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The Use of Imaging Tests for the Diagnosis and Management of Lung Nodules

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Cite this chapter as: Lumbreras B, Chilet-Rosell E, Parker LA. The Use of Imaging Tests for the Diagnosis and Management of Lung Nodules. In: Sergi CM, editor. *Metastasis*. Brisbane (AU): Exon Publications. Online first 2022 Mar 18.

Doi: https://doi.org/10.36255/exon-publications.metastasis.pulmonary-nodules

Abstract: Imaging tests have a central role in the diagnosis and management of lung cancer. Because of the increasing sensitivity of the current diagnostic imaging tests, and the implementation of screening programs, pulmonary nodules are more frequently detected in clinical practice. In addition, early detection of lung cancer and improvements in treatment have led to improved survival rates. As smoking was in the past more common among men, lung cancer has traditionally been considered as a male disease, particularly for older male smokers. However, this stereotype is no longer valid. A large number of studies point to a higher risk sensitivity in women than men for major lung cancer types. In this chapter, we describe the different clinical pathways in the management of solitary pulmonary nodules.

In: Consolato M. Sergi, editor. *Metastasis*. Exon Publications, Brisbane, Australia. ISBN: 978-0-6453320-2-5. Doi: https://doi.org/10.36255/exon-publications.metastasis

Keywords: epidemiology of lung cancer; imaging tests for lung cancer; management of lung cancer; patient communication in lung cancer; solitary pulmonary nodules

INTRODUCTION

According to the latest GLOBOCAN estimates, 2,206,771 new cases of lung cancer were diagnosed globally in 2020, accounting for 11.4% of all cancers diagnosed worldwide (1). In addition, in 2020, lung cancer was the leading cause of cancer-related deaths, accounting for 18.6% of the overall cancer mortality. With increased access to tobacco, especially in the low- and middle-income countries, the incidence of lung cancer continues to increase globally (2). While in many high-income countries lung cancer mortality has begun to plateau or decrease, evidence continues to show that this is not the case for women. Lung cancer incidence and mortality in women is increasing and it is the leading cause of mortality in women in Europe (3), because women have been slower to adopt, and then cease, tobacco smoking (4).

Increases in survival are likely the result of improvements in detection and treatment. The United States Preventive Services Task Force (USPSTF), in May 2021, issued recommendations for annual low dose computed tomography (LDCT) screening for eligible high-risk individuals (5). Furthermore, the European Union (EU) published a position statement on lung cancer screening in 2017, presenting the available evidence and issues that need to be addressed to ensure the successful implementation of LDCT lung cancer screening in Europe (6). Furthermore, with improved access to increasingly more sensitive imaging tests, physicians frequently visualize unexpected abnormalities in the lung tissue when ordering imaging for other purposes. Evidence suggests that approximately 1% of incidentally detected pulmonary nodules are malignant (7), and this situation offers an opportunity for earlier access to curative treatment. However, it is also important to prevent invasive and costly interventions in individuals presenting with benign nodules. As pulmonary nodules become more frequently identified due to increasingly sensitive imaging tests, and the widespread use of imaging for a range of indications including screening for lung cancer, it is clear that effective and efficient management of pulmonary nodules is crucial. Lastly, with the increase of lung cancer survivors due to early detection and new options of treatment, new management strategies are needed.

In this chapter, we discuss the management of pulmonary nodules for the early diagnosis of lung cancer. Furthermore, we describe the management strategies used once lung cancer is identified, particularly the use of imaging for surveillance and informing treatment decisions. Where possible, we integrate available evidence on the differences according to sex, and how gender biases in the clinical management may influence timely diagnosis and effective treatment of lung cancer in women. To introduce the issue, we start with a brief outline of the global epidemiology of lung cancer.

LUNG CANCER EPIDEMIOLOGY

In 2020, lung cancer represented 11.4% of all new cancer diagnoses around the world (8). Zhang et al. evaluated the geographic patterns and temporal trends in lung cancer incidence from 1978 to 2012 in 43 countries, with an emphasis on country- and sex-specific differences (9). This paper showed that in the last 40 years, the gap that existed between men and women in the incidence of lung cancer has decreased, since there has been a significant downward trend in men in 19 countries in contrast to an upward trend in women in 26 countries. The incidence rates of lung cancer in women increased in most European, North American, and Oceanian countries, with a rise in the average annual percentage from 0.9 to 5.2 (9). Taking current evidence into account, lung cancer can no longer be stereotyped as an older male smokers' disease. We know that men and women have different vulnerability and exposure to risk factors, and that the natural history of lung cancer may differ in women and men as a result of the different histologic types or hormonal factors. Recent epidemiological data suggest sex-specificity as a new and additional factor (10). In the following sections, we briefly summarize the different exposure and vulnerability in men and women to lung cancer risk factors.

Smoking

Although only a small proportion of smokers develop lung cancer, the relationship between smoking and this disease is well established. More than 85% of all patients diagnosed with lung cancer are current or former smokers and smoking can be attributed to approximately 80% of lung cancer fatalities (11). As smoking was in the past more common among men, lung cancer has traditionally been considered as a male disease, particularly for older male smokers. However, this stereotype is no longer valid. A large number of studies point to a higher risk sensitivity in women than men for major lung cancer types and have shown that this difference is greater in younger groups (12). Data suggest that smoking-related morbidity and mortality may have a greater impact on women than men, as a higher relative risk associated with ever smoking and level of smoking has been reported in women than men for all lung cancers (12.7 and 9.1 for ever-smoking and 27.9 vs 9.6 for level of smoking, respectively) (13).

Yet, we must emphasize that debate still exists regarding smoking habits and the differential lung cancer risk in women and men. Stapelfeld et al. stated that the controversy regarding differences between women and men in the association between smoking habit and lung cancer risk seem to be related to the epidemiological design of previous studies (10). While case-control studies tended to show a higher relative risk among women compared to men for the same level of smoking exposure, most cohort studies tend to find no difference or even a higher rate ratio in men. It is worth noting that the risk of death from cigarette smoking continues to increase among women, and that this increase means that risks are now nearly identical for men and women, as compared with persons who have never smoked. The analysis of temporal trends in mortality across three time periods (1959–1965, 1982–1988, and 2000–2010) in the United States revealed a large increase in deaths from lung cancer among women over the entire 50-year period (9).

In never-smokers, lung cancer is more common in women than in men, probably due to a greater incidence of passive smoking in women. For example, women married to men who smoke have been shown to have a 25-29% increased risk of developing lung cancer (14). In addition, women in all developing countries, and particularly in East and South Asian countries, are exposed to polycyclic aromatic hydrocarbons, which are associated with lung cancer, as result of using cooking oil and other biomass fuels in poorly ventilated areas. Regarding environmental air pollution, the relationship between particulate matter air pollution exposure and lung cancer has been analyzed in two cohorts: the Nurses' Health Study Cohort (15, 16), and the Women's Health Initiative (17). These studies showed an increased risk of incident lung cancer associated with ambient particulate matter exposures and with residential proximity to major roads among never-smoker women.

Hormones

Several studies have elucidated the relationship between exogenous hormone use (e.g., oral contraceptives and/or hormone replacement therapy) and lung cancer, as well as its molecular mechanisms. For example, cancer risk following treatment with hormone replacement therapy was studied in a population-based cohort of 23,244 women and found a relative risk of 1.26 of lung cancer, particularly high in the younger women group (18). A recent meta-analysis of cohort studies to evaluate this association showed that hormone replacement therapy used is associated with a decreased risk of lung cancer in women (19). However, an increased risk of lung cancer in women due to hormone replacement therapy and interactions with smoking (OR 32.4 in smokers) has been reported (20). Endogenous circulating levels of sex hormones can exacerbate the carcinogenic effects of tobacco (21). The induction by the toxic compounds of tobacco of the enzyme responsible for estrogenic metabolism, CYP1B1, leads to a heightened formation of reactive oxygen species, which in turn promotes carcinogenesis (21).

Histopathology

The World Health Organization classified lung tumors into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and large cell neuroendocrine carcinoma (22). Adenocarcinoma, squamous cell carcinoma, and large cell carcinomas are subtypes of non-small-cell lung carcinoma (NSCLC) which account for 85% of all lung cancer cases (23). Among them, adenocarcinoma is the most frequent subtype of lung cancer, both in women and men who smoke and non-smokers (24). All histological types of lung cancer have been related to a greater or lesser extent with smoking, with more evidence regarding the association with small cell and squamous cell carcinoma and less with adenocarcinoma. The predominance of adenocarcinoma is particularly striking among nonsmokers, and among nonsmokers with lung cancer, women outnumber men. There is emerging data supporting sex-based differences in the biology of lung cancer. Adenocarcinoma is more common in women and its incidence is increasing particularly in those who smoke, whereas male smokers are more likely to

develop squamous cell carcinoma (25). The increased incidence of adenocarcinoma among women has been attributed to several causes, including biologic factors (for example, 30% increase in lung cancer among women receiving estrogen replacement therapy) (18) and environmental factors (such as second-hand smoke, to which women are more often exposed (18–28).

DIAGNOSTIC STRATEGIES TO MANAGE PULMONARY NODULES

Pulmonary nodules are defined as focal opacities on radiological imaging that measure up to 3cm in diameter and are surrounded by lung tissue. They are commonly detected in clinical practice and although most are benign, a small number represent early lung cancer. It is important to understand how to proceed when a pulmonary nodule is found, in order to avoid harmful interventions in benign disease (7). In this section, we describe diagnostic strategies that aim to facilitate the timely and effective curative treatment of lung cancer while avoiding harmful interventions in nodules that will not go on to risk the life of the patient.

Firstly, it is important to discuss the mode of detection of pulmonary nodules: those that are detected during diagnostic screening in symptomatic patients, and those that are detected incidentally on imaging tests carried out for purposes unrelated to the detection of lung pathology. At the heart of the difference, we must consider the predictive value of lung cancer before interpreting the presence of the nodule. Predictive values will always be significantly lower in a person who does not have symptomatology compared to a person who is seeking care because the prevalence of disease is higher among symptomatic populations compared to asymptomatic populations (29, 30). Because lung cancer screening is carried out in high-risk populations, usually determined by age and smoking history, the likelihood of detecting lung cancer (or pre-test predictive value) is higher than in the general population. Applying the same reasoning, we can understand that the pre-test predictive value is lowest for incidentally detected nodules where reason for seeking care is unrelated to lung symptomology. When the predictive value is low, it is especially necessary to balance the potential benefit of early detection of lung cancer with the potential for overdiagnosis.

Overdiagnosis refers to the detection of an abnormality that is never going to cause harm during the persons remaining lifetime (31). This may be because the abnormality detected will resolve spontaneously, or never going to cause any harm, or the person has a limited remaining lifespan and is more likely to die of other causes before the abnormality represents a clinically relevant disease. In this scenario, overdiagnosis can be the diagnosis of a true disease, but the disease is not clinically relevant. However, it can trigger a cascade of new unnecessary diagnostic tests, and treatments that are not only costly to the health care system but may seriously impact the individual's health and quality of life (32, 33). Careful conservative management of incidentally or screening-detected pulmonary nodules is one way to avoid overdiagnosis. Several guidelines or statements have been released to aid this task.

For nodules detected during screening for lung cancer, the American College of Radiology Lung CT Screening Reporting and Data System (LUNG-RADS)

presents a tool for the standardization of reporting and management (34). Although lung cancer screening has yet to be widely implemented in Europe, the European Position Statement on Lung Cancer Screening, published in 2017, recommends management of nodules by a multi-disciplinary team (35). Outside of screening, we have the Fleischner Society's guidelines for the clinical management of incidentally CT-detected pulmonary nodules which was published in 2005 and has most recently been updated in 2017 (36). It applies to individuals over 35 years old who have no previous diagnosis of cancer. Additionally, we have the British Thoracic Society (BTS) comprehensive guideline published in 2015 to improve uniformity of clinical management of both incidentally- and screening-detected nodules (37). The BTS guideline applies to individuals over 18 years old regardless of their previous cancer status, although previous cancer is a factor which should be considered in baseline assessment. Despite the availability of these guidelines, clinicians' awareness of the guidance is poor (38), and low levels of adherence has been observed at both patient and clinician level (39).

Baseline assessment

In this section, we touch on the current thinking on how nodules should be managed to reduce the risk of overdiagnosis, considering initial baseline assessment and surveillance. Initial management of detected nodules should be determined by risk of malignancy. The predictive value for lung cancer can be estimated in observational studies and used to develop algorithms which can help doctors predict the likeliness of malignancy and the best clinical course to follow. One of the most widely used tool to calculate the predictive value of a pulmonary nodule is the Brock risk calculator, which incorporates factors such as nodule size and location, morphology, patient age, and sex (40). Although it was first developed in a screening population, it has been applied to other settings with notable success (41) and is now the recommended tool in the BTS guidance. A recent systematic review describes predictive models of solitary pulmonary nodule malignancy built from solitary pulmonary nodules (SPN) incidentally detected in clinical practice (42). Unfortunately, most of the predictive models were built from retrospective studies with poor levels of methodological quality. All in all, evidence suggests that the most important factors for predicting lung cancer are nodule size and the age of the patient, with larger nodules and older patients being risk factors for malignancy. Other factors such as the morphological characteristics of the nodule (43), exposure to known carcinogens, patient's characteristics, and clinical history are also factors that should be considered when considering the likeliness of malignancy.

Starting with size, most guidelines agree that a minimum size, measured in diameter or volume, is needed to initiate follow-up (44). It is assumed that the risk associated with clinical follow-up of smaller nodules would probably outweigh the benefits of potential early detection of a malignant nodule (36–37, 44). While volume assessment is widely considered more accurate than diameter measurement, especially in follow-up when changes in size need to be assessed, it may not always be available because it requires semi-automated volumetry using software to calculate the volume of the nodule after selection by a radiologist. According to the BTS guidance, nodules less than 5mm in diameter (or 80 mm3 in volume) in a person with no previous history of cancer should not be followed-up because

they are not thought to present a significant risk of malignancy (45). Similarly, according to the Fleischner guidelines, solitary pulmonary nodules of less than 6mm should not be followed up, unless nodule characteristics suggest high risk, in which case, a 12-month optional follow-up could be carried out depending on the preferences of the patient (36). Another exception when a nodule below this threshold might warrant follow-up is if the patient had a previous CT scan less than 2 years before, and no nodule was present, or if the patient has a history of malignancy (44). The lungs are the most common site of metastasis and so the likelihood of an incidentally detected pulmonary nodule being cancer is high.

Regarding the appearance of the nodules, certain morphological characteristics such as ground-glass appearance or part-solid state is suggestive of benign disease (46). Intensive follow-up of this type of nodule should be avoided, as it may lead to overdiagnosis (47). Repeat imaging scans can be carried out every 4 or 5 years, because even if they are malignant, they tend to be slow growing. On the other hand, irregular borders (or spiculation), and nodules with a more solid appearance increase the predictive value of nodules and should trigger further action (48). Similarly, a growing solid component of a part-solid nodule is concerning and should prompt active surveillance. The findings related to both size and morphological characteristics appear to be relevant for both men and women.

Regarding the location of the detected nodule, it is generally accepted that pulmonary nodules located in the upper lobes of the lung are more likely to develop into lung cancer. Both the Fleischner and Brock risk calculator consider this. Some evidence suggests this finding may be more relevant for men than for women because women who had a solitary pulmonary nodule detected by radiography in the upper lobes had similar rates of cancer to those with solitary pulmonary nodules in other areas (49). Furthermore, a recent systematic review of predictive models showed that nodule location was frequently considered as a potential variable in the predictive model but was rarely included as a predictive factor in the final model (42).

Patient factors that increase the likelihood of a pulmonary nodule being cancer include current or previous cigarette smoking, older age, sex, personal history of cancer, family history of lung cancer, emphysema, and exposure to asbestos or radon. In the Brock calculator, female sex is considered an independent predictive factor for nodule malignancy. The Fleischner guideline includes race as a risk factor for SPN malignancy, but it is not currently applied in the available predictive models. As mentioned previously, it is important to consider the role of tobacco smoking when estimating the likelihood of malignancy. While smoking is a factor that may increase our estimation of the predictive value, the absence of smoking history should never lower our estimation, particularly in women. In patients with a solitary pulmonary nodule detected by chest radiograph or CT, personal smoking history significantly increases the risk of lung cancer diagnosis and mortality overall. However, when stratified by sex, personal history of smoking was only a predictive factor in male patients (49). It is possible that the failure to detect a difference in non-smoking women is caused by exposure to secondhand smoke. The implication of this finding is significant because the predictive value of a SPN observed in a woman is a significant predictor of lung cancer, and if clinicians are more cautious or conservative in their management because the patient has no prior history of cigarette smoking, it could lead to detrimental delays in diagnosis and impede access to timely treatment for women.

Differences in the management of women and men after detection of a solitary pulmonary nodule have been observed (50). Men were more likely to have an immediate intervention after the detection of a solitary pulmonary nodule whereas further surveillance was the preferred course for women. This meant that the median time from nodule identification to lung cancer diagnosis was longer in women than men.

Surveillance

For larger nodules, guidance recommends surveillance at different intervals depending on the malignancy risk (51). The BTS guidance recommends scan intervals from baseline at 3 and 12 months, to allow for an estimation of the growth rate. The main indicator considered is volume doubling time (VDT), defined as the number of days until the volume of the nodule doubles in size, with a shorter doubling time being indicative of an aggressive lesion. VDT is usually calculated at 3 months where it is possible to estimate the time taken to double in size (VDT) by comparing the initial size with the size at 3 months. If the VDT is less than 400 days, then repeat imaging should be repeated at 12 months. When nodules show no significant growth on initial follow-up images, they may be declared stable and the patient can be discharged, especially when referring to well-defined solid nodules with benign morphology. If using diameter measurements to monitor the nodule growth, a total of 24 months of follow-up is generally required to assess stability whereas volume measurements may allow the assessment of stability in a shorter time frame (BTS, 12 months). The definition of what constitutes significant growth and when to cease follow-up is the subject of controversy as guidelines diverge (52), however both agree on the need to reduce the risk of unnecessary interventions, and patient anxiety derived from the follow-up of benign nodules.

APPROPRIATENESS OF IMAGING TESTS FOR LUNG CANCER MANAGEMENT

Despite the high mortality of patients with lung cancer, given the increasing incidence of the disease, there is a growing number of lung cancer survivors who need different management strategies including surveillance and treatment (53). In cancer staging, surveillance, and the study of treatment response, the use of imaging tests is a central issue in the management of lung cancer. However, there is evidence showing that cancer-related imaging is associated with inappropriate use including both overuse and underuse of recommended tests (54, 55). In addition, lung cancer management varies in different parts of the world (56). Several organizations such as National Comprehensive Cancer Network (NCCN) guidelines (57) and American College of Radiology (ACR) Appropriateness Criteria (58) have led efforts to improve appropriate use of imaging testing. However, previous studies have shown a lack of adherence to these guidelines. Moreover, in many low- and middle-income countries where smoking habit is increasing and the population is poorer and less-educated (59), the challenges to incorporate these

international guidelines (60) have led to low lung cancer survival (61). In this section, we describe the use of imaging tests in cancer staging and surveillance, the adherence to the available guidelines, and the differences in imaging test used according to the population characteristics.

Cancer staging

The clinical staging of lung cancer is a critical part of the evaluation because treatment options and prognosis vary depending on the stage of cancer. The tumor-node-metastases (TNM) classification is an internationally accepted and validated system for the management of patients with cancer, treatment planning, and prognosis assessment. This system is under continuous revision due to advances in both diagnostic imaging techniques and treatments. The eighth edition of the TNM staging system (TNM-8, 2018) is the most recently revised and modified, developed by the International Association for the Study of Lung Cancer (IASLC) (62). This classification is based on the patient's clinical history, pretreatment histologic samples, and the histologic type of the resected tumor. Nevertheless, it is primarily guided by non-invasive imaging techniques, including radiography, CT, magnetic resonance imaging (MRI), whole body 18-fluorodeoxyglucose (FDG) positron-emission tomography (PET), and fused or integrated PET/CT. Evidence suggests that a complete and accurate staging improves the outcome of these patients (63). Therefore, knowledge of the accuracy, advantages and disadvantages of these imaging techniques is critical when making the correct therapeutic decision. Chest CT helps to identify tumor location and the presence of mediastinal lymph node involvement. FDG-PET scanning accurately identifies mediastinal lymph node metastases and extrathoracic metastases, although it has a high cost and limited availability. In brain metastases, imaging with contrasted brain CT or MRI is required.

Guidelines detailing the use of imaging tests in staging patients with cancer are available, such as the ACR Appropriateness Criteria and the Clinical guidelines from the NCCN (57). Nevertheless, the adherence to these guidelines is low. For instance, given that the efficacy of PET imaging is superior to bone scintigraphy in the detection of bone metastasis (64), the use of both these techniques is not appropriate. However, a previous study showed a lack of adherence to available guidelines in patients with locally advanced lung cancer (65), where 25% of the 3,808 patients evaluated showed overuse of bone scintigraphy and PET. Another study focused on the follow-up of the Choosing Wisely recommendations from the Society of Thoracic Surgeons that recommend avoiding brain imaging in asymptomatic patients with early-stage non-small cell lung cancer (66). The results showed that one in eight patients underwent brain imaging, but none ultimately had intracranial metastasis.

Surveillance and treatment response

In this section, we describe the use of imaging tests in patients with lung cancer after curative resection of lung cancer and/or treatment. Due to high mortality of patients with lung cancer, surveillance is essential for early detection and treatment of recurrence and secondary cancers in these patients. Imaging tests also

play a relevant role in surveillance: according to a previous study of 1,294 patients, 93% of secondary cancers and 61% of recurrences were identified by surveillance scans (67). Although there is a consensus about the need for imaging surveillance, for instance after curative resection of lung cancer, guidelines differ greatly regarding relevant aspects such as the frequency and timing of this imaging surveillance. The main agencies focused on surveillance include NCCN (57), ACR (68), American College of Chest Physicians (69), American Society of Clinical Oncology (70) and the European Society of Medical Oncology (71). All of them recommend more frequent imaging in the first 2 years after surgery, when the risk of recurrence is higher. Nevertheless, as we previously commented for the management of pulmonary nodules, most of the guidelines are based on data from single center trials, where the patients may be different from those in clinical practice. In addition, data regarding the impact of the different frequency and timing of surveillance on survival are also contradictory. A previous study showed that more frequent surveillance was not associated with improvement in patients' survival, although this study did not stratify by lung cancer stage (72). In contrast, another study, after a 3-year survival evaluation, showed improvements in the detection of recurrence by imaging surveillance in comparison with detection by symptoms (73). Therefore, to accurately evaluate the strategy of imaging surveillance, a prospective study of patients in real-world practice is needed. Such a study should include patients with different stages of lung cancer and with different timing of recurrence.

In addition, several studies showed a lack of adherence to the available guidelines. The surveillance by CT and PET imaging of patients with lung cancer has increased in the last decade (54). However, according to Erb et al., the adherence to available guidelines for surveillance was poor: fewer than two-thirds of patients received recommended imaging, and almost 30% received non-recommended PET scans (74). Previous evidence also showed that over a third of the 1,200 patients who underwent lobectomy for pathologic stage I NSCLC, received minimal expected imaging studies for surveillance in the first five years after surgery (75).

The lack of adherence to available guidelines for carrying out imaging is not exclusive to oncology. A previous study showed a high prevalence of inappropriate use of medical imaging tests in clinical practice. This appropriateness depended not only on patient's sociodemographic and clinical characteristics but also on the referring physician (76). Therefore, poor adherence to the available guidelines could suggest lack of awareness or disagreement with the available guidelines. In this sense, according to a previous survey, nearly 80% of clinicians had never heard of the European recommendations on reducing radiation exposure associated with imaging tests (77).

PATIENT COMMUNICATION

In recent years we have seen a move towards more patient-centered health care. Clinicians are encouraged to reinforce the role of the patient when making any clinical decision. The updated Fleischner Society guidelines now acknowledge patient preference as a factor that needs to be considered and can impact the

frequency or interval length in surveillance of incidentally detected pulmonary nodules. Communication is key, and it is important to develop studies about how to effectively involve patients in decisions about their care and consider the type and format of the information presented (77). Patients tend to opt for further investigation even when risk is very low, so it will be essential to raise awareness about the potential risks associated with follow-up of small non-suspicious pulmonary nodules, while allowing some flexibility for situations where appeasing fear and anxiety of the patients may warrant a follow-up test. In addition, with the new treatment options, understanding patients' preferences regarding different strategies is essential. A previous study showed that in patients with early-stage lung cancer, maintaining independence and quality of life were more highly valued than survival or cancer recurrence (78).

CONCLUSION

Although progress in prevention, early detection, treatment, and surveillance has improved survival, lung cancer is still a major public health burden worldwide. With the implementation of screening programs and the increasing sensitivity of imaging tests, pulmonary nodules are more frequently detected. To reduce the use of unnecessary tests and reduce the probability of overdiagnosis, several guidelines are available. In addition, and given the increasing number of lung cancer survivors, further real-world research on imaging tests for staging and surveillance is needed to improve the accuracy of the available guidelines. Lastly, efforts are needed to improve clinicians' awareness on available recommendations and to increase the communication with the patient.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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