Review

Navigating patient journey in early diagnosis of lung cancer in India

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ABSTRACT

Lung cancer (LC) is one of the leading causes of cancer deaths worldwide. In India, the incidence of LC is increasing rapidly, and a majority of the patients are diagnosed at advanced stages of the disease when treatment is less likely to be effective. Recent therapeutic developments have significantly improved survival outcomes in patients with LC. Prompt specialist referral remains critical for early diagnosis for improved patient survival. In the Indian scenario, distinguishing LC from benign and endemic medical conditions such as tuberculosis can pose a challenge. Hence, awareness regarding the red flags—signs and symptoms that warrant further investigations and referral—is vital. This review is an effort toward encouraging general physicians to maintain a high index of clinical suspicion for those at risk of developing LC and assisting them in refering patients with concerning symptoms to specialists or multidisciplinary teams as early as possible.

KEY WORDS: Early diagnosis, general practice, incidental pulmonary nodule, lung cancer, patient navigation, red flags, referral pathway, screening, policy consideration

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INTRODUCTION

Lung cancer (LC) is the second most common cancer globally with 2,206,771 new cases and the leading cause of cancer-related deaths with 1,796,144 deaths in 2020.[1] Almost 3.3% of the world's new LC cases and 3.7% of LC-related deaths occurred in India in 2020.[1] LC has demonstrated an increasing trend in Indian women, from 7.9% in 2008 to 27.2% in 2018.[2] It is the second leading cause of cancer mortality in men in India, whereas in women it ranks fifth.[1]

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In India, 73%–93% of men and 23%–50% of women were found to be smokers at the time of diagnosis of LC[2]; approximately 59% of LC deaths in men and 15% of LC deaths in women were attributed to smoking.[3] Prevalence of LC is also high among younger patients (13.8%) and never-smokers (23.8%), and this could be possibly due to increased indoor air pollution and increased prevalence of oncogenic driver mutations, including epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements.[2]

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LC is histologically classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 92% of all LC cases with adenocarcinoma (43.8%) being the predominant histological type, followed by squamous cell carcinoma (SqCC) (26.2%), large cell (2.1%), and others (8.3%).[4] In India, the prevalence of adenocarcinoma has increased by 26.4%, SCLC by 5.2%, and NSCLC-not otherwise specified has decreased by 27.8%, over a period of 10 years.[2] However, in some parts of north and east India, both adenocarcinoma and SqCC are equally predominant (36.4% each).[5]

The 5-year survival rate remains poor (9.6%) in India as opposed to Europe (<20%) and the United States (US) (15%–19%), according to a global study conducted in 67 countries.[6] An ambidirectional feasibility study from north India reported a 5-year survival rate of 2%.[7]

In India, 80% of the patients with LC consult their general practitioner (GP) or primary care physician (PCP) despite severe respiratory symptoms.[8] Timely diagnosis and treatment remain critical for survival and improved prognosis of patients with LC. However, there is an unacceptable lag of up to 6 months from symptom onset to initiation of treatment compared with studies from Western countries.[9] The reasons for the delay may be multifactorial, such as accessibility to health care, patient awareness of the disease, and aggressiveness of the diagnostic approach. Most of these factors are modifiable and can have definite implications on patient survival.

This review is an effort towards encouraging physicians to maintain a high index of clinical suspicion for those at risk of LC and assisting them in referring patients with concerning symptoms to specialists or a multidisciplinary team (MDT) as early as possible for better patient outcomes.

UNPRECEDENTED SURVIVAL BENEFITS OF LUNG CANCER

Survival of LC can be improved by early diagnosis with multimodality management, and in advanced unresectable and metastatic disease by personalised treatment using precision medicine and novel therapies. Early stages of LC have a better prognosis; early diagnosis via screening programmes could be an effective approach for reducing LC mortality. This has been proven unequivocally in asymptomatic patients in the National Lung Screening Trial.[10]

The 5-year survival rate reported in stage I disease is up to 92% and in stage II is up to 60% compared with 10% in stage IV disease.[11] However, in India, only 3.5%–7.2% of patients are diagnosed at an early stage[2,5,12,13]; the majority (90%) are diagnosed at an advanced stage of the disease.[2,5] Early diagnosis of LC may allow surgical resection, the most effective treatment, with a 5-year survival rate ranging from 60%–80% for stage I and 30%–50% for stage II NSCLC.[14] In the US, with wider availability and adoption of modern imaging modalities and invasive mediastinal staging, an improvement in LC outcomes has been observed.[15]

Early-stage LC is generally treated with surgery (lobectomy, bilobectomy, pneumonectomy), with or without adjuvant chemotherapy and/or radiotherapy. In the last few years, treatment-related morbidity and mortality have decreased with surgeries like video-assisted thoracic surgery (VATS),[16] uniportal VATS,[17] awake surgery,[18] VATS without tracheal intubation,[19] and robotic VATS.[20] Adjuvant chemotherapeutic regimens have also been shown to increase survival in resected patients with stage II and stage III disease.[21] However, stereotactic body radiotherapy has emerged as one of the most significant advances in modern radiotherapy for early-stage inoperable NSCLC and those refusing surgery, since it can deliver extremely precise radiation to very high doses in a few fractions.[22] Particularly, in appropriately selected patients, it has demonstrated comparable local control rate and 5-year survival rates to surgery in stage I NSCLC.[23,24]

More recently, the biomarker-driven treatment—specifically tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have substantially improved outcomes in NSCLC with data for the same being largely available from their use in advanced unresectable or metastatic disease.[15,25-27] Patients with oncogenic driver alteration -positive LC can now be treated with ease of oral treatment options with good efficacy, tolerability, and proven overall survival benefit.[27] In those without targetable oncogenic driver alterations, immunotherapy has the potential to be an effective treatment option when used either singly (high PD-L1 expression) or in combination with chemotherapy (low or absent PD-L1 expression).

CHALLENGES OF EARLY DIAGNOSIS OF LUNG CANCER

LC poses a major diagnostic challenge for PCPs, particularly in its early stages due to non-specific symptoms such as cough, chest pain, weight loss, anorexia, and breathlessness with low predictive value for the diagnosis of cancer[28,29]; only about 22% of patients with LC initially present with haemoptysis.[30]

In India, the high endemicity of tuberculosis (TB) and the overlap of its symptomatology and radiological features with LC have created a scenario where a significant number of patients (up to 42.5%) have been misdiagnosed with TB, due to a low index of suspicion toward LC.[4,8,31–35] Anti-TB treatment is empirically commenced for sputum-acid-fast bacillus–negative patients with lung shadows that do not resolve with antibiotic treatment.[31,32] This could lead to a

substantial delay in diagnosis of LC, which in turn may lead to stage progression and higher mortality[4,8,9,31–35] [Table 1].

Other challenges at the primary care level may include lag time from symptom onset to the first visit to the PCP, delay due to investigation and symptomatic treatment, and the diagnostic procedure to establish the cancer diagnosis apart from the non-availability of advanced diagnostic procedures and specialists.[31] Low awareness of LC symptoms,[13] financial constraints and inadequate or inaccessible healthcare facilities are some of the factors shown to modify the healthcare-seeking behaviour at the grass-roots level.[8,35]

In some cases, LC develops against a background of chronic respiratory disease and symptoms of chronic cough, typically in patients who smoke, hindering and delaying the diagnosis of LC. Anecdotal evidence points to chronic obstructive pulmonary disease (COPD)[36] and past history of TB[37] being risk factors for the development of LC.

REFERRAL PATHWAY IN SUSPECTED LUNG CANCER

Current referral pattern

In several countries, a rapid referral pattern has been introduced between the primary care and specialist clinics for patients with suspected LC[38]; but in India, no such referral pattern exists. In India, although patients may have access to a specialist, most patients fail to seek the services of a specialist directly,[8,33] and a large number of patients on average have at least two GP consultations before presenting to the pulmonologist.[8]

As per recent evidence, around 15% of the patients in India consulted pulmonologists directly at the first visit without referral and 45.3% of patients consulted general medicine specialists and 27% of the physicians referred the patients to speciality centres for evaluation.[8]

Considering the current referral and the low index of suspicion for LC among GPs, streamlining referral pathways and services is imperative to improve LC care in India.[39]

Optimising the referral pathway

Early diagnosis of LC relies mainly on prompt patient presentation and timely referral of patients with symptoms suggestive of LC by GPs to a specialist.[8,31]

Risk factors

Smoking is a well-established principal risk factor for the development of LC.[2] Anecdotal evidence points to environmental factors such as exposure to second-hand smoke, radon, emissions from combustion of solid fuels (wood, charcoal, crop residues or dung), cooking fumes, environmental particulate matter, and occupational exposures as risk factors for the development of LC in never-smokers.[40]

Medical history

In addition to a family history of LC, the previous diagnosis of other cancers, history of COPD, TB and chronic bronchitis are found to be associated with long-term risk of LC.[36,37,41]

Overlapping symptoms

In several cases, symptoms of LC may be confounded by high levels of comorbidities. Patients with LC commonly experience multiple and synchronous symptoms [Supplementary Table S1].[9,30,33,34,42] Symptoms such as cough, dyspnoea, haemoptysis, loss of appetite, weight loss, fatigue, thoracic pain, and hoarseness of voice are the warning signs of LC, especially among high-risk individuals [Supplementary Table S2].[42,43]

Red flags

Red flags are warning signs and symptoms that suggest a potentially serious underlying disease. Symptoms such as haemoptysis, unintentional weight loss, persistent cough lasting longer than 6 weeks, and clubbing of fingers are red flag symptoms and signs that require investigation and the patient's prompt referral to a specialist.[42,43]

Individual red flag symptoms without taking other risk factors into account are likely to be inconsequential. Hence, the diagnostic approach to LC should focus on clinical history, classic symptoms,[42] symptom severity, or lack of response to treatment.

Table 1: Diagnostic delays in lung cancer in India[4,8,9,31-35]

Study	Type of study	Place of study	Period of study	No. of patients (*n*)	Stage of disease at diagnosis	Diagnosis delay from presentation of symptoms (months)	% of patients misdiagnosed as TB
Ramachandran *et al*.[8]	Prospective	Tamil Nadu	Nov 2006 to May 2007	96	Stage IIIB and IV	5.8	29.2
Chandra *et al*.[9]	Retrospective	New Delhi	Jan 2002 to Dec 2008	165	Stage IIIB and IV	4.8	17§
Noronha *et al*.[4]	Prospective	Mumbai	2008 to 2009	489	Stage I to IV	4	14.1
Shanthilal[31]	Retrospective	Karnataka	2011 to 2016	133	Stage III and IV	1.9*	17*
Singh *et al*.[32]	Prospective	New Delhi	Nov 2007 to Nov 2008	70	-	-	20
Gupta *et al*.[33]	Prospective	Jammu	2 years (year unspecified)	170	-	3	42.5
Dubey *et al*.[34]	Prospective	Madhya Pradesh	2012 to 2013	47	Stage IIIB, IV	5.7	23.4
Vashistha *et al*.[35]	Retrospective	New Delhi	2008 to 2016	1370	Stage I to IV	3.6	40*

ATT: Antituberculosis treatment; TB: Tuberculosis; *: Patients received ATT; -: Not available

Action on red flags

Typically, an immediate chest Xray (CXR) is suggested if two or more unexplained symptoms or any one of the red flags are present for more than 2 − 3 weeks. For patients with unresolved red flag symptoms, even in the presence of a clinical or microbiological diagnosis of TB, a chest computed tomography (CT) scan is suggested to detect possible underlying malignancy. Red flag symptoms suggestive of LC present for more than 3 weeks and CXR findings, either inconclusive or indicative of LC, should always lead to a referral to a specialist.[44] If a patient presents with typical features of LC, an immediate referral is indicated rather than further investigation at the primary care level [Figure 1].

MULTIDISCIPLINARY APPROACH FOR LUNG CANCER

The concept of a MDT is widely accepted as the gold standard of cancer care delivery across the world.[45,46] Studies evidenced improvements in the accuracy of staging, surgery referrals, the time interval from diagnosis to treatment and treatment receipt and clinical outcomes in LC through MDT care.[45,47,48]

The MDT panel for LC care generally comprises of a pulmonologist, medical oncologist, radiologist, thoracic surgeon, nurse, etc., and each member is assigned with clear roles and responsibilities towards the management of the patient.[48] The composition of the standard MDT panel along with the roles and responsibilities of each specialist is illustrated in Figure 2.[48] The GP can be a vital link between the patient and the MDT, leading to better coordination of referral, diagnosis and staging, and earlier assessment by oncologists and thoracic surgeons.[48] MDT approach helps to bring experts together to deliver the most appropriate evidence-based treatment options to individual patients.[49]

Pulmonologists play a leading role in the LC MDT care in the frontline along with medical oncologists, as they are the first point of referral for patients with suspicion of LC. In early-stage LC, the involvement of a pulmonologist[50] and collaboration between oncologists and surgeons[51] are associated with increased surgical resection rates and decreased mortality rates without increased cost among patients with cancer. Also, experienced surgeons or those working in high-volume centres and who attended regular MDT meetings are more likely to work closely with treating physicians in the context of decision-making regarding adjuvant therapies for patients following surgical treatment.[52] With technical advancements in imaging techniques and tissue diagnosis, interventional pulmonologists and interventional radiologists are valuable and integral members of the MDT.[53]

ROLE OF INTERVENTIONAL RADIOLOGY OR PULMONOLOGY FOR EARLY DIAGNOSIS OF LUNG CANCER

Imaging techniques for nodule or opacity detection

Nodule characteristics (size, density, conspicuity, morphology, location) and growth rate are the cardinal parameters for the probability of identifying LC when

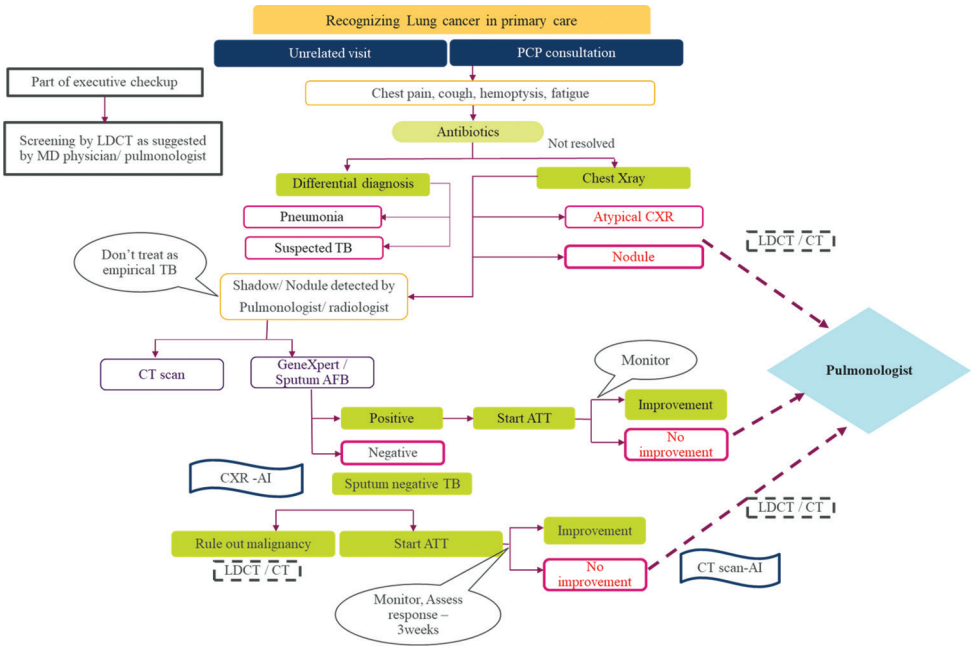

Figure 1: Referral pattern in lung cancer. AFB, Acid-fast bacillus; AI, Artificial intelligence; ATT, Anti-tuberculosis treatment; CT, Computed tomography; CXR, Chest X-ray; Genxpert, Cartridge based nucleic acid amplification test; PCP, Primary care physician; TB, Tuberculosis. : Differential diagnosis; : Actionable: : Expert opinion; : opportunity; : Alternate action pathway; : referral. *malignancy, if detected at any step, should be referred to MDT for further action

it presents as an incidental pulmonary nodule (IPN).[54] The risk of malignancy increases with an increase in nodule size. The risk is 0.2% for a pulmonary nodule (PN) of ≤3 mm, 0.9% for PN of 4 − 7 mm, 18% for PN of 8 − 20 mm, and 50% for PN of >20 mm.[55] The risk of malignancy was 83% in PN with irregular edges.[56] Other characteristics that are associated with a higher probability of malignancy are solitary PNs located in the upper lobes, PN with spiculated or lobulated margins (88%–94% or 58%, respectively),[55] eccentric or punctated lesions[55] pure ground glass (GG) opacities (59%–73%)[56] and an increased hazy lung attenuation on the faint nodular area.[55]

The Fleischner Society guideline recommends assessing patient risk factors and nodule characteristics such as size, density, multiplicity, morphology, and growth for the management of IPN.[54] Supplementary Table S3 presents a summary of clinical guidelines for the evaluation and management of solitary IPNs.[54,57,58]

Although low-dose CT (LDCT) is preferred for LC screening programs, CXR could still provide value in the screening and diagnosis of LC. Worldwide, CXR remains the most utilised diagnostic imaging procedure for suspected LC in primary care, with reported sensitivity ranging 77%–80% for the diagnosis of symptomatic LC[59]; incidental diagnosis of LC with CXR has also been reported.[60] The sensitivity of CXR may vary according to the tumour's size.[59] Hence, GPs should further consider an investigation, if necessary, in patients with persistent symptoms when CXR is negative. Moreover, PNs of ≤10 mm,[61] PNs in upper lobes, particularly the right lobe, and peripheral zones may be missed on CXRs, as they may be obscured by bony structures.[62,63] CXRs may not be sensitive enough to detect calcification and PN in apical (72%) or posterior segment (60%) and hilar zones.[62] Recommendations for reducing observer errors in LC identification via CXR are presented in Box 1.

A CT scan is more likely to show lung tumours than a routine CXR. Chest CT scan can detect small-sized PN (1–2 mm), and it can also provide specific information about the location, density, and edge characteristics of the PN.[64] However, it was recently reported that CT scans show similar GG opacities for coronavirus disease 2019 (COVID-19) and early LC, but with independent features. Hence, radiological features should be combined with epidemiological history, laboratory tests, pathological results, and short-term CT reexamination to aid differential diagnosis.[65] Contrast-enhanced CT (CECT) scan was found useful for the diagnosis of GG PNs.[66] Positron-emission tomography CT (PET-CT) scan demonstrated high accuracy in characterising PN (at least 8 mm) detected in LC with LDCT.[67] The accuracy and specificity are superior to CT scan and have less inter- and

Box 1: Steps for reducing observer errors in lung cancer identification on chest X-ray[62]

Develop a specific scan path on the CXR, which covers all the lung zones symmetrically to avoid missing any zones
Always check the blind zones (apices, hila, retro-cardiac and sub-diaphragmatic spaces) and the mediastinal lines and stripes carefully
Use lateral projection, if required
Consider inverse-intensity image as an additional tool to increase confidence in identifying lesions
Compare the most recent CXR with previous CXR if available and depending on the time interval, nodule stability over a prolonged duration abolishes the need for any further action

CXR: Chest X-ray

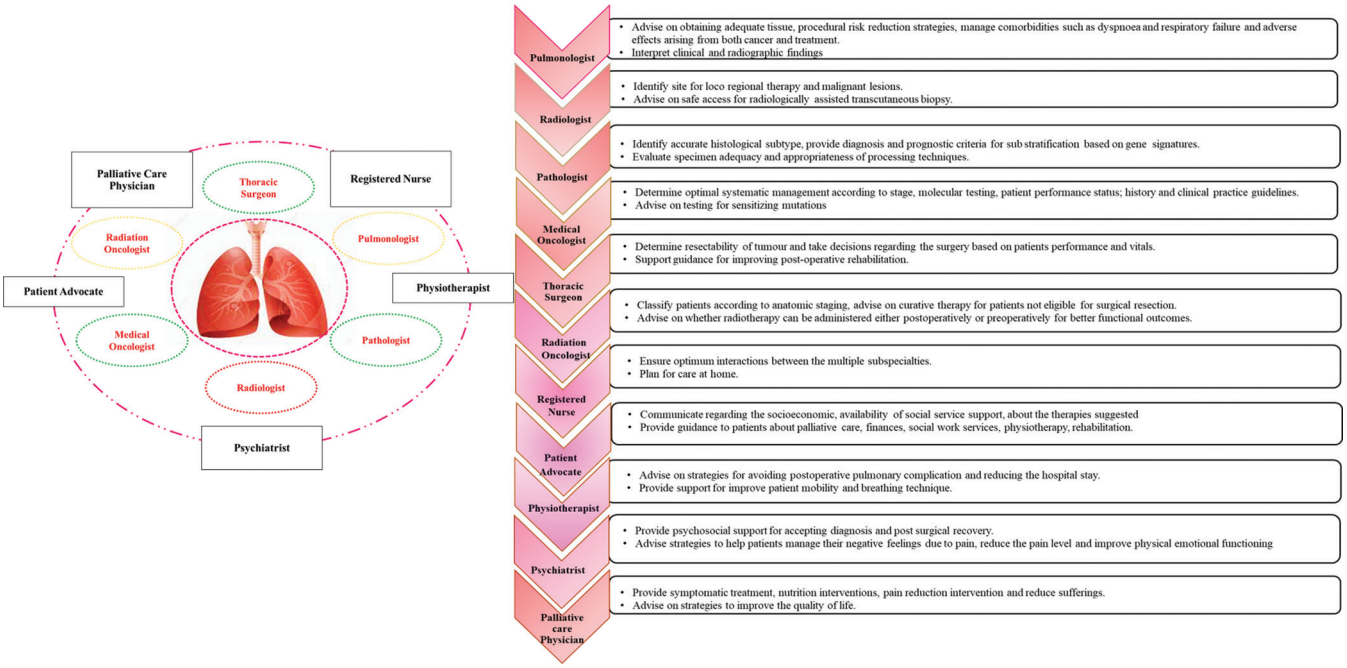

Figure 2: Multidisciplinary team care of patient with lung cancer

intra-observer variation.[67] In developing countries like India, owing to infectious conditions and TB, PET-CT may have a high false-positive rate and reduced specificity in characterising PN, limiting its use.[68,69] Hence, the GP must be aware of this limitation in the workup of PN, and differential diagnosis must be considered before further management decisions are taken.

Optimising tissue diagnosis

Obtaining tissue to ascertain the aetiology of a PN and establishing the diagnosis may be necessary in high-risk and intermediate-risk patients.[55] The optimal choice of technique to obtain tissue specimen depends on the type, location, and size of the lesion, comorbidities, and risk-benefit assessment of each potential strategy.

Flexible bronchoscopy is often used for the localisation of central lesions and transthoracic sampling for peripheral lesions. Over the past decade, although bronchoscopy services have witnessed their extensive use in India, they are being used only in major metropolitan cities.[70]

Different bronchoscopic techniques such as endobronchial ultrasound (EBUS), radial EBUS, electromagnetic navigation bronchoscopy, virtual 2D and 3D navigation bronchoscopy (such as Lung Point and Archimedes), and ultrathin bronchoscopy are available for the sampling of peripheral lesions. EBUS is most commonly offered by pulmonologists in India. A transthoracic biopsy is usually performed under ultrasonogram or CT by interventional radiologists. However, at present in India, less than 1% of healthcare facilities have a separate setup for interventional radiology.[71] For locating central lesions, either of the modalities is used depending on the available expertise and patient-specific factors. More recently, PET-guided biopsy has evolved as a promising technique for transthoracic sampling. It has demonstrated a 100% yield for evaluation of thoracic lesions in a patient with previous invasive sampling with inconclusive biopsy results.[72]

Most patients with the resectable disease typically undergo mediastinal staging, particularly among patients with some evidence of nodal involvement on imaging. Especially, in countries like India, where granulomatous diseases are endemic, establishing histopathological evidence of nodal involvement is particularly relevant. In India, only a few centres prefer performing mediastinal staging in all patients with resectable disease, regardless of a negative PET-CT.[73]

Mediastinoscopy is a popularly accepted diagnostic modality for mediastinal staging since it provides a larger amount of tissue for further analysis compared to endosonographic procedures. The literature has evidenced a similar yield and a lower complication rate for endoscopic procedures and mediastinoscopy. However, a higher false-negative rate has been reported for the endosonographic procedures.[74]

In recent times, peripheral blood sampling, a non-invasive way of biomarker testing is gaining importance in cancer detection because of its ease of use. Studies have reported the utility of circulating microRNAs,[75] circulating tumour DNA[76] and circulating tumour cells[77] in noninvasive diagnosis of early LC. However, active research is ongoing on the utility of these methods for diagnosing LC.

ROLE OF BIOMARKERS IN EARLY DIAGNOSIS OF LUNG CANCER

Serum biomarkers

Evaluation of tumour biomarkers in serum at an early stage of the disease has become an area of interest for many clinicians as they are minimally invasive. At the primary level, it could be useful for differentiating patients with overlapping features of TB and LC.[78] Abnormal marker levels can be considered as a criterion for the referral of patients with suspicion of LC for further evaluation to specialty centres. Mehta *et al*.[78] demonstrated a measurement of five tumour biomarker levels—carcinoembryonic antigen, SqCC-associated antigen, cytokeratin fragment 21-1, neuron specific-enolase, and pro-gastrinre-leasing peptide—to curtail the ambiguity of the diagnosis of LC.

Serum biomarkers are still an area of active research and cannot replace tissue for making a diagnosis of LC at present.

Molecular biomarkers

In lung adenocarcinomas, recognisable genetic driver alterations were found in 64% of the cases and their detection has implications on diagnosis, prognosis, and the use of targeted therapy.[79] A panel of molecular markers like *EGFR*, *ALK*, *HER2*, *BRAF*, *ROS1*, *RET,* and *MET* has been studied in LC.[80] The National Comprehensive Cancer Network® (NCCN®) currently recommends the actionable biomarkers such as *EGFR* (exon 19 deletions or exon 21 L858R), *ALK, KRAS, NTRK1/2/3, ROS1, RET, MET* exon 14 skipping and *BRAF V600E* testing for patients with metastatic non-squamous NSCLC before making therapy decisions, if clinically feasible.[81] However, molecular testing for these mutations or rearrangements can be considered in patients with metastatic SqCC if there is clinical suspicion of an adenocarcinoma component.[82] Programmed death-ligand 1 (PD-L1) expression and tumour mutational burden (TMB) has gained relevance as biomarkers in NSCLC, especially to evaluate clinical response to ICIs.[83] The NCCN recommends upfront PDL1 testing in newly diagnosed patients with metastatic NSCLC before commencing their treatment.[81]

In India, the prevalence of the two commonest oncogenic driver alterations, namely, *EGFR* mutations[2,84–86] is approximately 25.3%–30% and of *ALK* rearrangements[2,85] is approximately 10%–11.5%, and 33.6% have PD-L1 expression.[87] The national guidelines also recommend testing for *EGFR*, *ALK*, *ROS1* rearrangements, and PD-L1

overexpression for all patients with NSCLC in the frontline to provide improved treatment opportunities, including targeted therapy.[83]

SCREENING FOR LUNG CANCER IN INDIA AND POLICY CONSIDERATION

International guidelines recommend annual screening for LC with LDCT targeting high-risk patients (current or past smokers aged 50-80 years with a smoking history of 20 packyears).[88] In the National Lung Screening Trial[10] and NELSON trial,[89] about 56%−68% of the patients were detected at stage I or II. Consistently, in a study[90] 70% − 86% of the patients were diagnosed with stage I or II, which indicated that LDCT screening in community settings may significantly help in the early diagnosis of LC.[91] Besides, International Early LC Action Program results have shown a 10-year survival rate of 88% in patients with stage I disease, which was identified during screening.[92]

In many of the developing countries like Japan and Taiwan, national screening programmes are in place for early diagnosis of LC.[40] In 2016, the Ministry of Health and Family Welfare published an operational framework for the first national cancer screening programme in India.[93] According to a published framework, there will be mandatory screening for breast, oral and cervical cancer in 100 districts of India before the programme expands to other areas, targeting people over the age of 30 years.[93] However, despite the high LC incidence, no such organised national screening programmes exist in India. This may be attributed to a high prevalence of TB, poor infrastructure, logistic constraints, reluctance for screening among the high-risk population, and concerns regarding high false-positive rates.[78] In India, a policy change is an unmet need of the hour to include LC under national screening programmes along with cervical, breast, and oral cancer to propagate better outcomes for patients with LC. It could be implemented by identifying a feasible mechanism, high-risk individuals, appropriate screening tests and referral patterns, and diagnostic and therapeutic algorithms by conducting pilot studies to initiate a population-based lung screening programme.

Notably, because of the high prevalence of *EGFR* mutations and *ALK*/*ROS1* rearrangements and gradually improving access to novel TKIs in the country at considerably lower costs, the Indian Council of Medical Research (ICMR) has launched a nationwide Advanced Molecular Oncology Diagnostic Services project to provide biomarker testing for LC free of cost throughout the country.[85]

ROLE OF ARTIFICIAL INTELLIGENCE

In about 90% of the cases, misdiagnosis of LC occurs on CXR.[62] Despite advancements in technology, lesions can also be overlooked due to observer errors.[62] Automated detection techniques may be a valuable tool for automatic and precise identification of possible lesions or IPNs on CXR or CT scans and thus reduce diagnostic errors.[62]

Over the last decade, with its superior ability to recognise and quantify complex patterns in images, artificial intelligence (AI) demonstrated increased diagnostic accuracy and decreased false-positive rate with automatic precise identification of possible lesions or IPNs on radiographs of the lung in CXR or CT scans captured during planned screening programmes.[94,95] A diagnostic performance of an AI for detecting LC reported an overall sensitivity of 64% and specificity of 97% for cancer-positive CXR.[96] The application of AI in imaging diagnostics aid clinicians in the interpretation of CXR or CT images and creates an opportunity for incidental identification of suspected or known LC at earlier stages. Table 2 shows the role of AI in LC diagnosis through screening and incidental identification of suspected LC.[94–98]

Thus, AI can assess CXR and CT scans for IPN in diverse settings, including primary care, acting as a facilitator and timely referral for further evaluation. Besides, AI application with CXR could be effective and economical for screening and diagnosis of LC where there is a dearth of resources and expert manpower.

CONCLUSION

Early detection and optimal management of LC are instrumental in strengthening the robust cancer care and control system in the country. In India, there is an unmet need to decrease the lag period from symptom onset to initiation of treatment of LC compared to Western countries. Achieving early diagnosis of LC requires GPs to maintain a high level of suspicion and readiness to investigate patients at high-risk or those with non-resolving symptoms. Consultation with an MDT at the emergence of a red flag itself could be the key to providing a timely and accurate diagnosis and treatment of LC. CXRs and CT scans are the routine diagnostic imaging procedures utilised for suspected LC in primary care. Tissue diagnosis is the currently recommended approach and the gold standard for confirming the diagnosis of LC. AI can assess CXR and CT scans for incidental nodule identification in diverse settings, including primary care, acting as a facilitator for further evaluation. Incidental nodule detection programme in hospitals with MDT can be looked at as a complementary strategy to detect lung cancer. Proactive screening, referral to specialists, and aggressive follow-up can have the maximum impact on patient outcomes. Vigilant PCPs, early detection through wider adoption of LC screening in a high-risk population and improving access to cancer care are vital for the advancement of LC care in India.

Authors' contributions

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as

Table 2: Latest studies elucidating the role of artificial intelligence for nodule classification in screening, incidental identification of known or suspected lung cancer[94-98]

Study	Imaging modality	Study objective	Study criteria	Study findings	Implication
Nam *et al*.[94]	*CXR*	Detection of malignant PN on chest radiographs	A DLAD algorithm developed using 43,292 chest radiographs labelled and annotated by board-certified radiologists Algorithmic performance (radiographic classification and nodule detection) validated by one internal and four external datasets	AI vs radiologist Specificity: 95.2% vs NA Sensitivity: 80.7% vs 70.4% Rate of false-positive findings per image: 0.30 vs 0.25	The AI algorithm, DLAD, outperformed physicians in radiograph classification and nodule detection performance for malignant PN and enhanced physicians' performances when used as a second reader
Lee *et al*.[96]	*CXR*	Validate DL algorithm for LC detection in a screening population	Retrospective validation of DL algorithm for LC screening detection on chest radiographs in a health screening population Validation test cohort: 10,285 radiographs Screening cohort: 10,0525 radiographs	Validation results DL vs Radiologist Accuracy: 97% vs 100% Sensitivity: 64% vs 43% Specificity: 97%vs 100% FPR: 3.1% vs 0.3% Health screening results AI classification of cancer-positive CXR Sensitivity: 40% Specificity: 97% AI detection of visible LC Sensitivity: 83% Specificity: 97% AI detection of clearly visible LC Sensitivity: 100% Specificity: 97%	AI algorithm-DL detected LC nodules on chest radiograph with a performance comparable to that of radiologists, which will be helpful for radiologists in healthy populations with a low prevalence of LC
Liu *et al*.[97]	*CT scan*	Detection of LC nodules in the chest CT	Five thousand 5 mm and 1 mm chest CT films of T1 stage LC patients were used to train an AI algorithm. 500 thick chest CT films of T1 stage LC patients were tested by AI algorithm, and the sensitivity and specificity were compared with manual film reading	AI to read 500 cases of 5 mm chest CT: Sensitivity: 95.20% Specificity: 93.20% Kappa value: 0.926,1 AI to read 500 cases of 1 mm chest CT: Sensitivity: 96.40% Specificity: 95.60% Kappa value: 0.938,6	The detection rates of AI and manual reading were similar for 1 mm CT sets, with no significant difference. Sensitivity of AI for 5 mm CT sets, was better than manual reading, but the number of false positives increased, and the specificity was slightly worse. AI to automatically learn early LC chest CT images can achieve high sensitivity and specificity in early LC recognition and can assist doctors in diagnosis
Zhang *et al*.[95]	*CT scan*	Detect and classify PN derived from clinical CT images	Images obtained during screening from LUNA16 and Kaggle datasets were used to pretrain the AI-CNN model CT images from four hospitals in China were used for training and validating the algorithm Data from 50 patients who underwent surgical resection and had preoperative CT were prospectively collected for final assessment of the algorithm	Assessment of AI algorithm in 50-image evaluation set vs manual reading Accuracy: 92.0% vs 79.6% Sensitivity: 96.0% vs 81.3% Specificity: 88.0% vs 77.9%	AI compared with manual assessments exhibited significantly better performance with high sensitivity and specificity in detecting and classifying PN
Cui *et al*.[98]	*CT scan*	Identifying IPN in LDCT screening as part of routine healthcare	64,168 cases were used to retrospectively investigate the prevalence of non-calcified PNs in China by DL algorithm All CT images were automatically analysed by the DL algorithm at first. Then a junior radiologist checked the result given by the DL algorithm and revised the results when necessary Finally, an experienced radiologist confirmed the final decision and issued the diagnostic reports	AI vs Radiologist Performance (AUC): 0.86 vs 0.73 Sensitivity: 73% vs 83% Specificity 85% vs 64%	AI had better identification sensitivity and performance than radiologists, and was highly consistent with expert radiologists in terms of PN identification, regardless of nodule size With good performance, fast processing and efficiency, AI may serve as a radiologist's assistant

AI: Artificial intelligence; ANN: Artificial neural network; AUC: Area under curve; CNN: Convolutional neural network; CT: Computed tomography; CXR: Chest X-ray; DL: Deep learning; DLAD: Deep learning-based automatic detection; FPR: Falsepositive rate; IPN: Incidental pulmonary nodule; LC: Lung cancer; LDCT: Low-dose computed tomography; LUNA16: Lung nodule analysis 2016 challenge; NA: Not applicable; PN: Pulmonary nodule; SPN: Solitary pulmonary nodule

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY DATA

Supplementary Table S1: Population-based estimates of the frequencies of presenting symptoms among lung cancer patients[9,30,33,34,42]

Study	Study period	Setting	Sample size	Study population	Percentage (%) of occurrence of symptoms
Chandra *et al*.,[9]	2002-2008	Tertiary care	165	No limit	Coughing: 75.2 Shortness of breath: 66.9 Weight loss: 63.7 Chest pain: 63.1 Haemoptysis: 33.1 Hoarseness of voice: 29.3 Excessive weakness or fatigue: 26.8 Clubbing: 22.9 Dysphagia: 9.3 SVC: 8.0
Walter *et al*., [30]	2010-2012	Primary and secondary care data; self-reported symptoms before diagnosis	153	40+years	Haemoptysis: 21.6 Cough or worsening cough: 56.2 Breathlessness or worsening breathlessness: 41.2 Chest-shoulder pain: 35.3 Hoarseness: 12.4 Decreased appetite: 22.2 Unexplained weight loss: 15 Fatigue or tiredness: 45.1 Feeling different “in yourself”: 34.6
Gupta *et al*. [33]	Not specified	Tertiary care	170	No limit	Cough: 90.0 Loss of appetite and weight loss: 80.0 Expectoration: 79.4 Non-specific constitutional symptoms: 74.7 Chest pain or discomfort: 67.6 Shortness of breath: 54.7 Fever: 42.3 Lymphadenopathy: 30 Haemoptysis: 28.2 Hoarseness of voice: 24.7 Neurological signs: 14.7 SVC syndrome: 14.1 Bone pain: 11.7 Puffiness of face: 9.4 Asymptomatic: 3.5 Subcutaneous nodules: 3.5 HPOA: 2.9 Dysphagia: 1.7 Horner’s syndrome: 1.7 Gynaecomastia: 1.7 Deep vein thrombosis: 1.1

Contd.....

Supplementary Table S1: Contd...

Study	Study period	Setting	Sample size	Study population	Percentage (%) of occurrence of symptoms
Dubey *et al*. [34]	2012-2013	Tertiary care	62	No limit	Cough: 80.5 Chest: 74.4 Dyspnoea: 61.7 Decreased appetite: 44.6 Haemoptysis: 36.1 Weight loss: 23.4 Hoarseness of voice: 10.6 Fever: 22.2 Swelling over the face: 10.6 Dysphagia: 8.5 Vomiting: 4.2 Body ache: 12.7 Weakness: 6.3
Hamilton *et al*.[42]	1998-2002	Primary care, data from 21 general practices	247	40+years	Haemoptysis: 20 Weight loss: 27 Loss of appetite: 19 Dyspnoea: 56 Chest or rib pain: 42 Fatigue: 35 Finger clubbing: 4.5 Thrombocytosis: 14 Abnormal spirometry: 9.7

HPOA: Hypertrophic pulmonary osteoarthropathy, SVC: Superior vena cava

Supplementary Table S2: Risk rate and positive predictive rate for lung cancer[42,43]

Symptoms	Odds ratio 95% Confidence interval *P* value	Positive predictive value
Loss of appetite	86 (3.6 to 2100), 0.006	0.87 (0.6, 1.3)
Haemoptysis	32 (13 to 81), <0.001	2.4 (1.4, 4.1)
Cough	Not applicable	0.40 (0.3, 0.5)
Dyspnoea	4.7 (2.7 to 8.0), <0.001	0.66 (0.5, 0.8)
Loss of weight	4.3 (2.2 to 8.2), <0.001	1.1 (0.8, 1.6)
Fatigue	3.2 (1.7 to 6.0), <0.001	0.43 (0.3, 0.6)
Chest pain	2.9 (1.8 to 4.7), <0.001	0.82 (0.6, 1.1)
Finger clubbing	18 (1.7 to 190), 0.016	Not applicable
Thrombocytosis	9.3 (3.4 to 26), 0.001	1.6 (0.8, 3.1)
Abnormal spirometry	7.5 (2.8 to 21), 0.001	1.6 (0.9, 2.9)
Dyspnoea with fatigue	0.28 (0.11 to 0.73), 0.006	0.66 (0.5, 0.8)
Loss of appetite in patients over 70 years	0.13 (0.024 to 0.76), 0.02	0.87 (0.6, 1.3)

Supplementary Table S3: Summary of clinical guidelines for evaluation and management of incidental solitary pulmonary nodules[54,57,58]

Name of the society	Sub-solid nodules	Small solid nodules	Large solid nodules	Comments
Fleischner Society[54]	Solitary solid nodules <6 mm (<100 mm^3) Low-risk patients: No routine follow-up required High-risk patients: Optional CT at 12 months (particularly with suspicious nodule morphology and/or upper lobe location) Sub-solid single GGN <6 mm (<100 mm3) No routine follow-up required Sub-solid single part solid nodule <6 mm (<100 mm^3) No routine follow-up required	Solitary solid nodules 6-8 mm (100-250 mm^3) Low-risk patients: CT at 6-12 months, then consider CT at 18-24 months High-risk patients: CT at 6-12 months, then CT at 18-24 months Sub-solid single GGN ≥6 mm (>100 mm^3) CT at 6-12 months, then if persistent, CT every 2 years until 5 years Sub-solid single part solid nodule ≥6 mm (>100 mm^3) CT at 3-6 months, then if persistent and solid component remains <6 mm, annual CT until 5 years	Solitary solid nodule >8 mm (>250 mm^3) Low-risk and high-risk patients: Consider CT at 3 months, PET/CT, or tissue sampling	In low-risk patients: Nodules <6 mm do not require routine follow-up. Certain patients at high-risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up. In certain suspicious nodules, 6 mm, consider follow-up at 2 and 4 years. If solid component (s) or growth develops, consider resection. In practice, part solid nodules cannot be defined as such until ≥6 mm, and nodules, <6 mm do not usually require follow-up. Persistent part solid nodules with solid components ≥6 mm should be considered highly suspicious.
ACCP[57]	Single GGN ≤5 mm No routine follow-up required Single GGN >5 mm Annual CT chest for 3 years Single GGN >10 mm Repeat CT in 3 months followed by a biopsy if persistent Single part solid nodule ≤8 mm CT surveillance in 3, 12, and 24 months followed by annual CT for an additional 1-3 years Single part solid nodule >8 mm CT chest in 3 months followed by PET/CT (if solid component >8 mm) or biopsy if persistent or growing Single part solid nodule >15 mm PET/CT or biopsy PET does not reliably identify malignant nodules in this group, particularly pure GGNs TTNB has suboptimal sensitivity High likelihood of malignancy and need for longer surveillance	Nodule <8 mm Interval follow-up CT based on size and individual risk factors for cancer (generally 6-12 months) Size divided into ≤4, 4-6, 6-8 Does not recommend functional imaging or biopsy given most nodules in this group are benign and unreliability of diagnostic modalities	Nodule ≥8 mm CT surveillance, PET/CT, nonsurgical biopsy, or surgical biopsy are appropriate depending on the probability of cancer, surgical risk, and patient preference In low-risk (<5%) patients: CT surveillance In intermediate risk (5%-65%) patients: PET/CT for further risk stratification In high-risk (>65%) patients: Biopsy or resection. No PET, unless staging TTNB or bronchoscopy modalities depending on nodule location and centre expertise	Same algorithm for screening and incidental detected nodules. Low-risk <5%, intermediate risk 5%-65%, high-risk >65%. Low-risk defined as young, less smoking, no prior cancer, small nodule, regular margins and not located in upper lobes. High-risk is the opposite TTNB and intermediate features of both. Predictive model or clinical judgment appropriate (mentions Mayo as most validated). Solid nodule stable for ≥2 years; no follow-up.
BTS[58]	Nodule <5 mm (80 µl) No follow-up required Nodule ≥5 mm CT at 3 months, and if stable, use Brock model. If risk <10%, then CT surveillance at 1, 2, and 4 years. If risk>10% consider biopsy, resection or CT surveillance. If growth at 3 months consider resection, nonsurgical treatment, or CT surveillance.	Nodule <5 mm (80 µl) No follow-up required Nodule 5-6 mm CT surveillance at 1 year. Further evaluation will depend on the stability 6-8 mm (80-300 µl) CT surveillance at 3 months. If VDT <400 or clear growth requires further investigation. If stable, repeat CT in 1 year	Nodules ≥8 mm (≥300 µl) Brock model for risk assessment If <10%, CT surveillance If >10%, PET/CT and apply Herder model If <10% after Herder, CT surveillance If 10%-70% after Herder, CT surveillance, or biopsybased on risk and individual preference If >70% after Herder, surgery, nonsurgical biopsy, or nonsurgical treatment	Same algorithm for screening and incidentally detected nodules Applies to all adults ≥18 years old, and nodules detected in the context of current or prior malignancy Recommends using Brock model and then PET/CT and Herder model if risk is >10%

ACCP: American College of Chest Physicians; BTS: British Thoracic Society; CT: Computed tomography; GGN: Ground glass nodule; IPN: Indeterminate pulmonary nodule; PET: Positron-emission tomography; TTNB: Transthoracic needle biopsy; VDT: Volume doubling time. Summary of clinical guidelines for single pulmonary nodule. In general, guidelines recommend evaluation based on dominant/larger nodule. Refer to individual guidelines for management of multiple nodules. These recommendations are for IPN [no features of benign (fat), and not calcified in benign pattern]. All guidelines recommend reviewing prior imaging when IPN first identified nodule