Uniqueness of lung cancer in Southeast Asia

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Summary

Lung cancer varies between Caucasians and Asians. There have been differences recorded in the epidemiology, genomics, standard therapies and outcomes, with variations according to the geography and ethnicity which affect the decision for optimal treatment of the patients. To better understand the profile of lung cancer in Southeast Asia, with a focus on India, we have comprehensively reviewed the available data, and

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discuss the challenges and the way forward. A substantial proportion of patients with lung cancer in Southeast Asia are neversmokers, and adenocarcinoma is the common histopathologic subtype, found in approximately a third of the patients. *EGFR* mutations are noted in 23–30% of patients, and *ALK* rearrangements are noted in 5–7%. Therapies are similar to global standards, although access to newer modalities and molecules is a challenge. Collaborative research, political will with various policy changes and patient advocacy are urgently needed.

Introduction

As per the Global Cancer Observatory, lung cancer was the second most commonly diagnosed malignancy worldwide in 2020, with 2,206,771 new cases annually (11.6% of the total cancer cases), but the leading cause of cancer-related mortality, causing 1,796,144 deaths (18% of the cancer deaths).[1] In Southeast Asia, although lung cancer was the third most commonly diagnosed cancer (185,636 new cases; 7.8%), it surpassed other cancers as the commonest cause of cancer mortality, causing 166,260 (10.9%) deaths.[2] Most registries from Southeast Asian countries have reported lung cancer among the top five leading types of cancer.[3,4] In India, lung cancer accounts for an annual incidence of 72,510 cases (5.8%) and 66,279 deaths (7.8%).[5] Thus, lung cancer is a huge public health problem worldwide, but more so in Southeast Asia.

The contemporary management of lung cancer has been completely transformed by precision oncology. The molecular signature of lung cancer varies widely between Western (North American/European) and Asian patients. Geography and ethnicity also play a part in the risk factors, response to therapy, and prognosis. Thus, the optimal management of a Southeast Asian patient with lung cancer requires an in-depth understanding of the similarities, differences, and unique features. In most countries in Southeast Asia, various issues add to the complexities of management including lack of access to testing and newer molecular targeted therapies, financial difficulties, and prevalence of infectious diseases like tuberculosis. To better understand the profile of lung cancer in Southeast Asia, with a focus on India, we have comprehensively reviewed the available data, and discussed the challenges and the way forward.

Methods and search strategy

To compile this review, we contacted various domain experts and requested each to write a section compiling the data available for Southeast Asia in their area of expertise. This was intended to be a narrative review, and to be as inclusive as possible, all available literature was searched using PubMed, Google Scholar, Scopus, and abstracts of various oncology meetings. There were no specific search terms, and no limits placed on the search strategy, except for the section on tobacco smoking. For this, we conducted a literature search using the PubMed search engine using the keywords, 'lung cancer', 'pulmonary cancer', 'bronchogenic cancer', 'tobacco', 'smoking' and 'South East Asia,' along with the individual names of the countries. We included only articles that had been published after the year 2000. We identified 24 relevant studies (13 case–control studies, eight cohorts, two meta-analyses, and one cross-sectional study). For most studies, the eligibility criteria for cases were microscopically verified primary lung cancers. We included a total of 7963 cases and 10,765 controls from the case–control studies identified. Nine of these studies were from India (seven case–control studies and two cohort studies) covering nine states of India.

Epidemiology and risk factors

Lung cancer presents approximately a decade earlier in India as compared to Western countries, with a mean age at diagnosis of 54–70 years.[6] The earlier age of presentation in India is likely to be a combination of the overall population pyramid structure in India (younger population, with a median age of 28.2 years; compared to the USA in which the median age is 38 years, and China, with a median age of 39 years),[7] and the unique risk factors in the region, like air pollution and germline mutations, that predispose to non-smoking related lung cancers.[8] In India, the lung cancer age-standardised incidence rates (ASIR) increased from 6.62 per 100,000 in 1990 to 7.7 per 100,000 in 2019. The ASIR increased from 10.36 to 11.16 in men and 2.68 to 4.49 in women. Possible causes include tobacco smoking, and indoor and outdoor air pollution, especially considering the provocative data by Swanton et al. on the etiologic role of particulate matter of size ≤2.5 μm ($PM_{2.5}$).[9] The ASIR and mortality rates in neighbouring countries in the sub-continent are provided in Table 1.[1] The number of cases in metropolitan cities is expected to rise significantly by 2025 to 81,219 in men and 30,109 in women.[10] There is a male preponderance with over two-third (76%) of Indian lung cancer cases occurring in men. This echoes the disproportionate tobacco use

between the sexes, with 42.4% men and only 14.2% women consuming tobacco.[11]

Several studies have reported that a substantial proportion of persons with lung cancer in Southeast Asia are never-smokers: between 40 and 50% in studies from India, and 83% in South Asian women.[6,12,13] Important risk factors for lung cancer in non-smokers include air pollution (especially particulate matter, $PM_{2.5}$), which is a major concern in urban areas. Occupational exposure to asbestos in cement, mining, and other construction-based industries, and exposure to agents like chromium, cadmium, arsenic, and coal products at the workplace have also been implicated in the causation of lung cancer.[6,14] Second-hand smoke at home in the form of biomass fuel usage is common in rural and hilly terrains of Southeast Asia.[15] Factors like genetic susceptibility, hormonal status, and pre-existing lung disease have also been implicated in the rising lung cancer incidence in never-smokers.[8]

The estimated age-standardised 5-year survival for lung cancer in India (2010–2014) was 3.7% (95% confidence interval [CI], 1.6–5.7), as compared to the USA at 21.2% (95% CI, 21.1–21.3), and Japan at 32.9% (95% CI, 32.3–33.4).[16] Inequities in socioeconomic status and access to healthcare contribute to the differences in the lung cancer burden and mortality in low- and middle-income countries (LMICs).[10]

Tobacco consumption and legislation

Southeast Asian countries rank among the highest producers and consumers of tobacco.[17] India is the second largest consumer and third largest producer of tobacco in the world. Among adults, 42% of men and 14.2% women currently either smoke or use smokeless tobacco; khaini and bidi are the most used smokeless and smoked products, respectively. The mean age of starting daily tobacco use is 18.7 years.[11,18] Three of every 10 adults who work indoors have been exposed to second hand smoke in the workplace.[11] In rural areas of India and Nepal, sociocultural factors contribute to the use of smoked tobacco, especially local forms like tuibur (tobacco smoke infused with water) in the Northeastern region contributing to the highest age-adjusted incidence and mortality rate (AAMR) amongst men and women in the Aizawl district of Mizoram (India).[3] Thus, Southeast Asian countries are substantially affected by tobacco-related morbidity and mortality.[18]

A statistically significant association was observed between tobacco smoking and lung cancer,[19–24] with the odds ratios (OR) ranging from 1.7 (95% CI, 1.02–2.81) in the Northeast[23] to 12.3 (95% CI, 6.9–22.0) in Bhopal.[21] With regards to histology, tobacco users had a 5.2 times increased risk of developing small cell lung cancer (SCLC) and oat cell carcinoma, 3.9 times elevated risk of developing adenocarcinoma and 26.2 times higher risk of developing squamous cell carcinoma.[21]

The Nepalese case–control study, that included over 600 cases, reported five times greater odds of lung cancer developing in smokers (OR 4.95, 95% CI 3.5–7.01).[24] The risk reported by the Sri Lankan case–control study with 62 cases was double that noted in the Nepalese study (OR 10.71, 95% CI 3.54–32.59). About 84% of all male lung cancer cases in Sri Lanka could be attributed to smoking.[25] The estimates in a study from Bangladesh in 104 cases, reported an OR of 9.71, similar to the Sri Lankan study.[26] The two case–control studies from Pakistan reported an OR of 9.4 (95% CI 6.9–12.8) for Pakistan overall, and 22.8 (95% CI 13.9–37.3) for Karachi.[27]

Within tobacco smoking, several variables have been explored as contributory risk factors:

1) Dosage and duration of tobacco smoking: A statistically significant dose response relationship was observed in most of the studies, i.e., the risk of developing lung cancer increased with the number of products smoked per day and the years of continuing smoking.[19,21,23,25–28]
2) Type of tobacco product used:
   a) *Cigarettes*: Almost all studies implicated cigarette smoking as a risk factor with an OR between 2.5 and 20.1.
   b) *Hookah*: A study from the Kashmir valley of India reported that hookah smokers were at an almost six times higher risk of developing lung cancer than never-smokers (95% CI 3.95–8.60).[22]

Metrics for lung cancer incidence and mortality	India	Bangladesh	Pakistan	Sri Lanka	Nepal	Myanmar
Age standardised incidence rates for all cancers	97.1	106.2	110.4	105.4	80.9	136.8
Age standardised mortality rates for all cancers	63.1	75.3	74.3	57.2	54.8	99.0
Lung cancer, % (new cases)	5.5	8.3	5.9	11.0	12.2	11.0
Age-standardised incidence rate (lung cancer)	5.4	9.5	7.0	7.0	10.4	15.7
Age-standardised mortality rate (lung cancer)	4.9	8.8	6.2	11.4	9.5	9.5
Lung cancer rank by mortality	4	2	4	1	1	1
Population-based cancer registry	36	None	2	1	3	1

Table 1: Comparison of age-standardised incidence rates (ASR) and mortality rates of all cancers and of lung cancer, in India and the neighbouring countries (all ASRs are reported as per 100,000 persons); Date extracted from the *GLOBOCAN 2020* fact sheet, available online at https://gco.iarc.fr/.[1]

c) *Bidi/beedi*: Studies from India have reported a statistically significant association of bidi smoking with lung cancer and collectively, bidis have been proven to be more dangerous than cigarettes due to the high and uncontrolled concentration of carcinogens.[19,21,23] The ORs reported by these studies range from 6.1 to 18.3. A cohort study from Karunagapally (India) reported a high risk of developing lung cancer (relative risk [RR] 4.6, 95% CI 2.5–8.5) among bidi smokers.[19] An additional observation was that the lung cancer risk decreased more rapidly after cessation of cigarette smoking as compared to that of bidi.[19]

d) *Choor/Kankat* (loose tobacco rolled by the individual): This has been reported to be the most dangerous form of tobacco smoking in Nepal with an OR of 11.2 (95% CI 6.6–19.3).[24]

e) *Smokeless tobacco*: Smokeless tobacco was not noted to be a significant risk factor for lung cancer in most studies,[23,24,26] except for one study in Karachi (Pakistan) that reported a significantly elevated OR among heavy tobacco chewers.[27] The two possible explanations provided by the authors were confounding by tobacco smoking (as there was a correlation between smoking and chewing tobacco in their study population); and absorption of chewing-derived carcinogens by the respiratory tract with resulting carcinogenesis.[27]

Usage of multiple types of tobacco products led to a significantly increased risk.[21,27]

3) Tobacco cessation: Multiple studies have shown that the risk of lung cancer considerably decreases in those who decrease the amount of smoking and more so in those who completely quit smoking.[19,20,27]

4) Sex: Most studies included only men as their cases as lung cancer is the leading cancer site in men. A case–control study from Chandigarh (India) found that the OR for female smokers was lower than that for male smokers.[28]

There is a need to strengthen tobacco control strategies and programmes in the population. Southeast Asian countries lead the implementation of the World Health Organization (WHO) MPOWER programme (a set of six measures designed to lower the demand for tobacco) and ratification of the Framework Convention on Tobacco Control (FCTC). However, a lot of work is needed to achieve compliance to all laws by the public.[11,18,29]

Bhutan has been exemplary and has passed one of the world's strictest anti-tobacco legislations forbidding the use, advertisement, sale, or smuggling of tobacco.[29]

Maldives, and Nepal have comprehensively banned tobacco advertising and public smoking.[30]

The Global Adult Tobacco Survey (GATS) and Global Youth Tobacco Survey (GYTS) have estimated that 22% of the world's adult smokers (aged 15 years and above) and 34% of children (aged 13–15 years) who use tobacco reside in Southeast Asia.[11,18,31] Despite a decrease in the prevalence of tobacco use in the region from 47% in 2000 to 29% in 2018, with a further projected decline to 25% by 2025, it still remains the highest in the world.[18] Therefore, India established a countrywide telephonic "Tobacco Quit Line" service on Feb 02, 2019.[32] There is an abundance of literature about the effectiveness of such services for tobacco cessation and hence, for disease control.

Tuberculosis and lung cancer

Given that Southeast Asia is a hot spot for both tuberculosis (TB) and lung cancer, there has been an increasing cognizance of the coexistence of TB and lung cancer in recent years. TB and lung cancer present concurrently or sequentially, i.e., TB followed by lung cancer or lung cancer followed by TB. TB results in chronic inflammation and fibrosis, with the release of cytokines, especially tumour necrosis alpha (TNFα) which promotes epithelial metaplasia, angiogenesis, and lymphostasis.[33]

Data from the Postgraduate Institute of Medical Education and Research in Chandigarh, India, reported that 0.9% of patients with lung cancer had pleuro-pulmonary TB.[34]

The symptomatology, scan findings, and risk factors for TB and lung cancer are similar. Ramachandran et al. reported that 29% of their patients with lung cancer had been misdiagnosed as TB, and 27.1% were treated with antituberculous therapy (ATT) before the correct diagnosis was made.[35] Other Indian studies have reported misdiagnosis rates of 17–22%.[36]

Most tyrosine kinase inhibitors (TKI) are metabolised in the liver. Of the first-line ATT drugs, rifampicin, is a strong cytochrome (CYP3A4) inducer. Concomitant administration of rifampicin with a TKI significantly reduces the concentration (area under the curve [AUC]) of some molecules. Amongst the TKIs, alectinib and afatinib are the least affected. Isoniazid is a weak inhibitor of CYP23A, 3A with negligible effect on the drug levels of TKIs[37] (Supplementary Table S1). Hence, it is recommended to substitute rifampicin with rifabutin (weak inducer). An upward daily dose adjustment of TKI may be warranted when it is co-administered with rifabutin with monitoring of TKI drug levels (and close liver function monitoring in case of lorlatinib). If rifabutin is unavailable/not tolerated, a switch to a non-rifampicin-based ATT regimen or substitution to the least affected TKI after joint consultation

with TB/infectious disease expert on a case-by-case basis is recommended.

The blockade of the programmed cell death-1 (PD-1) ligand axis boosts the type 1 helper cell (Th1)- mediated inflammatory response and causes a worsening of TB lesions as seen in immune reconstitution inflammatory syndrome. Hence, in patients with lung cancer on immune checkpoint inhibitors (ICIs), delaying the dosing of ICI for 2–4 weeks after ATT initiation is advisable.

The Indian national TB guidelines recommend screening for latent TB infection (LTBI) in patients planned for immunosuppressive therapy and/or TNFα.[38] Currently, the Indian guidelines do not recommend specific LTBI screening in patients with lung cancer. Screening for LTBI may be considered in individuals with lung cancer with a history of TB, other risk factors, and due to receive ICI therapy, until appropriate guidelines are developed for this.

Pathology, biology, and molecular characteristics

Histopathology
The pathological spectrum of lung cancer in Southeast Asia appears to be following the global trends of increasing incidence of adenocarcinoma as compared to squamous cell carcinoma (SqCC), similar to most Western and other Asian countries.[6,12,39–41] One of the largest 10-year analyses from North India reported that adenocarcinoma was the most common pathological type (34%), followed by SqCC (28.6%) and SCLC (16.1%)[39] [Table 2].[12,13,39,41–56]

Biology
The genetic makeup of lung cancer in the Indian subcontinent is shaped by the intricate diversity of its people. Data from patients treated at four Indian tertiary hospitals were presented at a conference, "Lung Cancer Management in Indian Context". The prevalence of *EGFR* mutations and *ALK* rearrangements were reported to be 30% and 10%, respectively.[57] Fig. 1 provides a pictorial representation of the genomic alterations in Indian lung cancer.[58–63]

Molecular alterations underlying lung adenocarcinoma
EGFR mutations
The intermediate *EGFR* mutation rate, ranging from 23 to 30% among modern-day Indians compared to 10–15% among North Americans/Europeans and 27–62% among East Asians, reflects an amalgamation of genetic influences from Middle Easterners, Central Asians, and Europeans.[58,59,64–67] This is the result of different migration waves and the merging of major ancestral populations over thousands of years at various points in time. The PIONEER study conducted in 1482 patients with lung adenocarcinoma from seven Asian regions (mainland China, Hong Kong, India, Philippines, Taiwan, Thailand, and Vietnam) found that the *EGFR* mutation frequency was significantly associated with smoking history in pack-

Author	Place and year	Patient number	Male:Female ratio	Mean age, in years	Squamous cell carcinoma, in %	Adenocarcinoma, in %	Ratio of squamous cell carcinoma to adenocarcinoma
Jindal and Behera[43]	Chandigarh, 1990	1009	4.5:1	51	34.3	25.9	1.3
Gupta et al.[44]	Rajasthan, 1998	279	6.1:1	57	42.0	20.0	2.1
Prasad et al.[45]	Lucknow, 2004	400	4.3:1	57	46.5	18.5	2.5
Khan et al.[46]	Kashmir, 2006	321	11.3:1	–	77.3	5.3	14.6
Prasad et al.[47]	Lucknow, 2009	799	4.8:1	–	47.3	18.2	2.6
Rawat et al.[48]	Uttarakhand, 2009	203	8.2:1	56.4	44.8	19.4	2.3
Sheikh et al.[49]	Kashmir, 2010	783	7.0:1	57.8	71.3	2.6	27.4
Singh et al.[42]	Chandigarh, 2012	654	5.0:1	58.2	38.1	27.5	1.4
Dey et al.[50]	Kolkata, 2012	607	4.1:1	57.9	35.1	30.8	1.1
Noronha et al.[12]	Mumbai, 2012	489	3.5:1	56	26.2	43.8	0.6
Krishnamurthy et al.[13]	Tamil Nadu, 2012	258	3.5:1	56	15.8	42.6	0.4
Sharma et al.[51]	Himachal Pradesh, 2012	105	10.6:1	62.7	37.1	36.2	1.0
Malik et al.[52]	New Delhi, 2013	434	4.6:1	55	32.1	37.1	0.9
Mandal et al.[53]	Manipur, 2013	466	1.1:1	58.5	49.1	30.8	1.6
Baburao et al.[54]	Bangalore, 2015	96	3.0:1	–	47.9	28.1	1.7
Mohan et al.[41]	New Delhi, 2016	397	7.4:1	57.8	25.1	24.1	1.0
Murali et al.[55]	Chennai, 2017	678	3.2:1	–	16.1	51.2	0.3
Kaur et al.[56]	Chandigarh, 2017	1301	4.6:1	58.6	36.4	36.4	1.0
Mohan et al.[39]	Delhi, 2020	1862	4.9:1	58	28.6	34.0	0.8

Table 2: Lung cancer demography and histological subtypes in the Indian subcontinent.
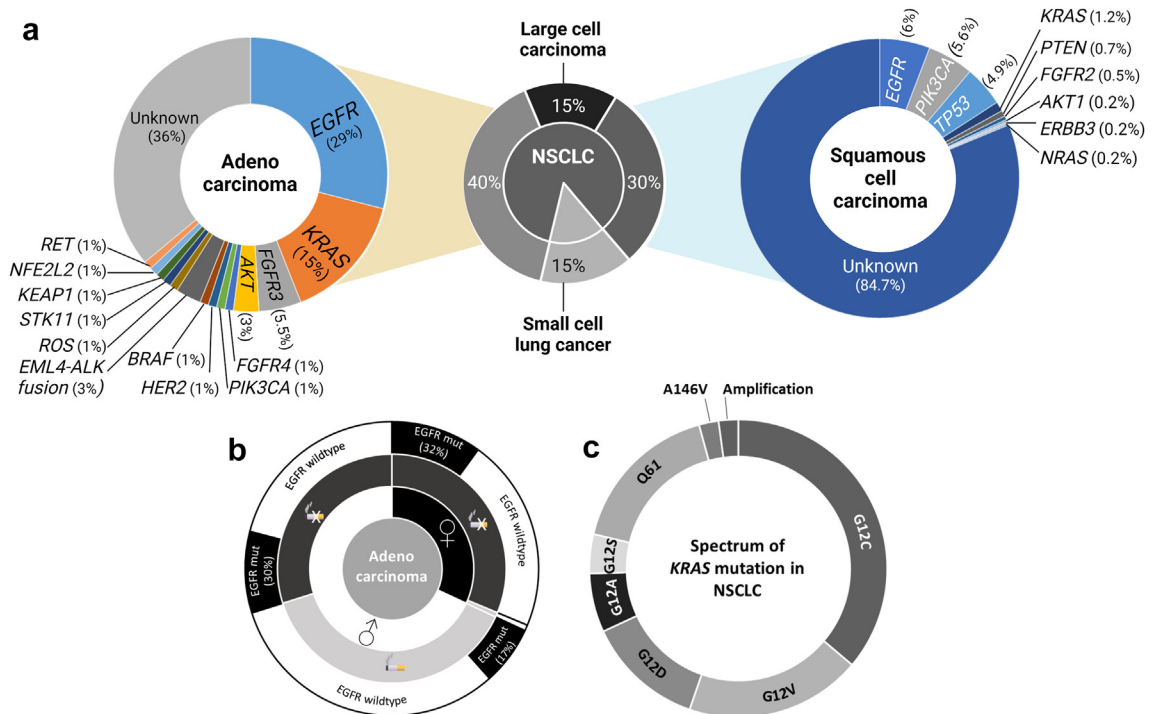
Fig. 1: Genomic landscape of lung cancer in the Indian subcontinent. (a) Pie charts showing histological distribution of lung cancer in India. Non-small cell lung cancer (NSCLC) constitutes 85% of cases, comprising predominantly lung adenocarcinoma and squamous cell carcinoma. Small cell lung cancer (SCLC) represents 15% of cases. The frequency of key genomic alterations in lung adenocarcinoma and squamous cell carcinoma is represented. *EGFR* mutations occur in 23–30% of lung adenocarcinoma, while *KRAS* and *ALK* alterations are present in 10–12% and 5–7%, respectively (Noronha et al., 2020[58] Noronha et al., 2024[59]). *FGFR3* mutations occur in 5.5% of cases (Chandrani et al., 2017[60]). The common mutations associated with *EGFR* and *KRAS* are shown. In squamous cell carcinoma, common mutations occur in *EGFR, PIK3CA, TP53, KRAS, PTEN, FGFR2, AKT1, ERBB3 and NRAS* (Joshi et al., 2021[61]). (b) Pie charts showing the relative prevalence of *EGFR*-mutant versus *EGFR* wildtype lung adenocarcinoma among males, females, smokers, and non-smokers (Chougule et al., 2013[62]). (c) Pie chart showing mutation spectrum of *KRAS* mutations identified in NSCLC cases from the Indian subcontinent (Batra et al., 2023[63]). NOTE: The frequency of gene alterations shown in the figure is not proportionate to their actual occurrence, as the figure is intended to represent the common genomic alterations rather than their precise frequencies.

years and ethnicity; people of Kinh (Vietnamese) ethnicity had the highest *EGFR* mutation rate at 64.2%, and Indians had the lowest at 21.9%.[67] Notably, *EGFR* exon 19 and 21 mutations are observed in 53% and 38% of lung adenocarcinoma patients of Indian origin, respectively, mirroring the prevalence in the East Asian population.[68] The incidence of de novo exon 20 insertions is 3.4%.[69] Women in India exhibit significantly higher *EGFR* mutation frequency (51.9%) compared to men (35.1%).[70] Brain metastasis has been reported as a correlated incidence to *EGFR* mutation in lung cancer.[70] Interestingly, the response to EGFR TKIs can differ among Indian patients, emphasizing the necessity for tailored treatment strategies based on the unique mutational landscape.[71]

KRAS mutations
In contrast to *EGFR* mutations, *KRAS* mutations are more frequent in North Americans/Europeans, with a prevalence ranging from 25 to 50%, compared to 5–15% among East Asians.[72] A recent study from the Rajiv

Gandhi Cancer Institute, a tertiary care hospital in Delhi, India, reported a 30.6% alteration rate in the *KRAS* gene with G12C in 17 (34%), G12V in 9 (18%), and G12D in 6 (12%) patients with lung cancer.[63]

ALK rearrangements
The prevalence of anaplastic lymphoma kinase (*ALK*) rearrangements ranges from 5 to 7%, similarly exhibiting disparities in prevalence among different ethnic groups within the Indian subcontinent.[73,74,88]

FGFR3 alterations
FGFR3 mutations were identified in 20 out of 363 (5.5%) patients of Indian origin with lung adenocarcinoma.[60] This finding implicates *FGFR3* as a novel therapeutic target in lung adenocarcinoma.

Molecular alterations underlying lung squamous carcinoma
Studies reveal that 19% of patients with SqCC harbour mutations across *TP53, CDKN2A, FGFR1, PTEN,*

KMT2C, LRP1B, FAT1, NFE2L2 and *PREX2*.[61] Among the therapeutically relevant frequent oncogenic mutations, EGFR TKI sensitive alterations were observed at a frequency of 6% in our cohort, significantly higher than that reported in The Cancer Genome Atlas (TCGA) and other studies; *KMT2D* mutations were observed at a frequency of 40%, compared to 10% and 24% in the North American and East Asian populations, respectively; and 10.7% alterations were noted in the *PI3K-AKT* pathway.[61]

Penetration of molecular testing

There are no formal data regarding the uptake of molecular testing in Southeast Asia, hence, we have used anecdotal data and personal communication to describe this. At the Tata Memorial Hospital (TMH) in Mumbai (India), we register around 2000 patients with lung cancer every year and perform molecular testing in over 900 (45%) patients, and almost 700 (35%) patients undergo programmed cell death ligand 1 (PD-L1) testing. Molecular testing is available in India, Pakistan, Nepal, and Bangladesh, but not in Sri Lanka, Bhutan, or Afghanistan. In Bangladesh, 37 centres have polymerase chain reaction (PCR) facility. Next generation sequencing (NGS) testing is widely available only in India; 3–4 laboratories in Pakistan, some centres in Nepal, and 5 centres in Bangladesh perform NGS/Illumina (4 have NGS, and one has both NGS and Illumina). Over two dozen laboratories in India perform NGS testing. Although we do not have formal data from these laboratories, but from personal communication, we conclude that annually, almost 5000 patients are undergoing NGS testing for lung cancer in India. Our Indian cancer registry data suggest that the incidence of new patients with lung cancer is around 70,000 per year. There is a disparity in the availability of molecular testing in academic centres and tier 1 or other cities. Molecular testing is available at three of the top 10 regional cancer centres in India. Almost all molecular laboratories are present in tier 1 or tier 2 Indian cities. Majority of molecular testing is done at central laboratories; most individual hospitals do not have in-house molecular laboratories. Molecular testing with NGS has increased over time. At TMH, almost 400 patients underwent NGS in 2021, 500 in 2022, and 900 in 2023. At Purbanchal Cancer Hospital in Jhapa, Nepal, 23 (11.2%) of a total of 205 patients with lung cancer underwent NGS testing in 2023.

Screening

Although early detection can significantly improve survival rates, lung cancer screening is currently not implemented in India. Supplementary Table S2 summarises the available data for lung cancer screening studies worldwide.

Data about lung cancer screening are sparse from India and Southeast Asia. Parang et al. performed a retrospective study on 350 Indian smokers to assess the effectiveness of low dose computed tomography (LDCT) in detecting nodules and cancers.[75] They concluded that in a population with more than 20 pack year smoking history, LDCT effectively detected potentially malignant lung nodules (especially in lung-RADS [Reporting and Data System] category 4).[75] Damaraju and colleagues, in a prospective observational study on 253 individuals found a screen positivity rate of 32% when applying the National Comprehensive Cancer Network (NCCN) cut-off of 6 mm, and 47.8% with the National Lung Screening Trial (NLST) cutoff of 4 mm.[76] Interestingly, lung cancer was diagnosed on biopsy in only four of the 253 screened individuals (1.6%), thereby concluding that regions with a high incidence of granulomatous diseases like TB and histoplasmosis can have high positivity on LDCT screening due to these chronic infections.

With scientific evidence mounting in support of lung cancer screening, a major issue to be addressed is the cost-benefit ratio of such an approach in LMICs like India. Other important factors to consider are the significant proportion of lung cancers in never smokers and the earlier age of diagnosis.[8,12,13] There is limited access to computed tomography (CT) scan machines and a small number of trained personnel who can interpret the scans.

The way ahead is an uphill task, but LMICs, especially from the Southeast Asian region need to come together to design a study to evaluate the benefit of lung cancer screening in this region.

Staging by radiologic imaging
Issues in the interpretation/implementation of optimal imaging in Southeast Asia
High incidence of TB

The appearance of spiculation, lobulation, thick-walled cavity (>3 mm) and a lower lobe mass favour lung cancer, but characteristic imaging features may not be present in all patients. Fluorodeoxyglucose (FDG) accumulates both in TB and lung cancer, and studies have shown that in TB-endemic areas, the specificity of FDG PET/CECT reduces from 77–86% to approximately 21–61%.[77] A study at TMH (Mumbai, India) reported that the false positive and false negative rates for PET-CT in diagnosing lung nodules were 65.2% and 5.5%, respectively; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG-PET/CT for detecting malignancy in pulmonary nodules were 94.4%, 34.7%, 81.9%, 66.6%, and 79.5%, respectively.[77] A study at the All India Institute of Medical Sciences (AIIMS; Delhi, India) reported that the sensitivity, specificity, accuracy, PPV, NPV, and

accuracy of PET-CT in mediastinal nodal staging (N2 disease) were 60%, 97%, 38%, 99%, and 96%, respectively.[78] Moreover, there was no statistical difference in the metabolic uptake of TB versus lung cancer in the median maximum standardised uptake (SUVmax) values.[77] The biopsy sample may, therefore, be sent for both histopathology (for lung cancer) as well as for GeneXpert (for TB).

Shortage of radiologists/interventional radiologists
There is a dearth of radiologists and interventional radiologists (IR) in many Asian countries with a poor radiologist-to-population ratio. In some Asian countries, there is only one radiologist available per million population.[79] As far as IR is concerned, there is only one IR available per 0.21 million population in India,[80] whereas, Pakistan has 32 IR fellows practicing within and outside the country.[81] In Myanmar, only nine IR were available in 2019.[82]

Availability
PET/CECT is not available in all hospitals with approximately 40% medical modalities being non-functional, hence, it is acceptable to perform contrast enhanced (CE) CT of the thorax, abdomen, and pelvis for staging, along with bone scan. To add to the impediment, less than one CT scanner per million population is available in low-income countries, compared to approximately 40 per million population in high-income countries.[83]

Treatment
Surgery
Due to the lack of robust screening programs in Southeast Asia and clinico-radiological as well as symptomatologic overlap with TB, most cases present in advanced and metastatic stages,[10] and even in those where curative intent treatment is feasible, a significant proportion are either unfit or unwilling for surgery.[84] The resection rate is Nepal has been reported to be 3–6.7%.[85] A study at AIIMS (Delhi), an Indian tertiary centre, highlighted that only 31.7% of patients with Stages I to IIIB NSCLC underwent curative intent therapy; and only 13.4% underwent curative resection.[86]

Pre-operative staging and evaluation
There has been an exponential increase in the adoption of endoscopic techniques in India in the past decade and only few centres continue to offer mediastinoscopy (Supplementary Fig. S1). In a survey among clinicians (surgical oncologists, thoracic surgeons, pulmonologists) treating patients with lung cancer in India, 89% responded that invasive mediastinal staging was required even in the presence of positive lymphadenopathy on PET scans, 56% recommended invasive mediastinal assessment even in the presence of negative mediastinal nodes on PET, 83% opined that endobronchial ultrasound (EBUS) was

the preferred approach, and only 11% voted for mediastinoscopy as the preferred investigation.[87] The survey also reported that the availability of mediastinoscopy and EBUS/endoscopic ultrasound was 53% and 60%, respectively, in most large academic institutions in India.

Surgical approach
The traditional surgical approach has been open thoracotomy, however surgeons in Southeast Asia and India have adopted minimally invasive surgery (MIS) including video-assisted thoracoscopic (VATS)[88] and robotic approaches.[89] The uptake of minimally invasive surgery has been slow due to few patients with small tumours, lack of high definition video equipment and disposables, and a steep learning curve associated with adopting MIS for pulmonary resection, especially in Southeast Asian countries,[40] with a high incidence of adhesions and granulomatous nodes. Cost is the major hindrance to widespread adoption of the VATS and robotic platforms. Table 3 summarises the surgical lung cancer data from Southeast Asia.[84,86,90–94]

Radiotherapy
According to the latest data from the International Atomic Energy Agency–Directory of Radiotherapy Centres (IAEA-DIRAC) (Supplementary Fig. S2), there are 451 radiotherapy (RT) centres in India with 779 megavoltage teletherapy machines, one light ion therapy, five kilovoltage therapy machines, and 413 brachytherapy machines.[95]

There is huge disparity between rural and urban sectors in terms of accessibility to RT facilities and cost of treatment.[96] The waiting period in private hospitals is shorter (usually less than a week) as compared to that in the public sector (typically ranges from 1 week to 2 months).[40] The Indian government has taken several initiatives to address these challenges, including plans to expand cancer treatment facilities and invest in additional RT machines.

Advances in RT delivery techniques have made treatment for lung cancer more effective and better tolerated. Many retrospective case series have discussed the role of stereotactic body radiation therapy (SBRT) which showed promising efficacy in appropriately selected populations.[97–102] An overall survival of 41% at 2 years has been reported in the largest series by Agrawal et al.[103] Table 4 summarises the RT data from Southeast Asia.[97–105]

Systemic therapy, outcomes, and patterns of practice
Table 5 summarises various studies from the region on systemic therapy in lung cancer. The major difference in treatment is due to a lack of access to newer molecules like targeted and immunotherapies.

Non-metastatic
In patients with locally advanced lung cancer, multiple studies have shown that concurrent chemoradiotherapy

First author	Country	Year of publication	Type of study	Results	Conclusions
Nair CK[84]	India	2017	Observational, retrospective (n = 1086)	More than half (55.2%) of the patients with lung cancer presented with distant metastases, 40.8% presented with locoregionally advanced disease and 4.1% presented with localised disease. Only 15.7% of patients received curative treatment; only 21 patients (2%) underwent surgery (alone or as part of a multimodality regimen)	High prevalence of tuberculosis and lack of widespread availability of thoracic oncologists could be the possible reasons for low percentage of patients treated with curative intent
Malik PS[86]	India	2014	Observational, retrospective	Among 104 patients with stage I-IIIB NSCLC, 31.7% patients underwent curative treatment; 14 (13.5%) underwent surgery and 19 (18.3%) received radical radiotherapy. Reasons for underutilisation of curative therapy included disease progression, lost to follow-up, and unindicated palliative radiation or systemic therapy like TKI. Patients treated with non-curative intent had inferior survival	Radical intent therapy is grossly underutilised, and results in inferior survival
Majeed FA[90]	Pakistan	2023	Observational, retrospective	Among 338 patients who underwent cervical mediastinoscopy and lymph node biopsy, 157 (46%) had tuberculosis, 34 (10.1%) had sarcoidosis, and 52 (15.3%) had a malignancy (NSCLC, SCLC, or metastatic carcinoma). Amongst the 60 patients who underwent staging, 33 (55%) had negative mediastinal disease. Complications occurred in 3.8%: 3 developed hoarseness of voice, 2 had wound infection requiring intervention.	Cervical mediastinoscopy is an effective and safe diagnostic tool for mediastinal nodal evaluation and staging for lung cancer
Mithi MT[91]	India	2024	Observational, retrospective	Less than 2% of patients with lung cancer underwent radical surgery. Among 92 patients with NSCLC who underwent curative surgery, right upper lobectomy was the most common surgery. DFS at 2- and 3-years were 65.4% and 60.8%, respectively. OS at 2- and 3-years were 74.3% and 70.6%, respectively.	Radical surgery is underutilised in patients with NSCLC. In patients who undergo curative surgery, survival appears to be similar to global standards.
Thakur B[92]	Nepal	2014	Observational, retrospective	Stage IIIB/IV was noted in 66.8%, and curative resection was done in 6.7%. Surgery was used as sole treatment in 38%; neoadjuvant and adjuvant therapies (chemotherapy/radiotherapy/ chemoradiotherapy) were added in 12% and 50%, respectively. Resections were R0 in 91%; in-hospital mortality was 2% (post pneumonectomy: 5.5%; post lobectomy: 1.5%; post sub-lobar resection: 0%). Median and 5-year OS were 36 months and 18%, respectively.	Patients with early-stage disease, R0 resection, and pathological N0-1 have the best survival.
Shah SH[93]	India	2017	Observational, retrospective	Among 48 patients with lung cancer who underwent major lung resections, 80% presented with symptoms and in advanced stages. Pneumonectomy was required in 41.6% and neoadjuvant chemotherapy in 45.8% of the patients. Morbidity and mortality were similar between pneumonectomy (25%, 5%) and lobectomy (21.2%, 3.5%). DFS at 1, 2, and 3 years were comparable after pneumonectomy (71.8%, 51.4%, 42.8%) and lobectomy (73.3%, 66.1%, 55.6%). Following neoadjuvant therapy, the type of surgery had no impact on survival.	Pneumonectomy is commonly done in Indian patients with lung cancer and leads to acceptable oncologic outcomes.
Kumar A[94]	India	2018	Observational, retrospective	In 102 patients (27 patients had lung cancer) undergoing VATS lobectomy, the conversion rate was 8.82% (n = 9). There were no postoperative complications in 82 (80.4%) patients; average blood loss was 211.37 mL; mean operative time was 173 min; median length of hospital stay was 5 days; median chest tube duration was 4.9 days. There was no in-hospital or 30-day mortality. Most common complication was prolonged air leak.	VATS lobectomy can be safely performed even in tuberculosis-endemic regions

ACRONYMS: NSCLC: Non small cell lung cancer; TKI: Tyrosine kinase inhibitor; SCLC: Small cell lung cancer; DFS: Disease free survival; OS: Overall survival; VATS: Video-assisted thoracoscopic surgery.

Table 3: Selected recent studies on surgical management of lung cancer from Southeast Asia.

Series

Study (Country, year)	Type of study	Number of patients	Disease stages included in analysis	Type of radiotherapy	Outcomes	Toxicity
Kundu et al. (India, 2013)[97]	Retrospective	8	I-IIA (T1-T2N0M0 [medically inoperable])	SBRT (48 Gy/6–8 fractions)	OS at 1.5 years–87.5%	Grade 2 pneumonitis—1/8 (12.5%) No Grade 3 or higher toxicities
Pathak et al. (India, 2016)[98]	Retrospective	22	Early lung cancer (T1, T2)	SBRT	At 12 months: OS-86.4%, LRFS-88.2%, DMFS-62%; At 18 months: OS-64.8%, LRFS-75.6%, DMFS-37.2%	NA
Madhavan et al. (India, 2017)[99]	Retrospective	9	Early lung cancer (T1-T2N0M0)	SBRT (48–54 Gy/3–4 fractions)	Median PFS-27 months (19.5–35.5); Median OS-28 months (20.5–35.5)	No grade ≥2 acute or late toxicities noted
Talapatra et al. (India, 2018)[100]	Retrospective	18	Early lung cancer	SBRT	1-year local control: 87.5%	Grade 2 radiation pneumonitis-2 (7%); Grade 3 radiation pneumonitis-1 (3.5%); Grade 2 esophagitis-3 (11.1%); Grade 1 radiation dermatitis-3 (11.1%)
Agarwal et al. (India, 2020)[101]	Retrospective	40	Early lung cancer (70% stage I)	SBRT: Median biologically effective dose (BED) for the initial cohort treated from 2007 to 2012: 77 Gy_{10} (range: 77–105); for the next cohort from 2013 to 2015: 105 Gy_{10} (range: 77–132)	2-yr OS-41%; 2-year local control: 94%; 2-year cancer-specific survival: 62%	Skin erythema (10%), grade 1 esophagitis (8%), chronic obstructive pulmonary disease exacerbation (10%). Grade ≥2 late radiation pneumonitis = 17.5%. Rib fracture in 1 patient.
Shrimali et al. (India, 2020)[102]	Retrospective	15	Lung primary (T1, T2 N0), oligometastatic lung metastasis	SBRT (40–60 Gy in 5–8 fractions with alternate-day treatment)	Locoregional control rate at 17 months: 93.3%	No acute or late toxicities
Agarwal et al. (India, 2016)[103]	Retrospective	171	II-III and selected IV	66% concurrent CRT; 28% sequential CRT	Median DFS—7 months Median OS—13 months	Grade 2 acute RT pneumonitis–6.4% Grade 2 esophagitis–32.2% Grade 3 esophagitis–4.1%
Agarwal et al. (India, 2014)[104]	Retrospective	52	IIB-IIIB	Radical CRT	NA	Grade 2+ pneumonitis—35.3%
Alagiyawanna et al. (Sri Lanka, 2022)[105]	Retrospective	349	I-IV (excluding metastasis to lungs from other primaries)	51% RT alone 20% concurrent CRT 17% sequential CRT	Median OS—12 months	NA

RT: radiotherapy, CRT: chemoradiotherapy, SBRT: stereotactic body radiation therapy, DFS: disease-free survival, OS: overall survival; PFS: progression-free survival; LRFS: locoregional recurrence free survival; DMFS: distant metastasis free survival; NA: not available.

Table 4: **Studies evaluating the role of radiation, or chemoradiotherapy in early and locally advanced lung cancer in Southeast Asia.**

Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
Locally advanced								
Locoregional advanced adenocarcinoma lung with N2 disease	Retrospective	Locoregionally advanced non-metastatic adenocarcinoma lung, with N2 disease, borderline for upfront definitive therapy, and planned for neoadjuvant therapy	2009–2016	Noronha[106]	Platinum + pemetrexed every 3 weeks for 2–4 cycles, followed by evaluation for definitive therapy	14 months (95% CI, 10.7–17.3); Following neoadjuvant chemotherapy, 72.9% underwent definitive therapy. Median PFS in patients who underwent definitive therapy = 15 months (11.2–18.8), versus 8 months (0.2–15.8) in those who did not undergo definitive therapy; P = 0.271	22 months (95% CI, 15.6–28.4); Median OS in patients who underwent definitive therapy = 25 months (19.6–30.4), versus 12 months (3.2–20.7) in those who did not undergo definitive therapy; P = 0.015	96
Stage IIIA	Retrospective	Stage III	2013–2017	Prabhash[107]	All (CRT, chemotherapy, sequential chemo followed by RT, TKI, RT alone, surgery, IO)	12.8 months (12.2–13.7)	42.3 months (38.1–46.8)	1874
Inoperable	Prospective observational	Inoperable Stage III NSCLC	2018–2019	Noronha[108]	CRT → Durvalumab	8.5 months (5.5–11.6)	Not reported	15
Locally advanced	Retrospective	Locally Advanced NSCLC	1992–1996	Sharma[109]	Sequential CRT (cisplatin + Ifosfamide + Mitomycin C) versus RT (60 Gy)	Not reported	20% versus 7.4% at 2 years	508
Unresectable	Prospective randomised phase III trial	Unresectable NSCLC	Not reported. Published in 2006	Dasgupta[110]	RT alone (65 Gy) versus sequential CRT (Cisplatin + Etoposide → 60 Gy → cisplatin + etoposide) versus concurrent CRT (cisplatin + etoposide with 50 Gy → cisplatin + etoposide)	16 months (5–20) versus 21 months versus 21 months (8–22)	59.4% versus 57% versus 66.6% at 2 years	103
Locally advanced	Retrospective	Locally advanced NSCLC	2007–2011	Agrawal[111]	Concurrent CRT versus sequential CRT	Not reported	12 months versus 12 months	55
Locally advanced	Retrospective	Locally advanced NSCLC	2008–2012	Agarwal[103]	Neoadjuvant chemotherapy-> CRT, CRT, CRT adjuvant, sequential CRT	7 months	13 months	171
Stage III	Retrospective	Stage III	2006–2015	Murali[55]	Concurrent CRT versus sequential CRT	31% versus 8% (P = 0.29) at 1 year	30% versus 0% (P = 0.51) at 1 year	169
Inoperable	Retrospective	Inoperable, locally advanced NSCLC	2011–2016	Shrimali[112]	Concurrent CRT versus sequential CRT/RT alone	Not reported	28 months versus 13 months; P < 0.001	213
Locally advanced	Retrospective	Locally advanced NSCLC	2007–2015	Srivastava[113]	Neoadjuvant chemotherapy→concurrent CRT versus concurrent CRT versus sequential CRT/RT alone	13 months versus 13 months versus 13 months	15 months versus 16 months (P = 0.75)	114
Locally advanced	Randomised prospective	Locally advanced NSCLC	2013–2014	Kumar[114]	CHARTWELL (accelerated hyperfractionation) versus CRT	11 months (8.8–13.1) versus 11 months (8.37–13.62)	12 months (11.38–12.6) versus 12 months (8.86–15.1)	60

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Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
(Continued from previous page)								
Stage III	Randomised prospective	Stage III NSCLC	2016–2017	Sardar[115]	Concurrent CRT versus neoadjuvant chemotherapy→concurrent CRT	9.9 months versus 11.8 months; P = 0.042	13.3 versus 13.6 months; P = 0.542	44
Locally advanced	Randomised prospective	Locally advanced NSCLC	2013–2014	Srinivasa[116]	CRT with paclitaxel + carboplatin versus cisplatin + etoposide	1-year PFS: 78% versus 83%; P = 0.674	Similar OS between the two arms; P = 0.898	36
Advanced stage: *EGFR* mutant								
EGFR sensitising mutation, first line	Phase III randomised trial	Advanced metastatic NSCLC with *EGFR* mutation	2012–2016	Patil[117,118]	Gefitinib versus pemetrexed + carboplatin chemotherapy→maintenance pemetrexed	Median PFS: 8.4 months (6.3–10.5) versus 5.6 months (4.2–7); P = 0.001; HR = 0.66 (0.51–0.85) Response rate: 63.5% versus 45.3% P = 0.003	18 months (15.2–20.8) versus 22.6 months (18.6–26.6); HR = 0.78 (0.56–1.09); P = 0.133; At follow-up of 104 months: median OS in gefitinib arm = 19.5 months (16.7–24.8) versus chemotherapy arm = 22.6 months (19.2–25.2); HR = 1.11 (0.87–1.39); P = 0.423	290
EGFR mutated, first line	Retrospective	*EGFR* positive NSCLC	2007–2018	Garg[121]	TKI (93% first generation, 7% second or third generation)	Median PFS: 9.3 months; Response rate: 65.9%	Not reported	483
Advanced NSCLC, in a clinically enriched population (*EGFR* mutation testing not done)	Retrospective observational	Stage IIIB or Stage IV NSCLC with the following clinical features: female sex, non-smoker, adenocarcinoma, poor PS	2009–2010	Louis[122]	Gefitinib 250 mg orally daily	Median PFS = 5 months (0–23); Response rate = 54.2%	7.5 months (1–26)	120
EGFR mutated NSCLC	Post hoc analysis of phase III randomised study	*EGFR* positive metastatic NSCLC-exon 19/21	2016–2018	Joshi[123]	Exon 19 versus 21; Patients randomised to gefitinib and pemetrexed + carboplatin	Median PFS: 9.3 months (6.8–11.7) versus 7.8 months (5.5–10); P = 0.699 Response rate: 72.9% versus 55.6%; P = 0.046	19.8 months (16.8–22.7) versus 16.5 months (10.9–22.1); P = 0.215	141
EGFR mutated NSCLC, first line	Phase III randomised trial	*EGFR* mutated lung cancer	2016–2018	Noronha[58,59]	Gefitinib + pemetrexed + carboplatin chemotherapy versus gefitinib alone	Median PFS: 16 months (13.5–18.5) versus 8 months (7–9); HR: 0.51 P < 0.001 Response rate: 75% versus 63%	Not reached versus 17 months (13.5–20.5); HR: 0.45; P < 0.001. At a median follow-up of 5 years, median OS in gefitinib + chemo: 27.5 months (24.8–30.8) versus gefitinib: 17.6 months (15.3–21.5), P < 0.001	350

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Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
(Continued from previous page)								
EGFR uncommon	Retrospective	Newly diagnosed advanced NSCLC, uncommon *EGFR* mutation	2013–2017	Kate[124]	TKI (first generation [FG], second generation [SG] third generation [TG])	Median PFS: FG-9.4 months (7.9–10.9), SG-15.3 months, TG-6 months (5.1–7.0); Response rate: FG-48.7%, SG-100%, TG-33.3%	FG-18.3 months (5.7–30.9), SG-Not reached, TG-15.9 months (6.6–25.2)	83
De novo T790M	Retrospective	De novo T790M-Mutated NSCLC	2015–2019	Panda[125]	All (TG, FG, gefitinib plus chemotherapy, chemotherapy alone, gefitinib plus bevacizumab)	Median PFS: 10.4 months (7.6–19.7) Response rate: 48.7%	24.9 months (15.7-NA)	39
EGFR 3rd line therapy	Post-hoc analysis of Phase III randomised trial	*EGFR* positive metastatic NSCLC on 3rd line treatment	2012–2016	Noronha[126]	Multiple (FG, oral chemotherapy, intravenous chemotherapy single agent, intravenous chemotherapy doublet)	Median PFS: 4.4 months (3.3–4.9) Response rate: 44%	8.3 months (6.8–9.8)	85
Advanced stage: *ALK* fusion								
ALK first line	Retrospective	*ALK* positive advanced NSCLC	2013–2018	Kapoor[127]	ALK TKI, chemotherapy, best supportive care	14.1 months (12.2–15.9)	30.7 months (27.3–34.2)	441
ALK first line	Retrospective	*ALK* positive NSCLC	Not reported; Published in 2020	Batra[128]	Crizotinib	11.8 months	20.6 months	25
ALK first line	Subgroup analysis of a phase III randomised trial (ASCEND-8)	*ALK* positive metastatic NSCLC	2015–2017	Cho[129]	Ceritinib 450 mg versus 600 mg versus 750 mg (fasting)	Not estimated (19.2-NE) versus 21.9 months (4.1 to NE) versus 8.2 months (5.4–16.6)	3-year OS: 93.1% (75.1–98.2) versus 74.8% (45.3–89.9) versus 70.9% (47.9 versus 85.1)	102
ALK first line	Retrospective	*ALK* positive NSCLC	2013–2019	Patel[74]	Crizotinib, ceritinib	11.1 months	24.7 months	250
ALK poor performance status (PS)	Retrospective	*ALK* positive NSCLC with ECOG PS 2–4	2013–2018	Singh[130]	ALK TKI, chemotherapy, best supportive care; PS 2–4 versus 0–1	PS 2–4: 9.3 months (6.6–12) versus PS 0–1: 14.9 months (13.4–16.4); HR = 1.38; P = 0.027	17.9 months (12.8–23.1) versus 33.5 months (28.6–38.4); HR = 1.89; P < 0.001	441
ALK 2nd/3rd line	Retrospective	*ALK* positive NSCLC; Post progression on crizotinib	2018–2019	Talreja[131]	Lorlatinib	Mean PFS = 9.6 months (range, 7.1–12.1)	Mean OS from the start of lorlatinib = 13.6 months (range, 10.6–16.6); Mean OS from the date of diagnosis = 53.5 months (44.8–62.2)	34

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Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
(Continued from previous page)								
ALK 2nd line and beyond	Retrospective	*ALK*-positive NSCLC post progression or intolerance on initial therapy, who received lorlatinib	2018–2019	Kumar[132]	Lorlatinib	Median PFS = 16 months (5.4–26.6)	Median OS = 22 months (9.9–34.1); Median OS from diagnosis = 55 months (42.6–67.4)	38
Advanced stage: other mutations								
ROS1	Retrospective	*ROS1* positive	2015–2017	Joshi[133]	Crizotinib	Estimated 2-year PFS = 54% Response rate: 81%	2-year OS: 54%	22
ROS1	Retrospective	Stage IV NSCLC adenocarcinoma; *ROS1* positive	2012–2019	Mehta[134]	Crizotinib	Estimated 1-year PFS—56.2% Response rate: 64.8%	Estimated 1-year OS- 36.9%	14
ROS1	Retrospective	*ROS1* rearranged advanced NSCLC	2015–2021	Panda[135]	Chemotherapy in 21 (30.9%), ROS1 TKI in 38 (55.9%) (crizotinib, ceritinib, entrectinib), other therapy in 9 (13.2%)	Median PFS = 13 (95% CI, 9.92–26.1) months; Estimated 3-year PFS = 26.4% (95% CI, 16.15–43.2), estimated 5-year PFS = 15.4% (6.74–35.2); Response rate (to ROS1 TKI) = 85.3%	Median OS = 37.9 (95% CI, 20.6-NA) months; estimated 3-year OS = 53.8% (95% CIM 40.3–71.8); estimated 5-year OS = 38.8% (95% CI, 24.1–62.5)	68
KRAS	Retrospective	Metastatic NSCLC; *KRAS* mutated	2014–2018	Lee[136]	Chemotherapy with or without immunotherapy, targeted therapy	4.5 months (3.4–5.9)	10.3 months (6.9–12.4)	216
KRAS	Retrospective	Metastatic NSCLC; *KRAS* mutated	2016–2020	Batra[63]	Chemotherapy	5.4 months (G12C cohort = 6.4 months, versus non-G12C cohort = 3.8 months)	11.1 months (95% CI, 6–18)	36
KRAS	Retrospective	*KRAS*-mutant lung cancer	2016–2022	Noronha[137]	First line: Chemotherapy in 80 (86.9%), TKI (not KRAS directed) in 9 (9.8%). One patient received sotorasib in second-line	Chemotherapy: Median PFS = 6 (95% CI, 2.8–9.2) months	Chemotherapy: Median OS = 12 (95% CI, 9.2–14.8) months	133
Advanced stage: Non-driver mutated, first line palliative setting								
Advanced untreated squamous cell lung cancer	Phase III randomised non-inferiority trial	Stage IIIB or IV NSCLC, in the first line setting, squamous histology	2013–2018	Patil[138]	Gemcitabine (days 1 and 8) + carboplatin every 21 days for a maximum of 6 cycles. Randomisation was to gemcitabine at standard dose (1000 mg/m^2 over 30 min) versus low dose (250 mg/m^2 over 6 h)	3.1 versus 4 months; HR = 0.95 (0.86–1.28)	6.8 versus 8.4 months; HR = 0.89 (0.72–1.1); P = 0.006 for non-inferiority	308
First line advanced NSCLC	Phase II randomised study	Stage IIIB/IV NSCLC, in the first line setting	2004–2005	Digumarti[139]	Chemotherapy (paclitaxel + carboplatin) + oral talactoferrin versus chemotherapy alone	7 months versus 4.2 months; HR = 0.85; P = 0.24	10.4 months versus 8.4 months; HR: 0.87; P = 0.26	110

Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
(Continued from previous page)								
First line, advanced NSCLC	Phase II randomised study	Stage IIIB (unresectable) or IV NSCLC	Not reported; Published in 2014	Babu[140]	Nimotuzumab plus chemotherapy (docetaxel + carboplatin) versus chemotherapy alone	4.9 versus 4.8 months; HR: 0.81 (0.53–1.22); P = 0.31	10.1 versus 10.4 months; HR: 0.84 (0.53–1.35); P = 0.48	110
Advanced first line NSCLC	Prospective observational	First line NSCLC patients who had completed chemotherapy during a 12 month period	Not reported. Published in 2010	Singh[141]	Chemotherapy (Taxane + platinum for fit patients; single agent docetaxel for unfit patients); Outcomes compared between patients who had intercycle chemotherapy delays versus patients who did not	Not reported	232 days versus 247 days (in patients with intercycle chemotherapy dose delays versus those without delays); P = 0.604	100
First line, non-driver mutated	Retrospective	Stages IIIB and IV	2002–2006	Rajappa[142]	Chemotherapy (platinum doublet)	6 months (2–70)	7 months (2–72)	294
First line, non-driver mutated	Retrospective	Stage IV NSCLC	2008–2012	Tiwana[143]	Chemotherapy (carboplatin + paclitaxel/ etoposide + cisplatin/ gemcitabine + cisplatin)	Not reported	5 ± 1.5 months; 2-year OS = 8%	138
Maintenance therapy following first line	Phase III randomised controlled trial	EGFR negative non-squamous metastatic NSCLC, post 4 cycles platinum doublet	2014–2017	Patil[144]	Randomisation to pemetrexed intravenously versus erlotinib orally	4.5 months versus 4.5 months; P = 0.94	16.6 months versus 18.3 months; P = 0.49	200
Maintenance therapy following first line in advanced adenocarcinoma	Retrospective	Locally advanced and metastatic adenocarcinoma, who had received first therapy with pemetrexed + carboplatin and the disease had responded or was stable	2011–2014	Pandey[145]	Pemetrexed maintenance	8 months	20 months	188
Advanced (stage IIIB/IV) NSCLC (elderly patients)	Prospective observational	Advanced NSCLC, patients aged ≥60 years	Not reported; published in 2012	Prasad[146]	Carboplatin (AUC 5) and gemcitabine (350 mg/m^2 over 4 h, on days 1,8) chemotherapy for 6 cycles	Not reported	11 months; Statistically improved OS noted in patients who completed 6 cycles of chemotherapy (versus <6 cycles), dose reduction versus no dose reduction, best response of partial response or stable disease (versus progressive disease), and those treated by a medical oncologist (versus other doctor)	75
Advanced NSCLC in the second or third line setting	Randomised double blind placebo controlled Phase II study	Stage IIIB or IV histologically confirmed NSCLC, with progression on first line platinum-based chemotherapy, or on second line therapy	2004–2006	Parikh[147]	Oral talactoferrin (1.5 g in 15 mL phosphate-based buffer) or placebo (15 mL phosphate-based buffer) twice a day	Talactoferrin = 7 weeks (90% CI, 6–13); Placebo = 6 weeks (90% CI, 6–7); HR, 0.73 (90% CI, 0.9–1.07), P = 0.05	Talactoferrin = 6.1 months (90% CI, 4.7–8.4); Placebo = 3.7 months (90% CI, 2.8–4.9); P = 0.04	100

(Table 5 continues on next page)

Series

Eligibility/Stage	Type of study	Eligibility criteria	Enrolment years	First author	Modality	Progression free survival	Overall survival	Number of patients
(Continued from previous page)								
Advanced recurrent NSCLC, and first line in patients ineligible for platinum	Retrospective analysis of prospectively collected data	Recurrent and treatment-naïve platinum-ineligible advanced NSCLC	2010–2011	Noronha[149]	Paclitaxel 80 mg/m² weekly	4 months	7 months	37
Advanced NSCLC in the second- or third-line setting	Retrospective analysis of the Indian patients enrolled in the phase III randomised ISEL study[290] and patients included in the gefitinib expanded access program	Locally advanced or metastatic NSCLC, post one or two lines of chemotherapy, with progression or intolerance (EGFR testing was not routine)	ISEL trial[290]: Not reported (published in 2005) Gefitinib expanded access program: 2002–2004	Parikh[150]	Randomisation was 2:1 to gefitinib 250 mg orally daily, or placebo	Not reported	Indian subset in the ISEL study: Gefitinib-6.4 months; Placebo-5.1 months; Gefitinib expanded access program: 6 months	Indian subset of the ISEL study = 77; Gefitinib expanded access program = 133
Various lines: First line (4%), second line (67%), third line and beyond (29%)	Retrospective analysis	NSCLC, who had received immunotherapy.	2016–2018	Kumar[152]	Nivolumab (n = 70), pembrolizumab (n = 9), atezolizumab (n = 9)	4.73 months (95% CI, 3.7–8.9)	11.6 months (95% CI, 7.33-Not reached)	88
Advanced non-driver mutated NSCLC, post progression on systemic therapy	Retrospective	Advanced NSCLC, with no driver mutation, progressed on systemic therapy	Not reported, published in 2022	Batra[153]	Immunotherapy	3.2 months	7.1 months	64

ACRONYMS: PFS: progression free survival; OS: overall survival; CRT: chemoradiotherapy; chemo: chemotherapy; RT: radiotherapy; TKI: tyrosine kinase inhibitor; IO: immune checkpoint inhibitor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; HR: hazard ratio; FG: first generation; SG: second generation; TG: third generation; ECOG: Eastern Cooperative Oncology Group; PS: performance status; NE: not estimated; AUC: area under the curve

Table 5: **Studies from India and Southeast Asia evaluating the role of systemic therapy in lung cancer.**

(CRT) is better than sequential chemotherapy followed by RT. Although prospective data from Dasgupta et al. were contradictory,[110] most studies favoured concurrent CRT. In terms of the concurrent chemotherapy regimen, paclitaxel + carboplatin was compared to cisplatin + etoposide by Srinivasa et al., who reported no difference in efficacy.[116] Our group from the TMH in Mumbai, India, had published regarding the use of pemetrexed + platinum as induction chemotherapy in patients with N2 (ipsilateral mediastinal nodal spread) disease planned for radical therapy.[106]

Metastatic
EGFR mutation. Overall, the maximum volume of Asian data available for NSCLC is for patients with *EGFR*-positive metastatic disease. Our group has conducted two phase III trials in this cohort of patents in the first-line setting. In the first study, we compared upfront gefitinib to pemetrexed + carboplatin,[117,118] and in the second study, we compared gefitinib to the combination of gefitinib with pemetrexed + carboplatin in 350 patients with *EGFR*-mutant NSCLC.[58,59] Considering that newer medicines like osimertinib are not accessible or affordable for most patients in Southeast Asia, the gefitinib + chemotherapy combination became the standard of care for patients with advanced *EGFR*-mutant NSCLC, as reflected in various guidelines.[119,120] Other published data include a retrospective audit by Garg et al.,[121] Louis et al. (in a cohort clinically enriched for a possibility of harbouring *EGFR* mutation prior to when *EGFR* testing was routine),[122] post-hoc subset analysis of the phase III randomised study evaluating the differential survival in exon 19 versus 21,[123] retrospective data on uncommon *EGFR* mutations,[124] de novo T790M,[125] and a retrospective analysis of third line treatment in patients with *EGFR*-positive NSCLC.[126]

ALK fusion. Multiple retrospective analyses have been reported for *ALK* positive metastatic NSCLC, especially in the first line setting. With ALK TKI (predominantly crizotinib), the median PFS is between 11 and 14 months based on data from Kapoor et al.,[127] Batra et al.,[128] and Patel et al.[74] A retrospective analysis by Singh et al. showed good outcomes (PFS of 9.4 months) with ALK TKI even in patients with a poor performance status (PS).[130] A small case series by Talreja et al. found that following progression on crizotinib, lorlatinib resulted in a mean PFS and OS of 9.6 and 13.6 months, respectively (calculating from the start of lorlatinib therapy); mean OS calculated from the date of diagnosis was 53.5 months.[131] A more recent retrospective analysis by Kumar et al. in 38 patients with *ALK*-positive NSCLC, therapy with lorlatinib in the second line and beyond setting (84% received ≥2 prior lines of therapy, 76.3% had received a second generation oral TKI) resulted in a median PFS of 16 months (95% CI, 5.4–26.6) and a

median OS of 22 months (95% CI, 9.9–34.1); median OS from diagnosis was similar to that reported by Talreja et al.[131] at 55 months. The most common grade ≥3 toxicities included hypercholesterolemia (13%) and hypertriglyceridemia (11%). There were neurologic adverse events in 16% patients.[132]

Other mutations. Data for other rare mutations are sparse. Analysis from Joshi et al.[133] and Mehta et al.[134] have reported a 2-year OS of 54% and a response rate of 64.8%, respectively, with crizotinib in patients with *ROS1*-positive disease. Our group at TMH (Mumbai, India) recently reported the outcomes of 70 patients with *ROS1*-altered NSCLC, which underscored the importance of access to therapy; the median OS and 3-year OS of patients who received ROS1-directed therapy in the first line were 48.59 months (95% CI, 37.85-NA) and 71.8%, respectively, compared to 10.9 months (95% CI, 7.16-NA) and 36.7%, respectively, for those who received first-line chemotherapy.[135] Patients with *KRAS*-mutated disease have been reported to have a poor PFS in studies from Lee et al. (4.5 months)[136] and Batra et al. (5.4 months).[63] A recent study on 133 patients with *KRAS*-mutant NSCLC from our group at TMH reported a median OS of 12 months.[137]

Driver mutation negative
First line. Retrospective studies in driver mutation negative NSCLC have reported that the median PFS ranges between 4 and 9 months and OS between 10 and 13 months.[141–143] Outcomes, particularly PFS, in SqCC are lower than those in adenocarcinoma. Most available data are for chemotherapy, either alone,[141–143] or with targeted drugs like talactoferrin (orally administered immunomodulatory drug),[139] or the EGFR-directed antibody, nimotuzumab.[140] Our group proved in a randomised phase III trial that low-dose gemcitabine (250 mg/m^2 intravenously over 6 h on days 1 and 8) with carboplatin led to a non-inferior OS as compared to standard dose gemcitabine (1000 mg/m^2 intravenously over 30 min on days 1 and 8) with carboplatin every 21 days for up to six cycles, in patients with advanced SqCC in the first line palliative setting.[138] We had found that in patients with *EGFR*-negative non-SqCC NSCLC who had received at least four cycles of first line platinum-based combination chemotherapy and had not progressed, maintenance therapy with oral erlotinib led to similar PFS, OS and quality of life as pemetrexed.[144] Data for immunotherapy or immunotherapy plus chemotherapy in the first line setting are sparse.

Second line and beyond. Parikh et al. showed in a randomised phase II study conducted in 100 Indian patients with relapsed refractory NSCLC that oral talactoferrin prolonged OS over placebo.[147] Unfortunately, a subsequent global phase III study (FORTIS-M) by

Ramalingam et al. failed to corroborate this benefit of oral talactoferrin.[148] Several retrospective analyses have been published by various institutes detailing the use of chemotherapy, targeted therapy, and immunotherapy. We found that weekly paclitaxel led to a median OS of 7 months.[149] Gefitinib in the second line setting (Indian subgroup analysis of the ISEL trial, as well as Indian patients who received gefitinib as part of the expanded access program) resulted in a median OS of 5.6 months.[150,151] Nivolumab resulted in a median OS of 11.6 and 7.1 months in studies by Kumar et al.[152] and Batra et al.,[153] respectively.

Research
Despite rapid developments in the field of thoracic oncology, both clinical and translational, the rising burden of lung cancer in India is juxtaposed against a lack of protected research time, and exceedingly busy clinical commitments.[154] The research output mainly comes from studies involving cancer genetics and medical oncology, which together account for ~30% of the total output. A search in the Clinical Trials Registry-India (CTRI website) revealed that there were two studies evaluating vaccines, five studies on AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) and indigenous forms of medicine, only one study on artificial intelligence (AI), although there are many real world studies ongoing, and eight studies on palliative care/quality of life (Supplementary Tables S3, S3A, and S3B). When compared to the rest of the world, the India-to-world ratio for the proportion of cancer research for lung cancer is 0.51.[40,155]

In terms of published literature, from 1989 to 2017 there were 7545 articles published from India on lung cancer with an annual growth rate of 18.8%.[155] However, the impact factor trend has plateaued. This could be overcome by dedicated clauses and policies under the National Cancer Control Program, and dedicated Research Methodology Workshops like AAZPIRE, and workshops conducted by the Indian Council for Medical Research (ICMR).

The 59th report of the parliamentary standing committee on health and family welfare revealed many lax standards and regulatory violations in clinical trials and marketing authorization. In 2007, a clinical trial registry for India was attempted however this was not supported legislatively. Of all the trials registered with the Clinical Trials Registry-India (CTRI), only 14.9% were related to lung cancer, with ~70% being conducted only in India, whereas the proportion of global clinical trials in the nation is alarmingly low at only ~2%.[156] This needs serious policy changes, and more international collaborative efforts, in order to increase access to newer molecules which are continually being developed for lung cancer.

Efforts to devise better screening and early detection have been ramped up, for example, the state of Maharashtra in India, in association with researchers and investigators from TMH in Mumbai, planned to roll out a cervical cancer screening statewide trial. However, a similar study in lung cancer is currently elusive owing to the cost required for LDCT scans.

Batra et al. have developed and validated an AI tool capable of predicting oncogene addiction with ~90% accuracy for *EGFR* mutated cases.[157] If validated more extensively, this may translate clinically into a valuable tool.

Gaps and the way forward
Although several guidelines exist, we require a set of dynamic guidelines which change with changing science, and are region-centric, i.e., developed from data generated in Southeast Asia rather than based on global data. To address the issue of availability of trained manpower, the government of India has modified the eligibility criteria established by various hospitals to train people which has led to a jump in the number of people who get trained every year. Several of these policies have started showing results, but many more policy changes will be required to solve the issue of providing optimal cancer care, especially for patients with lung cancer in our region. Considering the size and complexity of Southeast Asian countries, a whole gamut of research in lung cancer is necessary. There is an urgent need to conduct well-designed research studies in most areas, including epidemiology (investigating the aetiology of non-smoking lung cancer, and possible interventions), molecular and biological studies, screening, staging, therapies (in all modalities, including surgery, radiation, systemic therapies, supportive and palliative medicine), and prognosis. The immediate need would be implementation research which can provide data related to treatment access, ability to complete treatment and outcomes in different parts of the country. We also need to have comparative studies to choose the right treatment for our patients which can be delivered in our circumstances. These should be conducted in various areas considering the different challenges we face. Given the resource constraints and the inability to deliver treatment developed in the Western world, our region requires to do a lot more collaborative and innovative research to develop cost-effective cutting-edge treatments which would be useful for our patients. Generating data on the current situation through simple observational studies would be the first step, followed by various innovative interventional designs, including metronomic dosing, drug repurposing, and novel interventions.

Conclusion
Thus, lung cancer in Southeast Asia is similar but also very different in myriad aspects from that in the West, as well as other parts of Asia. A fair amount of work has

been done, but there is a lot more that can and should be done to ensure that all patients with lung cancer receive the same level of high-quality care, regardless of their geographical location or ethnicity.

References
1 Available online at: https://gco.iarc.fr/. Accessed January 5, 2024.
2 Available online at: https://gco.iarc.who.int/media/globocan/factsheets/populations/995-who-south-east-asia-searo-fact-sheet.pdf. Accessed March 21, 2024.
3 ICMR-NCDIR. *Report of national cancer registry programme (ICMR-NCDIR), India*; 2020. Available online at: https://ncdirindia.org/All_Reports/Report_2020/default.aspx. Accessed January 4, 2024.
4 Bray F, Colombet M, Aitken JF, eds. *C33-34. Cancer incidence in five continents, Vol. XII.* International Agency for Research on Cancer; 2023.
5 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249. https://doi.org/10.3322/caac.21660.
6 Noronha V, Pinninti R, Patil VM, Joshi A, Prabhash K. Lung cancer in the Indian subcontinent. *South Asian J Cancer.* 2016;5(3):95–103. https://doi.org/10.4103/2278-330X.187571. PMID: 27606290; PMCID: PMC4991146.
7 Available online at: https://www.worldometers.info/world-population/population-by-country/. Accessed March 25, 2024.
8 Akhtar N, Bansal JG. Risk factors of lung cancer in nonsmoker. *Curr Probl Cancer.* 2017;41(5):328–339.
9 Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. *Nature.* 2023;616(7955):159–167.
10 Nath A, Sathishkumar K, Das P, Sudarshan KL, Mathur P. A clinicoepidemiological profile of lung cancers in India - results from the national cancer registry programme. *Indian J Med Res.* 2022;155(2):264–272.
11 Available online at: https://ntcp.mohfw.gov.in/assets/document/surveys-reports-publications/Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017.pdf. Accessed May 2, 2024.
12 Noronha V, Dikshit R, Raut N, et al. Epidemiology of lung cancer in India: focus on the differences between non-smokers and smokers: a single-centre experience. *Indian J Cancer.* 2012;49(1):74–81.
13 Krishnamurthy A, Vijayalakshmi R, Gadigi V, Ranganathan R, Sagar TG. The relevance of "Nonsmoking-associated lung cancer" in India: a single-centre experience. *Indian J Cancer.* 2012;49(1):82–88.
14 Manjunath SN, Madabhavi VI, Sarkar SM, Kaushal SS. Risk factor profile of lung cancer patients: a study from the himalayan state of Indian subcontinent. *Asian Pac J Cancer Care.* 2022;7(2):239–246. https://doi.org/10.31557/apjcc.2022.7.2.239-246.
15 Sapkota A, Gajalakshmi V, Jetly DH, et al. Indoor air pollution from solid fuels and risk of hypopharyngeal/laryngeal and lung cancers: a multicentric case-control study from India. *Int J Epidemiol.* 2008;37(2):321–328. https://doi.org/10.1093/ije/dym261. Epub 2008 Jan 30. PMID: 18234740.
16 Allemani C, Matsuda T, Di Carlo V, et al, CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 2018;391:1023–1075.
17 UICC. *Cancer awareness, prevention and control: strategies for South Asia.* UICC; 2006. Available online at: https://www.uicc.org/resources/cancer-awareness-prevention-and-control-uicc-handbook-south-asia. Accessed January 5, 2024.
18 WHO. Tobacco control in the South-East Asia region. WHO Health Topics. Available online at: https://www.who.int/southeastasia/health-topics/tobacco/tobacco-control-in-the-south-east-asia-region. Accessed January 5, 2024.
19 Jayalekshmy PA, Akiba S, Nair MK, et al. Bidi smoking and lung cancer incidence among males in Karunagappally cohort in Kerala, India. *Int J Cancer.* 2008;123(6):1390–1397. https://doi.org/10.1002/ijc.23618.
20 Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. *Int J Cancer.* 2003;107(3):441–447. https://doi.org/10.1002/ijc.11377.
21 Dikshit RP, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. *Int J Epidemiol.* 2000;29(4):609–614. https://doi.org/10.1093/ije/29.4.609.
22 Koul PA, Hajni MR, Sheikh MA, et al. Hookah smoking and lung cancer in the Kashmir valley of the Indian subcontinent. *Asian Pac J Cancer Prev.* 2011;12:519–524.
23 Phukan RK, Borah PK, Saikia BJ, Das M, Sekhon GS, Mahanta J. Interaction of tobacco smoking and chewing with Angiotensin converting enzyme (insertion/deletion) gene polymorphisms and risk of lung cancer in a high risk area from northeast India. *Asian Pac J Cancer Prev.* 2014;15(24):10691–10695. https://doi.org/10.7314/apjcp.2014.15.24.10691.
24 Raspanti GA, Hashibe M, Siwakoti B, et al. Ethnic variation in consumption of traditional tobacco products and lung cancer risk in Nepal. *Asian Pac J Cancer Prev.* 2015;16(14):5721–5726. https://doi.org/10.7314/apjcp.2015.16.14.5721.
25 Chulasiri PU, Gunawardana NS, de Silva A. Smoking and lung cancer risk in Sri Lankan men: a case-control study. *Ceylon Med J.* 2017;62:25–28.
26 Mukti RF, Samadder PD, Al Emran A, et al. Score based risk assessment of lung cancer and its evaluation for Bangladeshi people. *Asian Pac J Cancer Prev.* 2014;15(17):7021–7027. https://doi.org/10.7314/apjcp.2014.
27 Bhurgri Y, Decullier E, Bhurgri A, et al. A case-control study of lung cancer in Karachi, Pakistan. *Int J Cancer.* 2002;98(6):952–955. https://doi.org/10.1002/ijc.10210.
28 Gupta D, Boffetta P, Gaborieau V, Jindal SK. Risk factors of lung cancer in Chandigarh, India. *Indian J Med Res.* 2001;113:142–150.
29 Tuangratananon T, Wangmo S, Widanapathirana N, et al. Implementation of national action plans on noncommunicable diseases, Bhutan, Cambodia, Indonesia, Philippines, Sri Lanka, Thailand and Viet Nam. *Bull World Health Organ.* 2019;97(2):129–141. https://doi.org/10.2471/BLT.18.220483.
30 WHO. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. Available online at: https://www.who.int/publications-detail-redirect/9789240032095.
31 Raja BK, Devi VNK. Prevalence of tobacco use among school-going adolescents in India: a systematic review of the literature. *Cancer Res Stat Treat.* 2018;1:110–115.
32 Available online at: https://ntcp.mohfw.gov.in/national_tobacco_quit_line_services. Accessed March 27, 2024. Last accessed on Mar 20, 2024.
33 Beig TY, Khan UH, Ganie BA, Tahir S, Shah S, Dhobi GN. Correlation between serum tumor necrosis factor-alpha (TNF-α) and clinical severity of tuberculosis: a hospital-based study. *Cureus.* 2023;15(2):e35626.
34 Singh N, Madan K, Aggarwal AN, Gupta N, Das A, Behera D. Pleuropulmonary tuberculosis following chemotherapy for lung cancer at a tertiary care center in India. *JPMER.* 2013;47:177–180.

35 Ramachandran K, Thankagunam B, Karuppusami R, Christopher DJ. Physician related delays in the diagnosis of lung cancer in India. *J Clin Diagn Res*. 2016;10(11):OC05.

36 Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. *Asian Pac J Cancer Prev*. 2009;10:453–456.

37 Flockhart DA. Drug interactions: cytochrome P450 drug interaction table. Indiana Univ. Sch. Med. Available online at: https://drug-interactions.medicine.iu.edu; 2007. Accessed October 13, 2023.

38 *Guidelines for programmatic management of TB preventive treatment in India*; 2021. Available online at: https://tbcindia.gov.in/WriteReadData/l892s/Guidelines%20for%20Programmatic%20Management%20of%20Tuberculosis%20Preventive%20Treatment%20in%20India.pdf. Accessed October 13, 2023.

39 Mohan A, Garg A, Gupta A, et al. Clinical profile of lung cancer in North India: a 10-year analysis of 1862 patients from a tertiary care center. *Lung India*. 2020;37(3):190–197.

40 Singh N, Agrawal S, Jiwnani S, et al. Lung cancer in India. *J Thorac Oncol*. 2021;16(8):1250–1266.

41 Mohan A, Latifi AN, Guleria R. Increasing incidence of adenocarcinoma lung in India: following the global trend? *Indian J Cancer*. 2016;53:92–542.

42 Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Quantified smoking status and non-small cell lung cancer stage at presentation: analysis of a North Indian cohort and a systematic review of literature. *J Thorac Dis*. 2012;4(5):474–484.

43 Jindal SK, Behera D. Clinical spectrum of primary lung cancer: review of Chandigarh experience of 10 years. *Lung India*. 1990;8:94–98.

44 Gupta RC, Purohit SD, Sharma MP, Bhardwaj S. Primary bronchogenic carcinoma: clinical profile of 279 cases from mid-west Rajasthan. *Indian J Chest Dis Allied Sci*. 1998;40:109–116, 45.

45 Prasad R, James P, Kesarwani V, et al. Clinicopathological study of bronchogenic carcinoma. *Respirology*. 2004;9:557–560.

46 Khan NA, Afroz F, Lone MM, Teli MA, Muzaffar M, Jan N. Profile of lung cancer in Kashmir, India: a five-year study. *Indian J Chest Dis Allied Sci*. 2006;48:187–190.

47 Prasad R, Verma SK, Sanjay. Comparison between young and old patients with bronchogenic carcinoma. *J Cancer Res Ther*. 2009;5:31–35.

48 Rawat J, Sindhwani G, Gaur D, Dua R, Saini S. Clinico-pathological profile of lung cancer in Uttarakhand. *Lung India*. 2009;26:74–76.

49 Sheikh S, Shah A, Arshed A, Makhdoomi R, Ahmad R. Histological pattern of primary malignant lung tumours diagnosed in a tertiary care hospital: 10 year study. *Asian Pac J Cancer Prev*. 2010;11:1341–1346.

50 Dey A, Biswas D, Saha SK, Kundu S, Kundu S, Sengupta A. Comparison study of clinicoradiological profile of primary lung cancer cases: an Eastern India experience. *Indian J Cancer*. 2012;49:89–95.

51 Sharma PK, Bansal R. Profile of lung cancer in predominantly Bidi smoking rural population of northern Himachal Pradesh. *Indian J Chest Dis Allied Sci*. 2013;55:75–78.

52 Malik PS, Sharma MC, Mohanti BK, et al. Clinico-pathological profile of lung cancer at AIIMS: a changing paradigm in India. *Asian Pac J Cancer Prev*. 2013;14:489–494.

53 Mandal SK, Singh TT, Sharma TD, Amrithalingam V. Clinico-pathology of lung cancer in a regional cancer center in Northeastern India. *Asian Pac J Cancer Prev*. 2013;14:7277–7281.

54 Baburao A, Narayanswamy H. Clinico-pathological profile and haematological abnormalities associated with lung cancer in Bangalore, India. *Asian Pac J Cancer Prev*. 2015;16:8235–8238.

55 Murali AN, Radhakrishnan V, Ganesan TS, et al. Outcomes in lung cancer: 9-year experience from a tertiary cancer center in India. *J Glob Oncol*. 2017;3(5):459–468.

56 Kaur H, Sehgal IS, Bal A, et al. Evolving epidemiology of lung cancer in India: reducing non-small cell lung cancer-not otherwise specified and quantifying tobacco smoke exposure are the key Indian. *J Cancer*. 2017;54:285–290.

57 Nakra T, Mehta A, Bal A, et al. Epidermal growth factor receptor mutation status in pulmonary adenocarcinoma: multi-institutional data discussion at national conference of "Lung Cancer Management in Indian context". *Curr Probl Cancer*. 2020;44(3):100561.

58 Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. *J Clin Oncol*. 2020;38(2):124–136.

59 Noronha V, Patil V, Menon N, et al. Gefitinib vs gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-variant lung cancer-long-term results of a randomized clinical trial. *JAMA Oncol*. 2024;25:e240584. https://doi.org/10.1001/jamaoncol.2024.0584. Epub ahead of print. PMID: 38662354; PMCID: PMC11046413.

60 Chandrani P, Prabhash K, Prasad R, et al. Drug-sensitive FGFR3 mutations in lung adenocarcinoma. *Ann Oncol*. 2017;28(3):597–603.

61 Joshi A, Mishra R, Desai S, et al. Molecular characterization of lung squamous cell carcinoma tumors reveals therapeutically relevant alterations. *Oncotarget*. 2021;12(6):578–588.

62 Chougule A, Prabhash K, Noronha V, et al. Frequency of EGFR mutations in 907 lung adenocarcioma patients of Indian ethnicity. *PLoS One*. 2013;8(10):e76164.

63 Batra U, Nathany S, Sharma M, et al. KRAS mutated non-small lung carcinoma: a real world context from the Indian subcontinent. *Cancer Med*. 2023;12(3):2869–2874.

64 Rajendra A, Noronha V, Joshi A, Patil VM, Menon N, Prabhash K. Epidermal growth factor receptor-mutated non-small-cell lung cancer: a primer on contemporary management. *Cancer Res Stat Treat*. 2019;2:36–53.

65 Sharma M, Basu DA, Nathany S, Amrith BP, Batra U. A narrative review of the role of common EGFR mutations in pathogenesis and treatment of non-small-cell lung carcinoma. *Cancer Res Stat Treat*. 2022;5:507–518.

66 Munde S, Barodawala S, Lila K, et al. Molecular analysis for EGFR, ALK, and ROS1 alterations in over 3000 Indian patients with non-small-cell lung cancer: a retrospective observational study. *Cancer Res Stat Treat*. 2024;7:11–18.

67 Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014;9(2):154–162. https://doi.org/10.1097/JTO.0000000000000033.

68 Batra U, Biswas B, Prabhash K, Krishna MV. Differential clinico-pathological features, treatments and outcomes in patients with Exon 19 deletion and Exon 21 L858R EGFR mutation-positive adenocarcinoma non-small-cell lung cancer. *BMJ Open Respir Res*. 2023;10(1):e001492.

69 Panda GS, Noronha V, Shetty O, et al. EGFR exon 20 insertion in non-small cell lung cancer. *Cancer Res Stat Treat*. 2022;5:122–130.

70 Thomas R, Balaram G, Varayathu H, et al. Molecular epidemiology and clinical characteristics of epidermal growth factor receptor mutations in NSCLC: a single-center experience from India. *J Cancer Res Ther*. 2023;19(5):1398–1406.

71 Noronha V, Prabhash K, Thavamani A, et al. EGFR mutations in Indian lung cancer patients: clinical correlation and outcome to EGFR targeted therapy. *PLoS One*. 2013;8(4):e61561.

72 Batra U, Nathany S. Biomarker series: KRAS- A narrative review. *Cancer Res Stat Treat*. 2021;4:516–523.

73 Nathany S, Sharma M, Batra U. ALK-driven NSCLC: a narrative review - Part I. *Cancer Res Stat Treat*. 2023;6:272–278.

74 Patel A, Batra U, Prasad KT, et al. Real world experience of treatment and outcome in ALK-rearranged metastatic nonsmall cell lung cancer: a multicenter study from India. *Curr Probl Cancer*. 2020;44(3):100571.

75 Parang S, Bhavin J. LDCT screening in smokers in India-a pilot, proof-of-concept study. *Indian J Radiol Imaging*. 2021;31:318–322.

76 Damaraju V, Singh N, Garg M, et al. Effect of prior pulmonary TB on low-dose computed tomography during lung cancer screening. *Int J Tuberc Lung Dis*. 2023;27(3):223–225.

77 Purandare NC, Pramesh CS, Agarwal JP, et al. Solitary pulmonary nodule evaluation in regions endemic for infectious diseases: do regional variations impact the effectiveness of fluorodeoxyglucose positron emission tomography/computed tomography. *Indian J Cancer*. 2017;54(1):271–275.

78 Khurse BB, Kumar S, Deo S, et al. Mediastinal nodal staging of non-small cell lung cancer using PET-CT in a tuberculosis-endemic country. *Ann Oncol*. 2017;28(Supplement 2):ii14–ii16. https://doi.org/10.1093/annonc/mdx086.

79 Jersild S. Radiologist sightings drop around the world. diagnostic Imaging. Available online at: https://www.diagnosticimaging.com/

view/radiologist-sightings-drop-around-world. Accessed December 25, 2023.

80 Hindustan times Only one interventional radiologist per 2.18 lakh population in India. Available online at: https://www.hindustantimes.com/lucknow/only-one-interventional-radiologist-per-2-18-lakh-population-in-india/story-pb2lhPo4dhwuCReTRxg6WP.html. Accessed December 25, 2023.

81 Azeemuddin M. Current status of interventional radiology in Pakistan. *Arab J Interv Radiol.* 2020;4:1–2.

82 Kuo BJ, Aung MO, Hnin NP, et al. The state of interventional radiology in Myanmar: a national report. *J Glob Radiol.* 2021;7:1.

83 Frija G, Blažić I, Frush DP, et al. How to improve access to medical imaging in low-and middle-income countries? *eClinicalMedicine.* 2021;38:101034.

84 Nair CK, Mathew AP, George PS. Lung cancer: presentation and pattern of care in a cancer center in South India. *Indian J Cancer.* 2017;54(1):164.

85 Shilpakar R, Paudel BD, Sharma R, et al. Lung cancer in Nepal. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* 2022;17(1):22–29.

86 Malik PS, Malik A, Deo SV, Mohan A, Mohanti BK, Raina V. Underutilization of curative treatment among patients with non small cell lung cancer: experience from a tertiary care centre in India. *Asian Pac J Cancer Prev APJCP.* 2014;15(6):2875–2878.

87 Chandveettil J, Kattepur AK, Pareekutty NM, Kumbakara R, Balasubramania S. Changing trends of invasive mediastinal evaluation in India: a questionnaire-based survey. *Cancer Res Stat Treat.* 2021;4:231–237.

88 Yendamuri S. Why India needs video-assisted thoracic surgery (VATS). *Natl Med J India.* 2017;30(2):101–102.

89 Kumar A, Asaf BB. Robotic thoracic surgery: the state of the art. *J Minimal Access Surg.* 2015;11(1):60–67.

90 Majeed FA, Raheem K, Zafar U, Chatha SS, Raza A, Rauf A. Cervical mediastinoscopy as a diagnostic tool for mediastinal lymphadenopathy. *J Coll Phys Surg Pak.* 2023;33(9):1062–1066.

91 Mithi MT, Sharma M, Puj K, et al. Surgery for lung cancer: insight from a state cancer centre in India. *Indian J Thorac Cardiovasc Surg.* 2024;40(1):50–57. https://doi.org/10.1007/s12055-023-01590-9. Epub 2023 Sep. 4.

92 Thakur B, Yonghui D, Devkota M, Poudel B, Baral P. Surgical results of non-small cell lung cancer in Nepal. *JNMA J Nepal Med Assoc.* 2014;52(196):992–996.

93 Shah SH, Goel A, Selvakumar VPP, Garg S, Siddiqui K, Kumar K. Role of pneumonectomy for lung cancer in current scenario: an Indian perspective. *Indian J Cancer.* 2017;54(1):236.

94 Kumar A, Asaf BB, Puri HV, Sharma MK, Lingaraju VC, Rajput VS. Video-assisted thoracoscopic surgery lobectomy: the first Indian report. *J Minimal Access Surg.* 2018;14(4):291.

95 AEA DIRAC. *Available from: division for human health: Dirac (DIrectory of RAdiotherapy centres) [iaea.org)].* 2023.

96 Gupta N, Chugh Y, Prinja S. Bridging the cancer care gap and inequities in radiation treatment in India: a narrative review. *Cancer Res Stat Treat.* 2023;6:554–561.

97 Kundu S, Mathew A, Munshi A, Prabhash K, Pramesh CS, Agarwal JP. Stereotactic body radiotherapy in early stage non-small cell lung cancer: first experience from an Indian Centre. *Indian J Cancer.* 2013;50:227–232.

98 Pathak RS, Tibdewal AR, G Laskar S, Chaudhari S, Agarwal JP. Volume changes with stereotactic body radiation therapy in early lung cancer: time trends and outcomes. *J Med Imaging Radiat Oncol.* 2016;60:661–667.

99 Madhavan R, Renilmon PS, Nair HM, et al. Stereotactic body radiation therapy for early-stage primary lung cancer, is an active breath coordinator necessary? An audit from a tertiary care center. *Indian J Cancer.* 2017;54:301–304.

100 Talapatra K, Majumder D, Chadha P, et al. Stereotactic body radiotherapy for lung tumors: dosimetric analysis and clinical outcome. *Indian J Cancer.* 2018;55:170–175.

101 Agarwal JP, Pilar A, Mummudi N, et al. Stereotactic body radiation therapy for medically inoperable early-stage lung cancer: Tata Memorial Hospital perspective and practice recommendations. *Indian J Cancer.* 2020;57:18–24.

102 Shrimali RK, Saha A, Arun B, et al. Setting up a lung stereotactic body radiotherapy service in a tertiary center in Eastern India: the process, quality assurance, and early experience. *J Can Res Ther.* 2020;16:888–899.

103 Agarwal JP, Hotwani C, Prabhash K, et al. Optimizing treatment and analysis of prognostic factors for locally advanced nonsmall cell lung cancer in resource-limited population. *Indian J Cancer.* 2016;53:96–101.

104 Agrawal S, Kumar S, Lawrence A, Das MK, Kumar S. Ipsilateral lung dose volume parameters predict radiation pneumonitis in addition to classical dose volume parameters in locally advanced NSCLC treated with combined modality therapy. *South Asian J Cancer.* 2014;3:13–15.

105 Alagiyawanna L, Wijesekera S, Peiris V, et al. Lung cancer survival in Sri Lanka. *South Asian J Cancer.* 2022;12(2):173–178. https://doi.org/10.1055/s-0042-1755576.

106 Noronha V, Zanwar S, Joshi A, et al. Practice patterns and outcomes for pemetrexed plus platinum doublet as neoadjuvant chemotherapy in adenocarcinomas of lung: looking beyond the usual paradigm. *Clin Oncol.* 2018;30(1):23–29.

107 Prabhash K, Tan DSW, Soo RA, et al. Real-world clinical practice and outcomes in treating stage III non-small cell lung cancer: KINDLE-Asia subset. *Front Oncol.* 2023;13:1117348. https://doi.org/10.3389/fonc.2023.1117348. PMID: 37051534; PMCID: PMC10083698.

108 Noronha V, Talreja VT, Patil V, et al. Real-world experience of patients with inoperable, stage III non-small-cell lung cancer treated with durvalumab after chemoradiotherapy: Indian experience. *South Asian J Cancer.* 2020;9(3):180–182. https://doi.org/10.1055/s-0040-1721177. Epub 2020 Dec 14. PMID: 34395331; PMCID: PMC8357451.

109 Sharma S, Sharma R, Bhowmik KT. Sequential chemoradiotherapy versus radiotherapy in the management of locally advanced non-small-cell lung cancer. *Adv Ther.* 2003;20:14–19.

110 Dasgupta A, Dasgupta C, Basu S, Majumdar A. A prospective and randomized study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemotherapy-radiotherapy in unresectable non small cell carcinoma of the lung. *J Cancer Res Ther.* 2006;2:47–51.

111 Agrawal S. Challenges in optimizing chemoradiation in locally advanced non small-cell lung cancers in India. *South Asian J Cancer.* 2013;2:265–271.

112 Shrimali RK, Nallathambi C, Saha A, et al. Radical radiotherapy or chemoradiotherapy for inoperable, locally advanced, non-small cell lung cancer: analysis of patient profile, treatment approaches, and outcomes for 213 patients at a tertiary cancer center. *Indian J Cancer.* 2018;55:125–133.

113 Srivastava S, Saini SK, Agarwal SK. Comparative analysis of concurrent and sequential chemoradiation in locally advanced lung cancer: a single institution experience. *Int J Res Med Sci.* 2019;7:4479–4483.

114 Kumar R, Kumar HS, Paramanandhan M, et al. Neo-adjuvant chemotherapy followed by either continuous hyper-fractionated accelerated radiation therapy week-end less or conventional chemo-radiotherapy in locally advanced NSCLC-A randomised prospective single institute study. *J Can Res Ther.* 2020;16:860–866.

115 Sardar PK, Shenoi LR. A prospective study comparing induction chemotherapy followed by chemoradiation versus chemoradiation alone in stage III non-small cell lung cancer. *Int J Med Res Rev.* 2020;8:76–85.

116 Srinivasa GY, Gupta M, Seam RK, Rana S, Verma S, Gupta M. A randomized prospective study comparing concomitant chemo-radiotherapy using paclitaxel-carboplatin with concomitant chemoradiotherapy using etoposide-cisplatin in inoperable or nonresectable locally advanced non-small cell lung cancer. *Clin Cancer Investig J.* 2020;9:27–33.

117 Patil VM, Noronha V, Joshi A, et al. Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open.* 2017;2(1):e000168. https://doi.org/10.1136/esmoopen-2017-000168. PMID: 28761735; PMCID: PMC5519810.

118 Singh A, Patil V, Menon N, et al. Phase III randomized controlled trial of gefitinib versus chemotherapy in EGFR-positive treatment-naïve metastatic lung cancer: long-term outcome after eight years. *Cancer Res Stat Treat.* 2024;7:19–26.

119 Prabhash K, Vora A, Limaye S, et al. Treatment of advanced non-small-cell lung cancer: first line, maintenance, and second line– Indian consensus statement update(under the aegis of lung cancer consortium Asia, Indian cooperative oncology Network,

Indian society of medical and pediatric oncology, molecular oncology society, and association of physicians of India). *Cancer Res Stat Treat*. 2021;4:279–314.

120 Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol*. 2019;30(2):171–210.

121 Garg A, Batra U, Choudhary P, et al. Clinical predictors of response to EGFR-tyrosine kinase inhibitors in EGFR-mutated non-small cell lung cancer: a real-world multicentric cohort analysis from India. *Curr Probl Cancer*. 2020;44(3):100570. https://doi.org/10.1016/j.currproblcancer.2020.100570. Epub 2020 Mar 20. PMID: 32498966.

122 Louis RA, Rajendranath R, Ganesan P, Sagar TG, Krishnamurthy A. First report of upfront treatment with gefitinib in comparison with chemotherapy in advanced non-small cell lung cancer patients from South India: analysis of 120 patients. *Indian J Med Paediatr Oncol*. 2012;33:146–154.

123 Joshi A, Patil V, Noronha V, et al. Efficacy of gefitinib in epidermal growth factor receptor-activating mutation-positive nonsmall cell lung cancer: does exon 19 deletion differ from exon 21 mutation? *Lung India*. 2018;35(1):27–30.

124 Kate S, Chougule A, Joshi A, et al. Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: a single center retrospective analysis. *Lung Cancer*. 2019;10:1–10. https://doi.org/10.2147/LCTT.S181406. PMID: 30774491; PMCID: PMC6357894.

125 Panda GS, Noronha V, Shah D, et al. Treatment pattern and outcomes in *de novo* T790M-mutated non-small cell lung cancer. *Ecancermedicalscience*. 2022;16:1385. https://doi.org/10.3332/ecancer.2022.1385. PMID: 35919239; PMCID: PMC9300400.

126 Noronha V, Pande N, Joshi A, et al. Third-line therapy in the epidermal growth factor receptor mutation-positive advanced nonsmall-cell lung cancer. *South Asian J Cancer*. 2020;9(1):47–49. https://doi.org/10.4103/sajc.sajc_28_19. PMID: 31956622; PMCID: PMC6956591.

127 Kapoor A, Noronha V, Patil V, et al. Clinical profile, practice pattern, and outcomes with first-line therapy in ALK-positive lung cancer: real-world data from resource-constrained settings. *JTO Clin Res Rep*. 2022;4:100443. https://doi.org/10.1016/j.jtocrr.2022.100443.

128 Batra U, Aggarwal M, Jain P, et al. Clinical outcome study of crizotinib in immunohistochemistry-proven echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion gene among Indian patients with adenocarcinoma lung. *South Asian J Cancer*. 2018;7(1):61–64. https://doi.org/10.4103/sajc.sajc_215_17. PMID: 29600239; PMCID: PMC5865102.

129 Cho BC, Kim DW, Batra U, et al. Efficacy and safety of ceritinib 450 mg/day with food and 750 mg/day in fasted state in treatment-naïve patients with ALK+ non-small cell lung cancer: results from the ASCEND-8 asian subgroup analysis. *Cancer Res Treat*. 2023;55(1):83–93. https://doi.org/10.4143/crt.2021.1571. Epub 2022 Mar 25. PMID: 35344649; PMCID: PMC9873336.

130 Singh A, Kapoor A, Noronha V, et al. ALK-positive advanced non-small cell lung cancer patients with poor performance status: outcomes in a real-world scenario. *Ecancermedicalscience*. 2022;16:1407. https://doi.org/10.3332/ecancer.2022.1407. PMID: 36072236; PMCID: PMC9377804.

131 Talreja VT, Noronha V, Patil VM, Joshi A, Prabhash K. Lorlatinib in anaplastic lymphoma kinase-positive non-small cell lung cancer: Indian experience. *South Asian J Cancer*. 2020;9(1):67–68. https://doi.org/10.4103/sajc.sajc_364_19. PMID: 31956629; PMCID: PMC6956572.

132 Kumar A, Kapoor A, Noronha V, et al. Lorlatinib in the second line and beyond for ALK positive lung cancer: real-world data from resource-constrained settings. *BJC Rep*. 2024;2:35. https://doi.org/10.1038/s44276-024-00055-9.

133 Joshi A, Pande N, Noronha V, et al. ROS1 mutation non-small cell lung cancer-access to optimal treatment and outcomes. *Ecancermedicalscience*. 2019;13:900. https://doi.org/10.3332/ecancer.2019.900. PMID: 30915158; PMCID: PMC6390829.

134 Mehta A, Saifi M, Batra U, Suryavanshi M, Gupta K. Incidence of *ROS1*-rearranged non-small-cell lung carcinoma in India and efficacy of crizotinib in lung adenocarcinoma patients. *Lung Cancer*. 2020;11:19–25. https://doi.org/10.2147/LCTT.S244366. PMID: 32158297; PMCID: PMC7047993.

135 Panda GS, Noronha V, Patil V, et al. Clinical outcomes of *ROS1*-positive non-small cell lung cancer with limited access to ROS1-

136 Lee J, Tan AC, Zhou S, et al. Clinical characteristics and outcomes in advanced *KRAS*-mutated NSCLC: a multicenter collaboration in Asia (ATORG-005). *JTO Clin Res Rep*. 2021;3(1):100261. https://doi.org/10.1016/j.jtocrr.2021.100261. PMID: 35024639; PMCID: PMC8728099.

137 Noronha V, Sarkar L, Patil V, et al. Clinical characteristics, outcomes and prognostic factors in KRAS mutant lung cancers: experience from a tertiary care cancer center in India. *Ecancermedicalscience*. 2024;18:1674. https://doi.org/10.3332/ecancer.2024.1674.

138 Patil V, Noronha V, Joshi A, et al. Phase III non-inferiority study evaluating efficacy and safety of low dose gemcitabine compared to standard dose gemcitabine with platinum in advanced squamous lung cancer. *eClinicalMedicine*. 2019;9:19–25. https://doi.org/10.1016/j.eclinm.2019.03.011. PMID: 31143878; PMCID: PMC6510888.

139 Digumarti R, Wang Y, Raman G, et al. A randomized, double-blind, placebo-controlled, phase II study of oral talactoferrin in combination with carboplatin and paclitaxel in previously untreated locally advanced or metastatic non-small cell lung cancer. *J Thorac Oncol*. 2011;6(6):1098–1103.

140 Babu KG, Prabhash K, Vaid AK, et al. Nimotuzumab plus chemotherapy versus chemotherapy alone in advanced non-small-cell lung cancer: a multicenter, randomized, open-label Phase II study. *OncoTargets Ther*. 2014;7:1051–1060. https://doi.org/10.2147/OTT.S63168. PMID: 24966687; PMCID: PMC4063861.

141 Singh N, Aggarwal AN, Behera D, Jindal SK. Intercycle delays during chemotherapy of non-small cell lung cancer in a health care resource-constrained setting and their effect on overall survival. *J Thorac Oncol*. 2010;5:236–239.

142 Rajappa S, Gundeti S, Talluri MR, Digumarti R. Chemotherapy for advanced lung cancer: a 5-year experience. *Indian J Cancer*. 2008;45:20–26.

143 Tiwana MS, Lee HN, Saini S, et al. Outcomes of patients with unresected stage III and stage IV non-small cell lung cancer: a single institution experience. *Lung India*. 2013;30:187–192.

144 Patil V, Joshi A, Noronha V, et al. Randomized phase 3 open label study of quality of life of patients on Pemetrexed versus Erlotinib as maintenance therapy for advanced non squamous non EGFR mutated non small cell lung cancer. *Oncotarget*. 2019;10:6297–6307.

145 Pandey AV, Phillip DS, Noronha V, et al. Maintenance pemetrexed in nonsmall cell lung carcinoma: outcome analysis from a tertiary care center. *Indian J Med Paediatr Oncol*. 2015;36:238–242.

146 Prasad N, Bakshi A, Deshmukh C, Hingmire S, Ranade A, Parikh P. Importance of dose intensity in treatment of advanced non-small cell lung cancer in the elderly. *South Asian J Cancer*. 2012;1:9–15.

147 Parikh PM, Vaid A, Advani SH, et al. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. *J Clin Oncol*. 2011;29:4129–4136.

148 Ramalingam S, Crawford J, Chang A, et al. Talactoferrin alfa versus placebo in patients with refractory advanced non-small-cell lung cancer (FORTIS-M trial). *Ann Oncol*. 2013;24(11):2875–2880. https://doi.org/10.1093/annonc/mdt371. Epub 2013 Sep 19. PMID: 24050956.

149 Noronha V, Patil VM, Joshi A, Prabhash K. Efficacy and safety of metronomic administration of paclitaxel for advanced recurrent non-small-cell lung cancer. *Indian J Cancer*. 2013;50:122–127.

150 Parikh P, Chang AY, Nag S, et al. Clinical experience with gefitinib in Indian patients. *J Thorac Oncol*. 2008;3:380–385.

151 Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005;366(9496):1527–1537. https://doi.org/10.1016/S0140-6736(05)67625-8.

152 Kumar S, Joga S, Biswas B, et al. Immune checkpoint inhibitors in advanced non–small cell lung cancer: a metacentric experience

tyrosine kinase inhibitors (TKIs): experience from an Indian tertiary referral centre. *Ecancermedicalscience*. 2024;18:1654. https://doi.org/10.3332/ecancer.2024.1654.

from India. *Curr Probl Cancer*. 2020;44(3):100549. https://doi.org/10.1016/j.currproblcancer.2020.100549.

153 Batra U, Chufal KS, Nathany S, et al. Immunotherapy in advanced non-small-cell lung cancer (NSCLC) after progression on chemotherapy: real-world results from a prospective institutional cohort. *Immunotherapy*. 2022;14(11):851–858. https://doi.org/10.2217/imt-2021-0170. Epub 2022 Jun 14. PMID: 35698820.

154 Noronha V. Making a case for cancer research in India. *Cancer Res Stat Treat*. 2018;1:71–74.

155 Sullivan R, Badwe RA, Rath GK, et al. Cancer research in India: national priorities, global results. *Lancet Oncol*. 2014;15(6):e213–e222.

156 Chakraborty S, Mallick I, Luu HN, et al. Geographic disparities in access to cancer clinical trials in India. *Ecancermedicalscience*. 2021;15:1161.

157 Batra U, Nathany S, Nath SK, et al. AI in NSCLC: PET-CT & histology model. AI in NSCLC: PET-CT & histology model. *J Clin Oncol*. 2022;40:e21044. https://doi.org/10.1200/JCO.2022.40.16_suppl.e21044.