Lung Cancer in Pakistan

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Epidemiology

Pakistan is the fifth most populous country in the world with an estimated population of more than 207 million located in South Central Asia between the Himalayas and Arabian Gulf. It has a population density of 260 per km^2 with 10 major metropolitan cities. Although each of these 10 cities has a population of more than 10 million, only 36.4% of the total population lives in urban areas. Administratively, it consists of four provinces and federal capital territory as illustrated in Figure 1.[1] Pakistan ranks as a low- to middle-income country with a gross national income per capita of USD 1410 according to the World Bank 2020 data.[2]

In the absence of a population-based cancer registry, reliable statistics on the incidence, prevalence, and mortality of lung cancer in Pakistan are not known. Nevertheless, two regional cancer registries, such as Karachi Cancer Registry (KCR) and Punjab Cancer Registry, provide vital statistics on lung cancer from the two largest metropolitan cities of Pakistan, that is, Karachi and Lahore.[3,4] Furthermore, GLOBOCON 2020 report provides estimates of incidence derived from the weighted and simple average of Pakistan, South Karachi (1998–2002, CI5 Vol. IX), Punjab (2010–2012) cancer registries and neighboring country rates applied to the 2020 national population.[5] As such, lung cancer accounts for 10,538 new cases from both sexes and all ages combined constituting approximately 5.9% of all new cancer cases. This makes lung cancer the second most common cancer in men and third most common cancer in both sexes combined in Pakistan.[5] Data from KCR 1995 to 2002 revealed the age-standardized incidence rates (ASIRs) per 100,000 population for cancer of the lung of 21.4 and 2.9 in males and females, respectively, in 1995 to 1997 and 25.5 and 4.2 per 100,000 in males and females, respectively, in 1998 to 2002 suggesting a 16% increase in men and 31% increase in women during this eight-year period.[6] The Punjab Cancer Registry in the Lahore district during 2010 to 2012 estimated the ASIR for lung cancer of 4.6 and 1.2 per 100,000 in males and females, respectively, which was much lower than the KCR data.[7] The noted difference is likely due to the geographic and lifestyle differences between the two regions as the use of tobacco and other tobacco-containing products was noted to be higher in KCR data. The GLOBOCON 2020 also provides estimates of national ASIR and revealed a rate of 11.2 and 2.7 for males and females, respectively, according to the methodology noted previously. Regardless of which data set to be used, the incidence of lung cancer is felt to be steadily rising in Pakistan and projected to increase to 19,140 new cases per year in 2040 according to the GLOBOCON 2020.[5] There are currently no mortality data available on lung cancer. Available data on mortality rates are estimated from national incidence estimates by modeling, using incidence: mortality ratios derived from cancer registry data in neighboring countries. On the basis of this method, lung cancer accounts for approximately 9.6% of all cancer-related deaths in 2020 with the age-standardized mortality rates of 6.2 per 100,000 population for both sexes combined.[5]

One of every two to three middle-aged men in Pakistan smoke cigarettes.[8] In 1998, a nationwide survey in Pakistan had found that 21.6% of the subjects aged 15 years or more were smokers with a higher proportion among males (36%) than females (9%), whereas a cross-sectional survey in 2004 reported an overall 34% prevalence of current smokers, with increased rates owing to the earlier age of onset (15–29 y) (OR = 4.2, 95% confidence interval [CI]: 2.1–7.3), unmarried (OR = 3.1, 95% CI: 1.9–5.4), educated (OR =

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Disclosure: The authors declare no conflict of interest, and there has been no significant financial support for this work that could have influenced its outcome.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.01.009

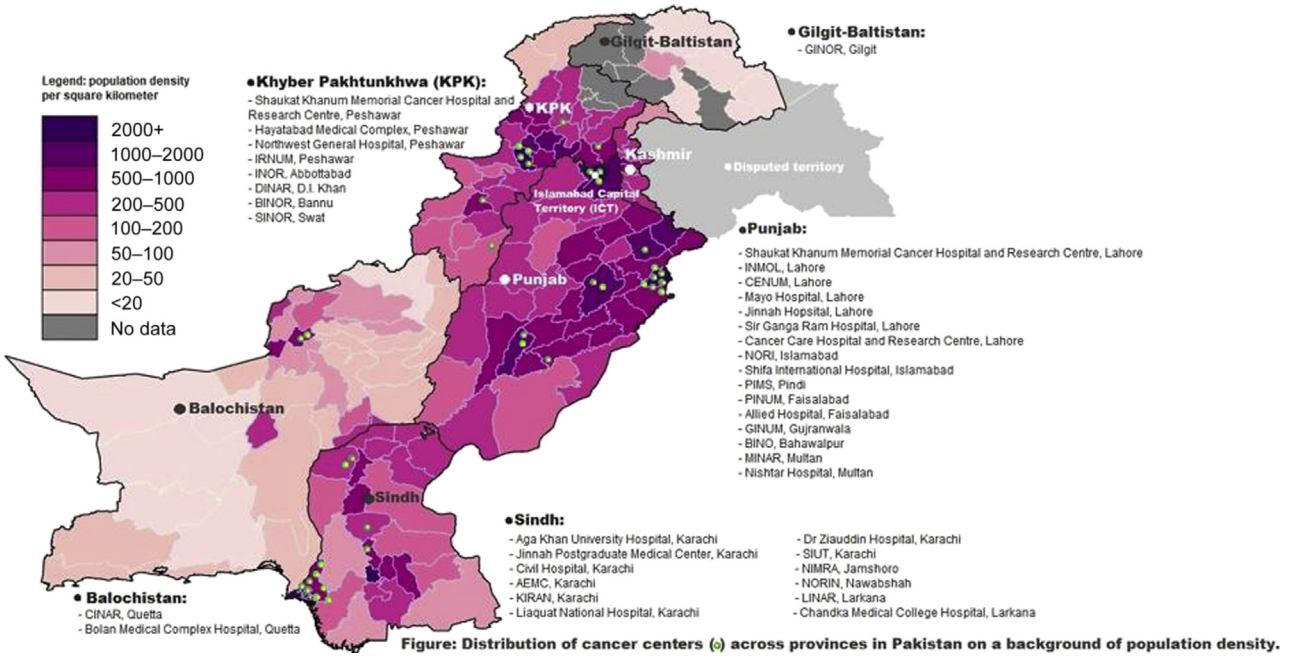

Figure 1. Distribution of cancer centers across provinces in Pakistan on a background of population density.

2.0, 95% CI: 1.2–3.3), and being student (OR = 3.2, 95% CI: 1.8–5.4).[9,10] Most (55%) began smoking when younger than 25 years, and 42% used tobacco in other forms as well.[10] It accounts for approximately 108,800 deaths from all tobacco-related diseases each year. Therefore, tobacco constituted a substantial proportion (20%) of population-attributable fraction of cancer-related deaths in 2017.[11] The National Health Survey of Pakistan revealed that tobacco use was common in Pakistan, with 54% of men and 20% of women using tobacco in one form or the other; prevalence of smoking increased with age among both males and females.[12] Men in the age range of 25 to 44 years had the highest prevalence of smoking (cigarettes and *beedis*), whereas, in the case of women, prevalence was highest between the ages of 45 and 64 years. *Huqqa* and chewing tobacco, however, was the most common among men and women aged 65 years and more. On the basis of this survey, smoking was more common in rural compared with urban areas and among the illiterate as opposed to the literate population.[12] A cross-sectional survey on a random sample of 632 urban school-going children revealed that 28% of the urban adolescents between the ages of 15 and 18 years currently smoke. Of these, 75% are regular smokers and 58% have been smoking for the last 2 years; 92% of those who smoke were aware of the hazards of smoking and 78% had even tried to give up.[13] The Cigarettes (Printing of Warning) Ordinance introduced in 1979 made it mandatory to have written warnings on all cigarette packs. In 2002, it was revised to Prohibition of Smoking Ordinance 2002, imposing a ban on sale to minors, restrictions on tobacco advertisement, declaration of schools as smoke free, and ban on tobacco use in all public places, transport, and indoor workplaces.

A case-control study involving 400 patients with lung cancer from all over the country revealed that smoking ($X^2 = 333.8$, $p \leq 0.0000001$), pesticide exposure ($X^2 = 50.9$, $p \leq 0.0000001$), and exposure to diesel exhaust ($X^2 = 51.8$, $p \leq 0.0000001$) were the top determinants of developing lung cancer in Pakistan.[14]

Screening for Lung Cancer

The Pakistan Cancer Control Project initiated by the WHO focal person categorized Pakistan as a low level of resource situation. The National Action Plan for Non-Communicable Diseases in 2002 identified screening and early detection of cancer as one of its priority areas while pointing out that owing to existing resource scarcity and capacity issues no formal screening or early detection program could be initiated at a national level.[15] Focus on behavioral communication strategies, monitoring and control of potential risks from industrial settings, capacity building, and continued medical education of the health care providers were identified as the main elements of risk mitigation strategy for all cancers, including lung cancer. Nevertheless, in the fee-for-service private health care settings, low-dose computed tomography (CT) chest scans are available for screening purposes for high-risk populations as per the discretion of the practicing physician in the community.

Diagnosis

There are no high-quality studies available to reveal data on the current diagnostic and management approaches for lung cancer in Pakistan. In the absence of a primary care referral system, lack of multidisciplinary team meetings (MDTs) at most facilities, and overcapacity at public health care systems, diagnostic workup of a suspected patient with lung cancer varies widely depending on the health care setting, available expertise, and stage of the disease at presentation. Thus, there is a large disparity in the standards of care that exists in the government-run public health care facilities and private health care setups. A vast majority of patients present at an advanced stage of the disease owing to several reasons. Important factors in this regard are lack of access to proper diagnostic services, delays in timely appointment of the services, and delays in the diagnosis of lung cancer. Owing to the high prevalence of tuberculosis, misdiagnosis and empirical treatment with anti-tuberculous therapy is not uncommon and leads to delays in diagnosis and treatment. Chest radiograph and CT chest with contrast are most often available at most public- and private-run facilities and serve as the baseline noninvasive imaging modalities for most of the patients. Positron emission tomography-CT scan is available at only a few select tertiary care centers in the country, and only a few patients are able to avail this service. Fiber-optic bronchoscopy, CT, or ultrasound-guided transthoracic biopsy and mediastinoscopy are present in both public and private settings albeit with varying availability. Where indicated, patients undergo diagnostic thoracentesis with cytology instead of a transthoracic biopsy. The endoscopic bronchial ultrasound and endoscopic ultrasound for mediastinal staging are not widely available, limited only to a few tertiary care private hospitals. The detail of the infrastructure is provided in Table 1.

In terms of pathologic diagnosis, most of the patients in the public setups only get a morphologic review. Nevertheless, immunohistochemistry testing is routinely available in most of the private laboratories. Molecular testing is limited to EGFR mutations and ALK rearrangements and is available at a few private laboratories not accessible to most of the patients owing to cost issues. Next-generation sequencing for broad testing panel is not currently available in Pakistan; however, it can be performed as a sent-out test abroad through third-party vendors at the discretion of the treating oncologist.

Surgical Management

As most of the patients present with advanced-stage disease, curative surgical resection plays a very limited role in the management of lung cancer. Furthermore, expertise in thoracic oncologic surgery is limited to tertiary care centers in Pakistan. In one large retrospective study from a tertiary care center, only 2.3% of the patients with lung cancer were deemed resectable and underwent curative surgery at the time of initial presentation.[16] Similarly, staging mediastinoscopy was performed in only approximately 2.7% of patients. Nevertheless, video-assisted thoracoscopic surgery and exploratory thoracotomy for tissue biopsy and wedge resection are performed routinely for diagnostic purposes, when appropriate, in unresectable and advanced cases.

Radiation Therapy and Infrastructure in Pakistan

Radiotherapy is used in the treatment of lung cancer across all stages both in curative and palliative settings.[17] In stage I lung cancer, it can be used with curative intent with stereotactic ablative radiotherapy. It can also be used as curative treatment in patients with stage II and III lung cancers especially for patients with

Table 1. Health System Capacity[a]

Characteristic (Per 10,000 Patients With Cancer)	Year	Number
Number of external beam radiotherapy units (photon, electron)	2019	3.3
Number of CT scanners	2020	17.2
Number of MRI scanners	2020	4.6
Number of PET or PET/CT scanners	2020	0.3
Number of radiation oncologists	2019	1.8
Number of medical physicists	2019	n/a
Number of surgeons	2012	128.7
Number of radiologists	2019	57.5
Number of nuclear medicine physicians	2019	14.4
Number of treatments (surgery/radiotherapy/chemotherapy)	2019	2
Pathology services	2019	Generally available
Palliative care availability (community/home-based care)	2019	Not available

[a]WHO—Cancer Country Profiles Pakistan 2020.
CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

medical co-morbidities precluding surgery or for unresectable tumors.[18] Radiotherapy is also most often used in stage 4 lung cancer to control symptoms arising from metastatic disease or the primary site.[19]

At present, there are a total of 27 cancer centers across Pakistan offering radiotherapy for treatment of lung cancer.[20] There is a large variation in the range of radiotherapy services offered across these centers from 2D to 3D conformal radiotherapy techniques to modern and complex radiotherapy techniques including intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), and stereotactic ablative radiotherapy. Cyber knife/gamma knife is also offered in very few cancer centers in Pakistan.

Table 2 summarizes the range of radiotherapy treatments offered across the country in 2021.

This table indicates that there is increased demand for more radiotherapy centers offering modern radiotherapy treatments, including IMRT, VMAT, and stereotactic radio surgery/stereotactic radiotherapy. Most of the centers are still using conventional techniques, including 2D and 3D conformal radiotherapy techniques, which can increase toxicity from radiotherapy.

Only three centers are offering stereotactic radio surgery/stereotactic radiotherapy which are most often used for stage 1 cancer and to treat oligometastatic disease. Currently, only one cancer center is offering gamma knife/cyber knife treatment.

The current standard of care for radiotherapy for stage 2 and 3 lung cancers is to offer image-guided adaptive radiotherapy using IMRT/VMAT with 4D planning CT, image guidance from cone beam CT, and treatment gating software.[21] Nevertheless, only five centers have 4D planning CT and seven centers have cone beam computed tomography facility across Pakistan.

Positron emission tomography-CT has an established role in delineating target volumes for radical radiotherapy in lung cancer[22]; however, only nine centers across the country have this facility.

Table 2. Radiotherapy Equipment Across the Cancer Centers

Radiotherapy Equipment Across the Cancer Centers	Number
Megavoltage radiotherapy units (n = 27)	
Co-60	17
LINAC	
Standard with MLC	17
LINAC with SRT	3
Simulation	
Conventional simulator	16
CT simulator	17
4D-CT	5
RTPS	
2D	17
3D	17
IMRT/VMAT	17
SRT/SRS	3
Gamma knife/cyber knife	1
Image verification	
Port films	24
CBCT	7

2D, two-dimensional; 3D, three-dimensional; 4D, four-dimensional; Co-60, cobalt-60; CT, computed tomography, MLC, multileaf collimator; IMRT, intensity-modulated radiotherapy; VMAT; volumetric arc therapy; LINAC, linear accelerator; SRS, stereotactic radio surgery; SRT, stereotactic radiotherapy; CBCT, cone beam computed tomography; RTPS, radiotherapy treatment planning software.

Systemic Therapy for Advanced-Stage Disease

Not all chemotherapeutic agents endorsed by best practice consensus guidelines are currently available in Pakistan. Most, if not all, of the cost of systemic therapy is borne out of pocket by the patients regardless of public or private setting. Government-run national health insurance initiatives cover only the cost of hospitalization. The data suggest that these benefits are not properly availed owing to low insurance literacy among the beneficiaries and lack of empaneled private providers.[23] Furthermore, the penetration of private insurance remains very low in the Pakistani population.[23] Therefore, choice and duration of systemic therapy are dependent heavily on the individual's affordability and access to therapeutic agents in both the private and public health care setups. In this regard, a large disparity, reflective of income inequality, exists in the standard of care ranging from the state of the art systemic therapy using imported drugs to abject inability to afford any meaningful treatment at all. This has led to rationing of health care services at certain health systems, for example, a large charity-based comprehensive cancer hospital trust that serves as a major referral center to a large population of Pakistan developed institutional guidelines using a cost-benefit approach to treat younger and potentially curable patients with available generic chemotherapy and radiotherapy while allocating most of older patients and patients with advanced cancer to palliative therapy alone.[24] Observations of community practice inform that taxane-based platinum doublet is preferred over pemetrexed in which cost becomes a major issue. A general schema outlining the most common practices in resource-deficient and resource-proficient (mostly private) setups are found in Figure 2*A* and *B*, respectively. The approved antineoplastic agents by the Drug Regulatory Authority of Pakistan used in the treatment of lung cancer are found in Table 3.

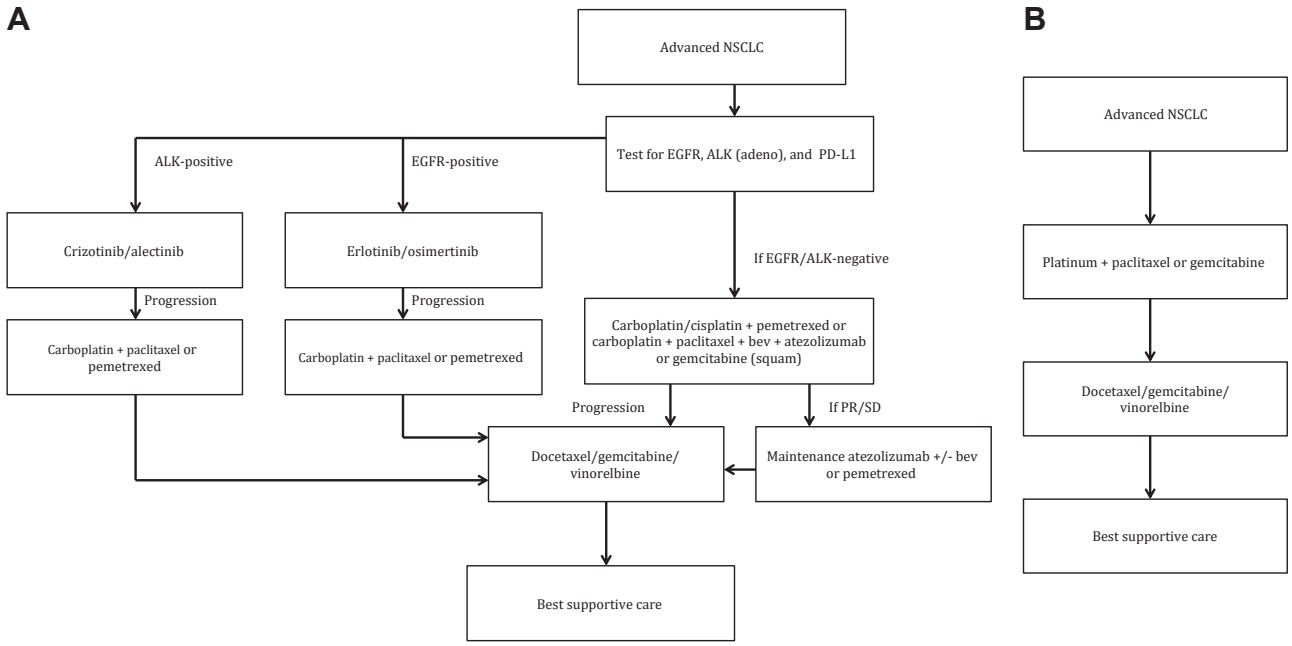

Figure 2. (*A*) Treatment algorithm in resource-proficient setting. (*B*) Treatment algorithm in resource-deficient setting. Adeno, adenocarcinoma; Bev, bevacizumab; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

Targeted therapies such as EGFR tyrosine kinase inhibitors and ALK inhibitors are available albeit first-generation drugs such as erlotinib and crizotinib most often. The newer third-generation medicines in respective classes usually require a time-consuming and cumbersome import process through the Drug Regulatory Authority of Pakistan. A recent real-world data study from a tertiary care center on EGFR-mutant lung carcinoma highlights the prevalence, diagnosis, challenges, and outcomes of EGFR tyrosine kinase inhibitors in the Pakistani population.[25] Immunotherapy, that is, checkpoint inhibitor, is largely limited to atezolizumab, which is the only registered product in the country at present.

For patients with SCLC, the available antineoplastic regimens across Pakistan are doublets containing platinum/etoposide and CAV regimen containing cyclophosphamide, adriamycin, and vincristine. These are used in either first- or second-line settings depending on the performance status of the patient.

Palliative Care

Palliative care is a new specialty in Pakistan in its early stages of development with only a few tertiary care centers providing a dedicated palliative care service. Similarly, there are only a small number of formally trained palliative care physicians and nurses in the country. Thus, most of the palliative and end-of-life care service is provided by the treating oncologist or a general physician. The National Action plan developed in 2004 highlighted the importance of palliative care services in the context of developing country with limited resources; however, no measurable implementation has occurred outside of a few private setups. Availability and procurement of opioids are also a major problem owing to a very complex and cumbersome bureaucratic process instituted by the regulatory authorities.[24]

Challenges and Solutions

Overall, the provision of cancer care in general and lung cancer care in particular is beset by numerous and complex challenges and therefore remains suboptimal in Pakistan. Broadly speaking, the challenges can be categorized into three major domains of (1) lack of public awareness on lung cancer, (2) inadequate and ill-equipped infrastructure and personnel, and (3) inadequate training in oncology.[24] Addressing these

Table 3. List of Approved Medicines for Lung Cancer in Pakistan

1. Carboplatin
2. Cisplatin
3. Docetaxel
4. Etoposide
5. Gemcitabine
6. Irinotecan
7. Paclitaxel
8. Vinorelbine
9. Erlotinib
10. Atezolizumab[a]

[a]Not on the essential medicine list.

challenges requires a broad-based multipronged effort at a national level appropriate to the current resources of the country. Such an approach should focus on improving public health literacy, cancer prevention and screening program, national cancer registry, infrastructure development, education, training, and research.

CRediT Authorship Contribution Statement

Hassan Shahryar Sheikh: Conceptualization, Methodology, Visualization, Investigation, Data analysis, Data collection, Data curation, Writing - original draft, Writing - review & editing, Supervision, Validation.

Kiran Munawar: Data analysis, Data collection, Data curation, Software, Writing - original draft, Visualization, Validation, Writing - review & editing.

Fareeha Sheikh: Writing - original draft, Writing - review & editing, Validation, Data collection.

Muhammad Fawad Ul Qamar: Data collection, Data curation, Writing - original draft, Writing - review & editing, Validation.

References

1. *Pakistan National Census Report 2017*. Government of Pakistan; 2017.
2. The World Bank country data—Pakistan. https://data.worldbank.org/country/pakistan. Accessed January 3, 2022.
3. Bhurgri Y, Bhurgri A, Nishter S, et al. Pakistan—country profile of cancer and cancer control 1995-2004. *J Pak Med Assoc*. 2006;56:124-130.
4. Punjab cancer registry. http://punjabcancerregistry.org.pk/. Accessed January 3, 2022.
5. GLOBOCON 2020. https://gco.iarc.fr/today. Accessed January 3, 2022.
6. Bhurgri Y, Bhurgri A, Usman A, et al. Patho-epidemiology of lung cancer in Karachi (1995-2002). *Asian Pac J Cancer Prev*. 2006;7:60-64.
7. Badar F, Mahmood S, Yusuf MA, Sultan F. Epidemiology of cancers in Lahore, Pakistan, 2010-2012: a cross-sectional study. *BMJ Open*. 2016;6:e011828.
8. Ahmad K, Jafary F, Jehan I, et al. Prevalence and predictors of smoking in Pakistan: results of the National Health Survey of Pakistan. *Eur J Cardiovasc Prev Rehabil*. 2005;12:203-208.
9. Alam SE. Prevalence and pattern of smoking in Pakistan. *J Pak Med Assoc*. 1998;48:64-66.
10. Khuwaja AK, Kadir MM. Smoking among adult males in an urban community of Karachi, Pakistan. *Southeast Asian J Trop Med Public Health*. 2004;35:999-1004.
11. International Cancer Control Partnership Geneva: WHO. https://www.iccp-portal.org/who-cancer-country-profiles-pakistan-2020. Accessed January 3, 2022.
12. Fatmi Z, Hadden WC, Razzak JA, Qureshi HI, Hyder AA, Pappas G. Incidence, patterns and severity of reported unintentional injuries in Pakistan for persons five years and older: results of the National Health Survey of Pakistan 1990-94. *BMC Public Health*. 2007;7:152.
13. National action plan for prevention and control of non-communicable diseases. *Minist Health Gov Pak World Health Organ Pak Off Heartfile, Islamabad; 2004*.
14. Luqman M, Javed MM, Daud S, Raheem N, Ahmad J, Khan AU. Risk factors for lung cancer in the Pakistani population. *Asian Pac J Cancer Prev*. 2014;15:3035-3039.
15. Nishtar S, Ahmed A, Bhurgri Y, et al. Prevention and control of cancers: National Action Plan for NCD Prevention, Control and Health Promotion in Pakistan. *J Pak Med Assoc*. 2004;54(12 suppl 3):S45-S56.
16. Khan MR, Hasan SB, Sami SA. Non-small cell lung cancer: disease spectrum and management in a tertiary care hospital. *J Pak Med Assoc*. 2000;50:330-333.
17. Brown S, Banfill K, Aznar MC, Whitehurst P, Finn CF. The evolving role of radiotherapy in non-small cell lung cancer. *Br J Radiol*. 2019;92:20190524.
18. Baker S, Dahele M, Lagerwaard FJ, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. *Radiat Oncol*. 2016;11:115.
19. Jumeau R, Vilotte F, Durham AD, Ozsahin EM. Current landscape of palliative radiotherapy for non-small-cell lung cancer. *Transl Lung Cancer Res*. 2019;8(suppl 2):S192-S201.
20. List of cancer hospitals in Pakistan - Wikipedia. https://en.wikipedia.org/wiki/List_of_cancer_hospitals_in_Pakistan. Accessed January 15, 2022.
21. Wang J, Zhou Z, Liang J, et al. Intensity-modulated radiation therapy may improve local-regional tumor control for locally advanced non-small cell lung cancer compared with three-dimensional conformal radiation therapy. *Oncologist*. 2016;21:1530-1537.
22. Grootjans W, de Geus-Oei LF, Bussink J. Image-guided adaptive radiotherapy in patients with locally advanced non-small cell lung cancer: the art of PET. *Q J Nucl Med Mol Imaging*. 2018;62:369-384.
23. Khalid F, Raza W, Hotchkiss DR, Soelaeman RH. Health services utilization and out-of-pocket (OOP) expenditures in public and private facilities in Pakistan: an empirical analysis of the 2013-14 OOP health expenditure survey. *BMC Health Serv Res*. 2021;21:178.
24. Yusuf A. Cancer care in Pakistan. *Jpn J Clin Oncol*. 2013;43:771-775.
25. Munawar K, Sheikh H. P76.75 clinical outcomes ad toxicity profiles of patients with EGFR-mutation positive non-small-cell lung cancer. *J Thorac Oncol*. 2021;16:S621-S622.