy of the lung. SEER Training [Internet]. 2018 Sep 20 [cited 2022 Jun 30]. Available from: https://training.seer.cancer.gov/lung/anatomy/
16. Chaudhry R, Bordoni B. Anatomythorax lungs. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan 31 [cited 2022 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470197/
17. Brown K, Lynch DT. Histology, lung. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 May 8 [cited 2022 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534789/
18. Zhang C, Myers JL. Atlas of lung pathology. New York: Springer; 2018.
19. Rejeki M, Pratiwi EN. Diagnosis dan prognosis kanker paru, probabilitas metastasis dan upaya prevensinya. In: Universitas 'Aisyiyah Surakarta, editors. Proceeding of The 12th University Research Colloquium 2020;2015 Sep 12; Surakarta, Jawa Tengah. Sukakarta: Universitas 'Aisyiyah Surakarta; 2020.p.73–8.
20. Siddiqui F, Vaqar S, Siddiqui AH. Lung cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 May 5 [cited 2022 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482357/
21. Sari FP, Satrio K, Sastrawan IGG. Transient receptor potential ankyrin 1 (TRPA1) sebagai target terapi mutakhir dalam penatalaksanaan small cell lung cancer. Essence Sci Med J 2018;1:30–5.
22. Robot RY, Durry MF, Kairupan CF. Morfologi, patogenesis, dan imunoterapi kanker paru tipe adenokarsinoma. Med Scope J 2021 May;3(1):74–82.
23. Purnamawati, Tandrian C, Sumbayak EM, Kertadjaja W. Analisis kejadian kanker paru primer di indonesia pada tahun 2014-2019. J Kedokt Meditek 2021;27(2):164–72.
24. UK's National Health Service. Lung cancer: causes. National Health Service [Internet]. 2019 Aug 15 [cited 2022 Jun 20]. Available from: https://www.nhs.uk/conditions/lung-cancer/causes/
25. American Cancer Society. Lung cancer risk factors: smoking & lung cancer. Cancer [Internet]. 2019 Oct 1 [cited 2022 Jun 17]. Available from: https://www.cancer.org/cancer/lung-cancer/causes-risks-prevention/risk-factors.html
26. Centers for Disease Control and Prevention (CDC). What are the risk factors for lung cancer?. Centers for Disease Control and Prevention (CDC) [Internet]. 2021 Oct 18 [cited 2022 Jun 20]. Available from: https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm
27. US Pharmacist. Lung cancer pathophysiology, etiology, and risk factors. US Pharmacist [Internet]. 2021 Nov 11 [cited 2022 Jun 30]. Available from: https://www.uspharmacist.com/article/lung-cancer- pathophysiology-etiology-and- risk-factors
28. Romaszko A, Doboszynska A. Multiple primary lung cancer: a literature review. Adv Clin Exp Med 2018 Apr 19;27.
29. Basumallik N, Agarwal M. Small Cell Lung Cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 July 12 [cited 2022 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482458
30. WHO Classification of Tumours Editorial Board.

No title. In: WHO classification of tumours thoracic tumours 5th ed. Lyon: International Agency for Research on Cancer Press; 2021.
31. UK's National Health Service. Lung cancer. National Health Service [Internet]. 2019 Aug 15 [cited 2022 Jun 20]. Available from: https://www.nhs.uk/conditions/lung-cancer/
32. Myers DJ, Wallen JM. Lung Adenocarcinoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 June 21 [cited 2022 Jun 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519578/
33. Harvard Health Publishing. Adenocarcinoma of the lung. Harvard Health Publishing [Internet]. 2020 Jun 22 [cited 2022 Jun 20]. Available from: https://www.health.harvard.edu/a_to_z/adenocarcinoma-of-the- lung-a-to-z