review articles

Toward Improved Outcomes for Patients With Lung Cancer Globally: The Essential Role of Radiology and Nuclear Medicine

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abstract

PURPOSE Key to achieving better population-based outcomes for patients with lung cancer is the improvement of medical imaging and nuclear medicine infrastructure globally. This paper aims to outline why and spark relevant health systems strengthening.

METHODS The paper synthesizes the global lung cancer landscape, imaging referral guidelines (including resource-stratified ones), the reliance of TNM staging upon imaging, relevant multinational health technology assessments, and precisely how treatment selection and in turn patient outcomes hinge upon imaging findings. The final discussion presents data on current global gaps in both diagnostics (including imaging) and therapies and how, informed by such data, improved population-based outcomes are tangible through strategic planning.

RESULTS Imaging findings are central to appropriate lung cancer patient management and can variably lead to life-prolonging interventions and/or to life-enhancing palliative measures. Early-stage lung cancer can be treated with curative intent but, unfortunately, most patients with lung cancer still present at advanced stages and many patients lack access to both diagnostics and therapies. Furthermore, half of lung cancer cases occur in low- and middle-income countries. The role of medical imaging and nuclear medicine in lung cancer management, as outlined herein, may help inform strategic planning.

CONCLUSION Lung cancer is the number one cancer killer worldwide. The essential role that medical imaging and nuclear medicine play in early diagnosis and disease staging cannot be overstated, pivotal in selecting the many patients for whom measurably improved outcomes are attainable. Prevention synergized with patient-centered, compassionate, high-quality lung cancer management provision mandate that strategic population-based planning, including universal health coverage strategies, should extend well beyond the scope of disease prevention to include both curative and noncurative treatment options for the millions afflicted with lung cancer.

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INTRODUCTION

The Landscape

Lung cancer remains a leading cause of premature death (among people younger than 75 years) worldwide.[1] In fact lung cancer alone represents 11.6% of all incident cancer diagnoses and 18.4% of mortality attributable to cancer globally, and therefore has a pronounced humanitarian as well as socioeconomic effect.[2–4] Lung cancer claimed 1.8 million lives in 2018 and its prevalence is rising among women, currently surpassing breast cancer in 28 countries[4] (Fig 1). Furthermore, half of lung cancer cases occur in low- and middle-income countries (LMICs).[5]

Addressing the root causes has led to lower disease rates in multiple countries.[6] As well, those with early-stage lung cancer can be treated with curative intent.[7] Unfortunately, most patients with lung cancer still present at advanced stages. The essential role that medical imaging and nuclear medicine play in early diagnosis and in accurate disease staging cannot be overstated, pivotal in selecting patients for whom measurably improved outcomes are attainable.[8–10] Moreover, guidelines for appropriately triaging those with incurable disease are based largely upon imaging findings. This can variably lead to life-prolonging interventions and to a range of life-enhancing palliative measures.

Lung Cancer History, Global Public Health, and Imaging

In the 1940s and 1950s, the proven link between tobacco and a growing lung cancer epidemic was recognized.[11] The World Health Organization reacted and the WHO Lung Cancer Classification was first published in 1967 to support uniformity of pathologic diagnoses and monitor the crisis.[12] The WHO divides

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CONTEXT

Key Objective

In tackling the number one cancer killer—lung cancer—why should public health and universal health coverage strategies extend beyond the scope of disease prevention, alone, to include both curative and noncurative treatment options for patients with lung cancer worldwide and how is *medical imaging* essential toward achieving these improved population-based lung cancer outcomes? This paper aspires to galvanize high-level strategic dialogues on how medical imaging infrastructure improvement is a key puzzle piece to achieving improved population-based lung cancer outcomes.

Knowledge Generated

The evidence base is presented on how imaging is key to lung cancer management and should therefore figure among relevant essential elements in universal health coverage strategies.

Relevance

The content can help our peers, especially policymakers in low-resource settings, to strengthen infrastructure that could more effectively address not only the prevention of lung cancer but also the management of the many afflicted.

lung cancer into two main categories, small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC), with the latter accounting for approximately 80% of lung cancer cases.[4]

According to the WHO, tobacco use is the most important risk factor for cancer and is responsible for approximately 22% of cancer deaths, including cancers of nonpulmonary origin.[13] Today, 80% of lung cancer is linked to cigarette smoking[14] and accounts for 1.5 million lung cancer deaths per year.[11] The WHO further reports that air pollution causes up to 29% of global mortality from lung cancer.[15] Nearly all deaths (94%) secondary to air pollution overall

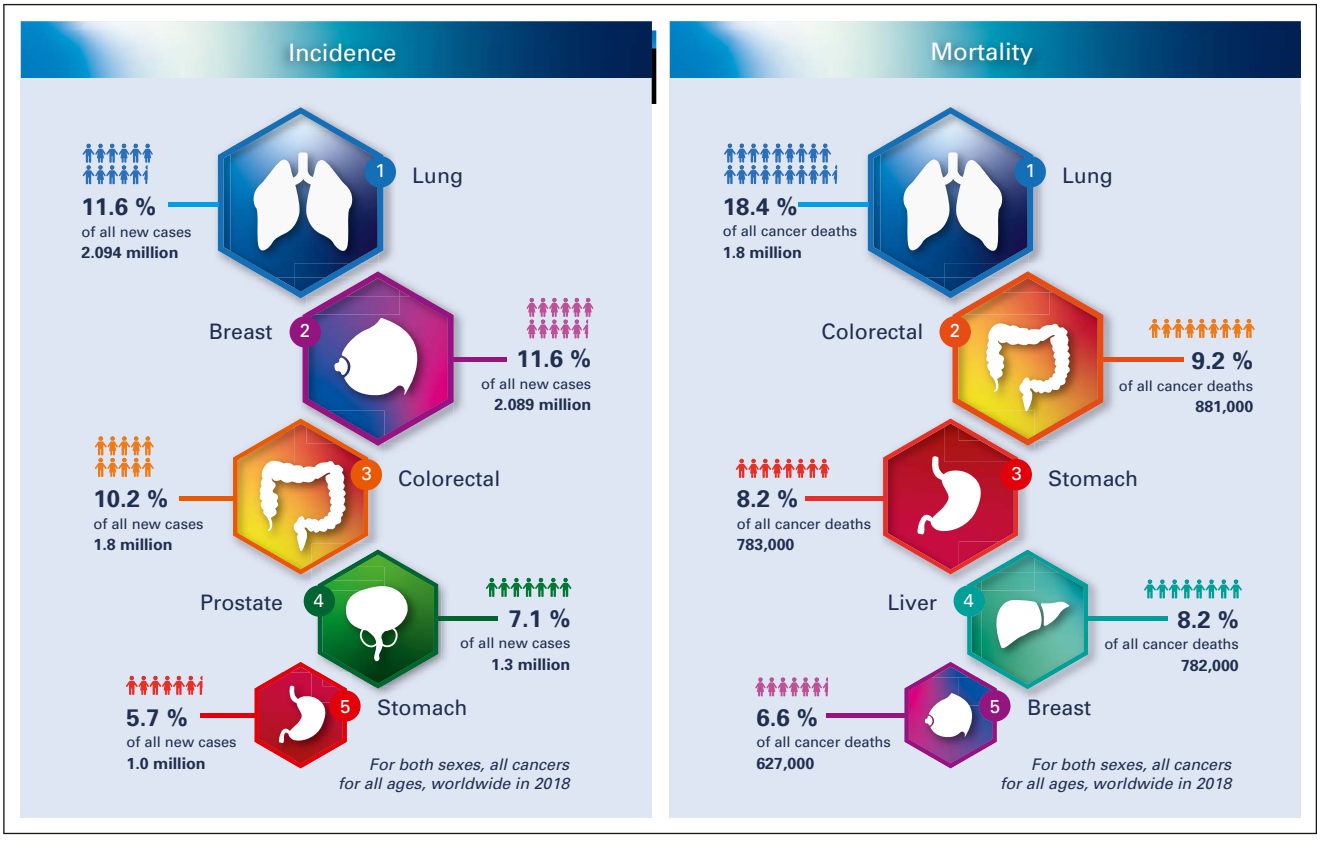

FIG 1. Global incidence and mortality of common cancers worldwide in 2018. Data Source: the International Agency for Research on Cancer Global Cancer Observatory 2018 statistics. Graphic production: the International Atomic Energy Agency.

occur in LMICs, and 92% of the world population resides in areas where air pollution exceeds safe limits.[16]

The public health sphere is waging war to address both social determinants and environmental causes (eg, air pollution, radon, and asbestos) of lung cancer, acknowledging a particularly steep rise in disease rates in LMICs' populations.[5] Managing the millions *afflicted*, as well as those who stand to become afflicted with lung cancer, is a concurrent health priority that does not explicitly feature in prevailing global strategies for noncommunicable diseases.[17,18] Eradication of the etiologies of lung cancer should coexist synergistically with broad implementation of impactful interventions for those in whom lung cancer has developed, particularly given the indolent, often decades-long time interval between exposure and the development of lung cancer.[19,20]

Medical imaging and nuclear medicine play an essential role in the screening, early diagnosis, accurate staging, therapy planning, and follow-up of patients with lung cancer. Although a detailed roadmap for how LMICs should go about establishing or improving their lung cancer management infrastructure does not exist, several clinical management guidelines provide vital basic guidance.

Where Imaging Fits in Resource-Stratified Guidelines

Resource-stratified guidelines such as those of the National Comprehensive Cancer Network (NCCN) aim to empower LMICs by defining appropriate treatment pathways on the basis of available resources, to deliver a tool for governments and health care providers to identify treatment options that will provide the best possible outcomes, given specific resource constraints.[21,22] Regarding imaging of NSCLC, NCCN guidelines note the most important radiologic factor is change or stability compared with a previous imaging study, highlighting the importance of serial imaging in the decision tree. Standard NCCN guidelines differ from resource-stratified guidelines, as the latter are segregated into *Basic Resources*, *Core Resources*, and *Enhanced Resources*.

NCCN *Basic Resources* (Version 3.2020, August 18, 2020) recommendations do not include medical imaging or nuclear medicine for NSCLC. By contrast, NCCN Core Resources (Version 3.2020, August 18, 2020) guidelines for NSCLC include chest radiography, abdominal ultrasound, bone x-rays, and scintigraphy as guided by symptoms. Small biopsies or cytology specimens intended for initial diagnosis are also mentioned.

For NCCN *Enhanced Resources* (Version 3.2020, August 18, 2020), multiple additional imaging modalities for NSCLC are included, such as computed tomography (CT; chest and upper abdomen with contrast, including adrenals) and CT follow-up. Low-dose CT (LDCT) is also advised for those at high risk of developing lung cancer. Biopsy (image-guided transthoracic biopsy) is included as well as warranted biopsy of lesions suspicious for metastasis. Bone x-rays, bone scintigraphy, and brain CT with contrast may be considered, as guided by symptoms. Surgical exploration, radiotherapy, and chemoradiation figure in this resource category, as well as procedures such as thoracentesis and pericardiocentesis. Invasive surgical mediastinal staging (mediastinoscopy and mediastinotomy) has also been incorporated.

Surveillance after completion of definitive therapy (surgery ± chemotherapy) includes chest CT every 6 months for 2-3 years, and then LDCT annually. Surveillance after completion of definitive therapy (where primary treatment included radiotherapy) entails chest CT every 3-6 months for 3 years, then LDCT every 6 months for 2 years, and then LDCT annually.

METHODS

Non–Resource-Stratified Guidelines, Where Imaging Fits

Following are comparative guidelines used in high-resource settings. These in mind, countries may assess where they fit in the resource-stratification spectrum and plan realistic next steps with a long-term vision. Implementation of less complex imaging (ultrasound, x-ray, and CT) must sustainably take place before the installation of more complex modalities.

Standard NCCN Guidelines for NSCLC (Version 6.2020, June 15, 2020), not restricted by resource-stratification, additionally include [^{18}F]-fluorodeoxyglucose with positron emission tomography/CT ([^{18}F]-FDG-PET/CT) scanning, brain magnetic resonance imaging (MRI; with contrast), and MRI (with contrast) of spine plus thoracic inlet (for superior sulcus lesions abutting the spine or subclavian vessels). Nodal evaluation by endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS via the esophagus), and CT-guided biopsy are also recommended interventions.

The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines—also designed for high-income countries—suggest considering (for early and locally advanced NSCLC diagnosis, treatment, and follow-up) chest x-ray, CT thorax, [^{18}F]-FDG-PET/CT, EBUS, EUS, mediastinoscopy, mediastinotomy, or video-assisted thoracoscopy surgery investigations including video-assisted mediastinoscopy or video-assisted lymphadenectomy, and MRI as mandatory imaging modalities, with bone scintigraphy and contrast-enhanced CT of the brain optional[23,24] (Table 1, version July 2017 of the guidelines, and the Second ESMO Consensus Conference on Lung Cancer).

The ESMO Clinical Practice Guidelines and their Pan Asia Adaptation[25] (2018) also issued recommendations. For screening, LDCT is preferred, whereas other modalities including chest x-ray are not recommended. Follow-up after completion of definitive therapy (surgery ± chemotherapy) includes chest CT (preferably contrast-enhanced) every 6 months for 2 years or at least at 12 and 24 months and then annually. Follow-up after definitive chemoradiation

TABLE 1. Extracted From ESMO Clinical Practice Guidelines for Early and Locally Advanced Non–Small-Cell Lung Cancer (July 2017) for High-Resource Settings

Workup for Diagnosis and Staging	Mandatory	Optional
General	Medical history[a]	
	Physical examination[a]	
	Assessing comorbidity	
	PS	
Imaging	X-ray thorax	
	CT thorax[a]	Bone scintigraphy
	MRI brain[b]	Contrast-enhanced CT brain
Laboratory	Blood cell counts	
	Renal function	
	Liver enzymes	
	Bone parameters	
Cardiopulmonary function	FVC, FEV1, DLCO	
	ECG	
	If indicated: CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy[b,c]	
	EBUS/EUS mediastinal nodes[a]	Mediastinoscopy
	CT-guided biopsy	

NOTE. Reproduced with permission from ESMO and the publisher.

Abbreviations: CAG, coronary angiography; CPET, cardiopulmonary exercise testing; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endoscopic bronchial ultrasound; ESMO, European Society of Medical Oncology; EUS, endoscopic ultrasound; FEV1, forced expiratory volume in 1 second; FVC, forced expiratory vital capacity; MRI, magnetic resonance imaging; PS, performance status.

[a]Tests needed for clinical staging.

[b]See text.

[c]Depending on site and size of tumor with biopsy/aspiration/brush/washing.

recommends [^{18}F]-FDG-PET/CT in cases where local relapse is suspected.

RESULTS

TNM Staging: Its Dependency Upon Radiology and Nuclear Medicine

The eighth lung cancer TNM classification and clinical staging system were implemented internationally in 2018 and classify early-stage NSCLC disease as stages I or II with negative nodes.[26] Locally advanced disease is classified as stages II or III with positive nodes. Advanced or metastatic disease is stage IV. This TNM staging for lung cancer is nearly always based upon imaging and nuclear medicine. [^{18}F]-FDG-PET/CT is accepted as standard in initial staging of patients with lung cancer.[27] The addition of [^{18}F]-FDG-PET/CT to the diagnostic workup reduces the frequency of futile thoracotomies by 20%.[28,29] Furthermore, [^{18}F]-FDG-PET/CT scan can unmask sites of metastatic disease.[29]

Accurate assessment of disease extent via medical imaging is critical. The maximum standard uptake value of a NSCLC nodule on dedicated PET is an independent predictor of stage and tumor characteristics. It is a more powerful independent predictor than the TNM stage for recurrence and survival for patients with early-stage resected cancer. [30] The *Lancet* reported that addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non–small-cell lung cancer.[28]

Even so, taking into account all clinical management guidelines, delays in accurate diagnosis may sometimes occur because of over-reliance on imaging alone; in some cases, a lower-than-usual threshold for accompanying histopathologic diagnosis is warranted, especially when clinical management decisions would significantly change and a high index of suspicion exists. Evidence-based clinical discretion and patient involvement in such decisions align with a tailored, ethical approach: precision, patient-centered medicine.

Primary Tumor Detection, Staging and Treatment Planning (T)

CT is the first-line modality for accurate T staging. Hybrid [^{18}F]-FDG-PET/CT imaging has revolutionized NSCLC staging and treatment planning. Conventional chest

radiography has limited utility in T staging. Although a chest x-ray can show obvious mediastinal or chest wall invasion with advanced disease or large tumors, its sensitivity is limited; so, patients are referred to more advanced imaging to better delineate disease extent and potential resectability.[27] In all stages, surgeons need precise imaging characterization such as proximity of the tumor to vasculature, the bronchial tree, and pulmonary fissures, as the operative approach will alter accordingly.[10]

Nodal Assessment (N)

[^{18}F]-FDG-PET/CT in lung cancer staging has improved the capacity to evaluate mediastinal and hilar nodal disease accurately. [^{18}F]-FDG-PET demonstrates better staging accuracy than CT, with a respective sensitivity (79%) and specificity (91%) for [^{18}F]-FDG-PET compared with 60% and 77% for CT.[31] A recent meta-analysis of [^{18}F]-FDG-PET illustrated sensitivity (72%) and specificity (91%) for mediastinal nodal disease.[27] [^{18}F]-FDG-PET/CT can direct surgical or image-guided mediastinal nodal sampling to the most suspicious nodes. As discussed above, NCCN and ESMO guidelines recommend definitive histologic sampling and staging.

Detection of Metastatic Disease (M)

Both intrathoracic and extrathoracic metastatic disease is characterized on the basis of imaging including nuclear medicine findings. Since more than half of the patients with lung cancer present with metastasis at initial diagnosis,[7] reporting suspected distant metastases to the care team dramatically changes clinical management. Adrenal, skeletal, intracranial, and hepatic metastatic lesions are particularly common in NSCLC. Of note, [^{18}F]-FDG-PET/CT is not recommended for the detection of brain metastases, where MRI is preferable. Skeletal metastatic disease can be evaluated by [^{18}F]-FDG-PET/CT or, when PET/CT is not available, bone scintigraphy (eg, ^{99}m-Tc diphosphonate bone scan); both are more sensitive than conventional x-rays, although [^{18}F]-FDG-PET/CT shows greater sensitivity and specificity (92% and 98%, respectively) than bone scans (86% and 87% respectively).[10] FDG-PET/CT can reduce the number of futile thoracotomies.[29]

Imaging is particularly pivotal in the spectrum of oligometastatic disease—oligometastatic at the time of initial presentation, oligorecurrent, oligopersistent, and/or oligoprogressive. This holds especially true in the context of targeted therapies for lung cancer, including palliative ones.

Imaging Guidelines, Indeterminate Pulmonary Nodules, and Imaging of Lung Cancer Manifestations

As an example, The Canadian Association of Radiology Diagnostic Imaging Referral Guidelines[32] include recommendations for imaging the solitary pulmonary nodule (Fig 2), pulmonary metastases, the suspected mediastinal lesion on chest x-ray, suspected lymphadenopathy, evaluation of incidental nodules smaller than 8 mm detected on

Clinical/ Diagnostic Problem	Investigation	Recommendation (grade)	Dose	Comment
K20. **Staging SC**	CT chest incl. upper abdomen	Indicated [B]	☢☢☢	Scans to include entire liver and adrenal glands.
	Brain MRI	Indicated [A]	0	Stage I
	CT head	Specialized indication [A]	☢☢	If MRI is contraindicated
	Chest MRI	Not indicated [C]	0	Limited value
	PET/CT	Indicated [B]	☢☢☢☢	Limited-disease SCLC: for evaluation and staging where combined modality therapy with chemotherapy and radiotherapy is being considered.
	Bone scan	Not indicated if PET performed [C]	☢☢☢	Limited value following PET/CT
K21. **SPN**	CT chest	Indicated [B]	☢☢☢	To differentiate between benign and potentially malignant lesions.
	PET/CT	Indicated [A]	☢☢☢☢	1. SPN for which a diagnosis could not be established by a needle biopsy because of unsuccessful attempted needle biopsy; 2. The SPN is accessible to needle biopsy; or 3. The existence of a contraindication to the use of needle biopsy.

FIG 2. The Canadian Association of Radiology diagnostic imaging referral guidelines for SC staging and evaluation of the solitary pulmonary nodule. Reproduced with permission. CT, computed tomography; incl., including; MRI, magnetic resonance imaging; PET, positron emission tomography; SC, small cell; SCLC, small-cell lung cancer; SPN, solitary pulmonary nodule.

nonscreening CT (using Fleischner Society Guidelines, updated 2017),[33] and staging of both NSCLC (Fig 3) and small cell[34] (Fig 2).

For reference, other major clinical imaging referral guidelines include the American College of Radiology Appropriateness Criteria, the Diagnostic Imaging Pathways of Western Australia, the European Society of Radiology iGuide, the European Association of Nuclear Medicine Clinical Decision Support, the Diagnostic Imaging Pathways of Western Australia, and the Royal College of Radiology iRefer.

In addition, for indeterminate pulmonary nodules and suspected adenopathy in the context of LMICs, lung cancer imaging guidelines implemented in high-income countries, although valuable to referring medical practitioners and radiologists globally, may or may not need to be further adapted locally. For example, in countries with a particularly high epidemiologic burden of granulomatous diseases such as tuberculosis, guideline adaptation locally may further incorporate such confounding epidemiologic variables. Clinical and laboratory features of granulomatous diseases, combined with distinct imaging features such as calcification patterns of pulmonary nodules or nodes, can prove extremely helpful in favoring one diagnosis over another, a discussion of which is beyond the scope of this paper.

Treatment Choices, Disease Stage, and Imaging of Lung Cancer

Surgery. Surgical resection may be performed for stages I, II, and IIIA NSCLC in patients deemed good surgical candidates, meaning that the tumor is resectable and the patient can tolerate the operation.[35] Surgery for stage IIIA disease must follow chemotherapy/immunotherapy and/or radiation therapy to be feasible and potentially successful. Surgical outcomes for stage II disease are improved with postoperative systemic therapy. Determination of resectability hinges upon imaging, biopsies (often image-guided), and the patient's performance status. When appropriate, VATS can decrease morbidity and risk compared with open thoracotomy. As well, CT-guided percutaneous radiofrequency ablation or microwave ablation of lung tumors can be considered in inoperable patients and for certain metastases (eg, hepatic).[36,37]

Radiotherapy. All radiotherapy treatments require optimal imaging: CT is the basis for target volume definition and treatment planning and is today complemented with respiration-correlated 4D-CT. Standard CT can be enriched by tumor biology information gained on [18F]-FDG-PET/CT. As well, [18F]-FDG-PET/CT can be used during target delineation for radiotherapy. Patients with early-stage NSCLC ineligible for surgical resection benefit from radiotherapy,[38] with improved survival after stereotactic body radiotherapy.[39] In locally advanced unresectable NSCLC, concurrent radiochemotherapy followed by maintenance immune checkpoint inhibition has become standard of care.[40] In the situation of imaging-defined limited metastatic disease, the so-called oligometastatic disease, randomized phase II trials suggest an overall survival (OS) advantage of adding radical local therapy, mostly radiotherapy, to standard-of-care systemic therapy.[41–43] Also, to improve the quality of life of patients with NSCLC who do not respond to chemotherapy or

Clinical/ Diagnostic Problem	Investigation	Recommendation (grade)	Dose	Comment
K19. **Staging NSCLC**	CT chest/ abdomen	Indicated [A]	☢☢☢	Lymph nodes > 1 cm in the short axis are considered suspicious. Should be performed before bronchoscopy or biopsy procedure.
	Chest MRI	Specialized Investigation [C]	0	Chest wall invasion or Pancoast tumours.
	PET/CT	Indicated [A]	☢☢☢☢	NSCLC for which curative surgical resection is being considered on the basis of negative standard imaging tests; or For clinical stage III NSCLC, which is being considered for potentially curative combined modality therapy with radical radiotherapy and chemotherapy
	Brain MRI	Indicated [B]	0	For patients with neurologic symptoms
	Brain CT	Specialized indication [B]	☢	For patients with neurologic symptoms if MRI contraindicated
	Bone scan	Not indicated if PET performed [C]	☢☢☢	For patients with bone symptoms

FIG 3. The Canadian Association of Radiology diagnostic imaging referral guidelines for NSCLC staging. Reproduced with permission. CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; PET, positron emission tomography.

surgery, radiotherapy forms an integral part of palliative care.[44] For example, 42% of patients diagnosed with SCLC and 27% of patients diagnosed with NSCLC in England during 2013-2014 had curative or palliative radiotherapy as part of their primary cancer treatment. [45]

Medical Treatments Including Chemotherapy. Around 40% of patients with lung cancer are diagnosed at stage IV,[46] for whom treatment goals include a reduction of disease-related adverse events, palliation, and potential prolongation of life. In LMICs, the percentage of patients presenting with stage IV disease is much higher, and, among those with stage IV disease, the burden of disease is often higher than seen in middle-income countries. [45]

Complexities of novel systemic regimens and their contingencies upon histologic tumor markers, genomics, and other molecular testing, including quite promising recent advances in targeted therapies paired with specific somatic mutations, and immunotherapy combined with chemotherapy for those without other molecular profiles, for patients with NSCLC,[47] are beyond the scope of this paper. For advanced disease, new options depend on genomic profiling, targeted therapies, and checkpoint inhibitors unavailable in most of the world. Specifically, subsets of patients with metastatic lung cancer deemed eligible for targeted therapies or immunotherapies are now surviving longer, and the hope is to improve population-based outcomes in years to come.[48] During treatment with either chemotherapy or targeted therapies, repeated imaging with CT (thorax, abdomen, and pelvis) should be used to assess treatment efficacy and decision of duration or a switch to another regimen. In the case of new symptoms, additional imaging may be required (eg, CT or [^{18}F]-FDG-PET/CT, brain MRI). Imaging also often guides placement of central venous catheters sometimes needed to deliver systemic therapy.

Despite significantly less availability and use of immunotherapy in LMICs compared with high-income countries, immunotherapy is being used in metastatic and adjuvant therapy settings in a diverse range of global sites. The impact of immunotherapy-related imaging changes and relatively unique response assessment criteria could represent areas of continued and future research, aligned with precision medicine and an increasingly patient-centered, tailored approach.

Adjuvant Therapy. Adjuvant therapy can include chemotherapy, radiotherapy, and/or targeted therapy. Patients with stage IIA and IIB NSCLC usually receive chemotherapy after surgery to kill any remaining cancer to prolong survival. [49] With stage IIIa, the number of nodal stations involved should be considered for treatment decisions to align with guidelines. Since a multimodality approach is recommended, the sequence of use for surgery, radiation, and chemotherapy is best proposed in a Multidisciplinary Tumor Board meeting.

A pooled analysis by the Lung Adjuvant Cisplatin Evaluation group, published in 2008, updated the previous meta-analysis of 1995.[50] All resected stages considered, adjuvant cisplatin-based chemotherapy reduced the risk of death by 11% with an OS benefit of 5.4% at 5 years, with statistical significance in stages II and III. Among chemotherapy regimens used, vinorelbine-cisplatin reduced the risk of death by 20% with a survival benefit of 8.9% at 5 years more pronounced in stages II (11.6%) and III (14.7%), establishing vinorelbine-cisplatin as a standard of care in the adjuvant setting.[49] In patients treated surgically for early-stage NSCLC, postoperative radiotherapy is recommended in case of upstaging to pathologic N2 disease, on the basis of nonrandomized clinical trials.[51,52]

Stage-Specific Presentation and Link to Survival: Where Medical Imaging Fits

A shift to earlier stages at the time of lung cancer diagnosis can improve survival rates.[53,54] NSCLC patients with stage I disease who undergo surgical resection have a 5-year survival rate of 54% compared with 6% 5-year survival rate of untreated stage I.[55] Data from the UK Office for National Statistics show respective 1-year and 5-year net survival as 83% and 35% (for stage I) versus 17% and 6% (for stage IV).[56] Five-year age-standardized net survival for lung cancer in men has increased from 5% during 1971-1972 to a predicted survival of 8% during 2010-2011 in England and Wales—an absolute survival difference of 4%.[45] In women, five-year survival increased from 4% to 12% over the same period.[45] In 2018, a UK group in conjunction with the National Institute for Health Research and the National Health Service published a Health Technology Assessment (HTA) on lung cancer screening with LDCT for "High-risk populations: a systematic review and economic evaluation," comparing and contrasting prior LDCT studies. They concluded that with a higher cost-effectiveness threshold of £30,000 per quality-adjusted life-years, a single LDCT offered to people age 60-75 years with a predicted risk of lung cancer of at least 3% is predicted to be cost-effective.[57]

The HTA section of the Malaysian Ministry of Health and The International Network for Agencies for Health Technology Assessment also conducted HTA to determine whether LDCT should be used for the early detection of lung cancer in high-risk patients in Malaysia. The Malaysian conclusion was that LDCT could be used among the high-risk group for research.[58]

Taking the US example, roughly half of those diagnosed with lung cancer die within 1 year but 5-year survival increases to 56% when disease is limited to the lung; however, only 16% of patients with lung cancer are diagnosed at such an early stage.[59–61] On the basis of the largest relevant randomized controlled trial to date, the National Lung Screening Trial,[62] the US Preventive Services Task Force (USPSTF) recommends LDCT annually in those

age 50-80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years; this imaging is intended to be discontinued once a person has not smoked for 15 years or has developed a concurrent ailment that substantially limits life expectancy or the ability or willingness to have curative lung surgery.[63] This updated recommendation was issued in March 2021. Currently, more than 8 million Americans are categorized as high-risk for lung cancer and are recommended to undergo annual LDCT, with the potential to avert an estimated 12,000 lung cancer deaths annually.[64] The USPSTF discusses effectiveness of early detection and treatment, comparing and contrasting strengths and limitations of prior LDCT trials.[63]

The Cochrane Collaboration[65] independently conducted a systematic review of available evidence in parallel with the USPSTF, concluding that LDCT resulted in reduced lung cancer mortality in high-risk smokers, but further data are required on cost-effectiveness as well as relative harms and benefits for different risk groups and settings.[66]

In January 2020, *The New England Journal of Medicine* published the latest NELSON results, the Dutch-Belgian Randomized Lung Cancer Screening Trial. LDCT screening of more than 15,000 individuals over a 10-year follow-up showed that total lung cancer deaths fell by about 33% in women and 24% in men compared with high-risk patients who had not undergone LDCT screening.[67,68] This in turn prompted lobbying of French parliament to initiate similar CT screening and studies in France.[69]

This discussion illustrates that nations should consider performing their own HTAs, incorporating local epidemiology, cost-effectiveness, and other factors into their own decisions. Ultimately, the effectiveness of LDCT depends on being able to access at-risk patient populations, having adequate radiologist expertise, and having thoracic surgery or stereotactic body radiation therapy for treatment of early-stage cancers that might be discovered.

Also worth noting, multiple modern imaging and information technology innovations show promise but have yet to be tested broadly. For example, recent machine learning and quantitative imaging demonstrate that radiomic texture features of intratumoral and peritumoral regions on non–contrast-enhanced CT thorax images can predict the time to tumor progression, response to chemotherapy, and OS.[70]

The International Atomic Energy Agency (IAEA) published *A Guide to Clinical PET in Oncology: Improving Clinical Management of Cancer Patients* in which it is explained that the HTA is a methodology used to evaluate new technologies proposed for introduction into medical practice and is often performed by those responsible for health care financing. The aim of the HTA exercise is to study the utility of a diagnostic test described on one or more levels of a hierarchy, with higher levels relating more closely to the social impact.[71] Discussed therein is a comparison of dominant prior HTAs for oncologic indications and [^{18}F]-FDG-PET/CT.

With exceptions, solitary solid pulmonary nodules $>$ 1 cm are usually benign if [^{18}F]-FDG-PET/CT is negative.[72] In April 2019, *Clinical and Translational Imaging* published, "Evidence-based indications for the planning of PET or PET/CT capacities are needed," using HTA data as the basis for a PET/CT investment decision in an Austrian region.[73] Several similar HTA examples have prompted national decisions to invest in medical imaging, not limited to lung cancer, alone. In the United Kingdom, it was recently announced that the government will invest 200 million pounds (225 million euros) to replace outdated mammography, CT, and MRI units[75] with new systems. This (initiative) will significantly improve the ability of the National Health Service to diagnose cancer and will support the commitment in the National Health Service Long Term Plan to ensure 55,000 more people survive cancer each year.[76,77]

However, the paucity of HTAs for medical imaging modalities, overall, could inspire tomorrow's research agenda across a spectrum of prioritized clinical indications. For example, in the context of tuberculosis endemicity in several LMICs, upscaling conventional radiography and CT may be prioritized, but would greatly benefit other patients too, including those with lung cancer. Therefore, strategic medical imaging infrastructural goals should incorporate multifaceted local epidemiologic needs, considering the multipurpose nature of imaging modalities such as CT, embedded in diverse clinical management guidelines, which range from cancers to cardiovascular diseases to COVID-19 complications.

DISCUSSION

In conclusion, although the devastating social impact of lung cancer, specifically, is beyond comprehensive quantification, its economic impact is estimated to include 60,846 years of potential productive life lost annually and productivity losses of €13.1 billion over 10 years, information that may assist decision makers in the allocation of resources, reducing the burden of lung cancer in working-age individuals[78] across the world.

Addressing both the global causes and consequences of lung cancer is a fair, patient-centered, ethical, and beneficial approach. Seventy-percent of all cancer deaths occur in LMICs, where 10% of mortality is attributable to cancer.[79,80] However, early lung cancer diagnosis becomes less important when there is no thoracic surgery for resection, the case in many countries. Likewise, stereotactic body radiation therapy as an alternative for surgery is often nonexistent.[81] Twenty-eight African countries do not have a single radiotherapy unit.[82,83]

Cancer treatment services overall are available in more than 90% of high-income countries compared with fewer than 30% of low-income countries[13] and, in 2017, only 26% of

low-income countries reported having pathology services generally available in the public sector.[13] IMAGINE (the IAEA Medical Imaging and Nuclear Medicine global resources database) illustrates similar inequities between countries for the availability of medical imaging technologies and relevant skilled human resources.[84] The shortfall of expertise on-site in LMICs to read imaging modalities could perhaps be bridged, in part, by the use of IT innovations such as teleradiology or machine learning and artificial intelligence, although these would need to be validated for efficacy and safety; comply with ethical frameworks and good governance; and be assessed for cost-effectiveness in local conditions.

These issues constitute public health challenges, as well as reasons for hope. Caught early, lung cancer can be treated with curative or life-prolonging intent.[13] Non–resource-constrained guidelines for all stages of lung cancer include medical imaging for diagnosis, staging, treatment monitoring, follow-up, interventional radiology (such as image-guided biopsy), and planning for surgery and radiotherapy. As well, imaging can characterize advanced disease, avoid unnecessary treatments, and guide quality-of-life-enhancing palliation.

However, before investing in and deploying advanced imaging modalities, it is important to have the basic modalities available (x-rays, ultrasound, and CTs) and ensure their sustainability. This should go hand in hand with the availability of therapeutic capabilities. Although multinational clinical imaging referral guidelines exist, stepwise roadmaps for sustainable upscaling are sparse. In 2019, the IAEA and WHO jointly published a milestones roadmap for medical imaging and nuclear medicine within the context of national cancer control programs.[85] Undoubtedly, among the imaging modalities for cancer, CT occupies a prime place and offers a large number of applications. However, modalities such as PET-CT provide additional information, giving patients the best possible alternatives.

Relevant long-term goals for establishing and improving imaging infrastructure can be statistically modeled as a companion to conducting HTAs in more countries to draw better local conclusions about affordable and appropriate implementation, rationally tailored to individual country profiles. This strategy also aligns with landmark World Health Assembly resolutions on cancer (WHA70.12), HTA (WHA67.23), and palliative care (WHA67.19); ongoing dialogue to make the right investments in universal health coverage; and a *Lancet Oncology* Commission on Medical Imaging and Nuclear Medicine published March 2021.[86]

Lung cancer is the number one cancer killer. Patient-centered, compassionate, high-quality lung cancer management provision mandates that population-based planning should extend beyond disease prevention to include both curative and noncurative treatment options for the millions afflicted. Ministries of health will not view lung cancer–related imaging needs in isolation and will need to weigh these needs together with the diagnostic and treatment needs of other cancers such as breast cancer, lymphomas, etc. In all of these circumstances, the impact on obtaining a cure, the extension of survival, and the improvement in the patient's quality of life must be taken into account. In this aim, progressive extension of the benefits of medical imaging and nuclear medicine is fundamental toward enabling the highest attainable standard of health, enshrined as a human right.[87]

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