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Review Article

Non-Small Cell Lung Cancer: A Primer for the General Clinician

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Abstract

Lung cancer is the world's number one cancer diagnosis and cause of cancer death. Expectantly reversing this trend is annual screening by low-dose computed tomography (CT) which has recently been shown to improve survival. Recent guidelines and new technologies are available for diagnosis and staging if lung cancer is suspected. Once confirmed, there is a growing armamentarium of therapies available that can be individualized to each patient. The purpose of this article is to provide a broad overview of non-small cell lung cancer, by far the predominant form of lung cancer.

Keywords: *Non-Small Cell Lung Cancer; Primer*

Introduction

There is an epidemic of lung cancer in the world today. While tobacco smoking is the predominant risk factor, several other exposures also have been shown to trigger this deadly disease. Lung cancer screening by low-dose computed tomography (LDCT), recently shown to reduce lung cancer mortality, may finally be a tool that will be able to quell the tide. One reason that lung cancer is so lethal is the fact that has often progressed to an advanced stage before symptoms appear. However, there are signs of which the clinician should be aware that can raise suspicion for malignancy and could lead to a diagnosis sooner. There are various modalities to approach diagnosis and staging, with even more treatments available. Given the complexity of lung cancer management, particularly non-small cell lung cancer (NSCLC), this review is intended to provide a broad yet expansive understanding of this predominant form of lung cancer.

Epidemiology

Lung cancer is the most common cancer diagnosis and cause of cancer death in the world [1]. Approximately 1.8 million new cases were found in 2012 with 1.6 million fatalities. While the slight majority of cases occurs in less developed nations, it is estimated that, in 2018, the United States itself will have over 230,000 new cases leading to more deaths than from breast, prostate, and colon cancers combined [2]. In fact, it continues to hold this inauspicious standing despite recent small decreases in incidence and mortality rates due to reductions in smoking [3].

The World Health Organization divides lung cancer into two main classes: non-small cell lung cancer and small cell lung cancer [4]. Non-small cell lung cancer (NSCLC) is about four times as common as small cell lung cancer (SCLC) and can be further subdivided into non-squamous carcinoma and squamous cell carcinoma. Non-squamous carcinoma includes adenocarcinoma (the most common type of lung cancer) and large cell carcinoma, among other histologic subtypes [5].

In terms of risk factors, smoking is the chief cause of lung cancer but only a small minority of smokers will develop the disease in their lifetime [6]. Smoking intensity (e.g. number of packs per day) and lifetime duration correlate with risk [7]. Conversely, smoking cessation

reduces the hazard. In fact, the earlier in life that one stops smoking, the greater the life expectancy and the lower the lifetime lung cancer risk [8,9]. Similarly, as the period of abstinence increases, the risk of lung cancer decreases [10]. For patients that are unable to quit entirely, simply reducing consumption also reduces the threat of future malignancy. For example, patients that smoke approximately one pack per day can significantly reduce their risk of developing lung cancer by decreasing smoking intensity by 50% (though the risk reduction is not as pronounced as in those who have quit entirely) [11]. Indeed, any form of smoking increases lung cancer risk. Secondhand smoke has a well-established dose-response relationship with lung cancer [12]. Cigar and pipe smoking also increase the likelihood above that of non-smokers [13,14].

Other risks include advancing age; lung cancer is unusual (though not unseen) until approximately the fifth decade of life.[2] Men are slightly more affected than women, likely reflecting differences in smoking history. Interestingly, asbestos exposure acts synergistically with tobacco; radon and concurrent interstitial lung disease such as idiopathic pulmonary fibrosis and certain pneumoconiosis are also risk factors [15-18]. COPD and a family history of lung cancer have additionally been shown to increase chances of developing lung cancer later in life [19,20].

Screening

Lung cancer is by far the major cause of cancer deaths because, in many patients, it is at an advanced stage at the time it is discovered. The largest study evaluating screening with chest X-ray (CXR) was the Prostate, Lung, Colorectal and Ovarian (PLCO) trial which randomized over 150,000 patients to either yearly CXR or usual care [21]. There was no difference in lung cancer incidence and lung cancer mortality rates between the groups. Indeed, several studies have shown a lack of benefit of screening with CXR, leading to a recommendation against these practices by the most recent guidelines of the American College of Chest Physicians (ACCP) [22]. Similarly, analysis of sputum cytology lacks strong supportive evidence and is not recommended as a screening tool [23].

Several studies have investigated the role of low-dose computed tomography (LDCT) in lung cancer screening [24,25]. By far, the largest is the National Lung Screening Trial (NLST), published in 2011, which included over 50,000 patients and also had longer follow-up than prior studies [26]. Researchers discovered a 20% reduction in lung cancer mortality by annual LDCT compared to CXR. Entry criteria were age 55 to 74 years old with at least 30 pack-years of smoking history and current smoking status or having quit within the past 15 years. Patients who had a prior diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 15 pounds in the preceding year were excluded. Three annual screenings were offered in each arm. A screen by LDCT was considered positive if it detected a nodule ≥ 4 mm in diameter or other finding suspicious for lung cancer; a screen by CXR was positive if it revealed a nodule or mass of any size or other finding suspicious for lung cancer. More lung cancers were detected by LDCT as well as more incidental yet clinically significant abnormalities not suspicious for lung cancer. Interestingly, there was also a statistically significant decrease in overall mortality by 6.7%. These benefits were not found in earlier, much smaller studies [24,25].

Of note, some pause has been expressed over the enthusiasm for LDCT screening (not only with the NLST but also with other studies) due to the high rate of detected nodules that are deemed to be benign (over 90%). In the NLST, for example, one-fourth of the scans showed a positive result but over 96% were not malignant; similar findings occurred in the CXR arm. Nevertheless, across all studies, this led to rare invasive procedures to diagnose detected findings (1 - 4%) with a minority of these procedures being for ultimately benign diseases [22]. Compared to the total that were screened in the NLST, the rate of death or major complications from diagnostic procedures was very low.

Another apprehension with recurring LDCT is radiation exposure. It is estimated that a single low-dose CT will expose a patient to approximately 1.5 mSV of radiation. The average annual dose provided by background radiation (in the United States) is 3 - 4 mSv [22]. Of course, a detected nodule may lead to further imaging which would increase the total exposure. Accordingly, the average total exposure for each NLST participant over 3 years was approximately 8 mSv [22]. However, based on data from prior studies on imaging

and radiation, it is projected that for one radiation-induced cancer, 2500 patients would have to be screened [27]. Taken together, the mortality benefit of screening far outweighs the possible risks. Moreover, radiation-induced cancer takes many years to develop. As such, particularly in older patients, this risk may never materialize in one's lifetime.

Given the above, the ACCP guidelines recommend annual LDCT screening for patients that meet the same entry criteria used for the NLST [22]. The United States Preventive Services Task Force (USPSTF) also suggests adoption of this practice, giving LDCT a grade B recommendation and extending the target population to patients up to 80 years old (with other inclusion benchmarks being the same as the ACCP guidelines) [28]. In addition to the ACCP, several other organizations also now advocate for annual LDCT screening with minor variations in patient selection criteria; these include the American Association of Thoracic Surgery, the American Cancer Society, the American Thoracic Society, and the National Comprehensive Cancer Network [29-32].

Finally, it is important to recognize that "screening is a process, not simply a test" [22]. To that point, a common emphasis among the various societal recommendations is that a lung cancer screening program should be a multidisciplinary effort among various specialties coordinating every phase of the process: from patient/provider education to the screening test itself to structured image interpretation/reporting to further evaluation and treatment of any findings [22,31]. A smoking cessation program is also recommended and, in fact, required for coverage by Medicare. Consequently, it has been recommended that screening be performed in centers similar to those where the NLST was conducted [31].

Clinical Manifestations

As mentioned previously, many patients with lung cancer present in later stages. This is due to the fact that many cases are relatively asymptomatic until tumor burden is of sufficient magnitude to cause symptoms, either due to locally advanced disease or metastases. Symptoms may also be caused by paraneoplastic syndromes.

Cough occurs in approximately half of lung cancer patients; a new cough in a former or current smoker should alert the clinician to the possibility of new-onset malignancy [33,34]. Even if there is clear evidence of another etiology, this should be followed to resolution both clinically and radiographically because of the possibility of underlying cancer. For example, a common presenting symptom of lung cancer is post-obstructive pneumonia. In such cases, pneumonia may be apparent symptomatically and on imaging but with the tumor hidden within one's lung infiltrate or consolidation. Symptoms will often resolve-at least temporarily-with antibiotics but the obstruction will not be evident on imaging until the pneumonic component has cleared, unveiling the underlying mass. Recurrent pneumonia in the same location should generate concern for cancer as a possible underlying process [35].

Dyspnea is also frequently present in lung cancer patients and varied potential causes exist [33,34]. Symptoms may be due to tumor affecting the airways (either due to intraluminal, extraluminal, or mixed obstruction) causing variable degrees of distal atelectasis (or infection as mentioned previously) [36]. Partial obstruction can lead to wheezing and be mistaken for asthma. Tumor can also infiltrate the lung parenchyma, taking the appearance of interstitial lung disease; this is known as lymphangitic spread. Involvement of the pleura can lead to pneumothorax and/or pleural effusion. As with other malignancies, patients are at risk of pulmonary embolism as well. These can all cause significant dyspnea alone but they can also be present simultaneously.

Hemoptysis is the initial symptom in about one-fourth of lung cancer patients but is typically not massive [33,37]. Though there is no clear 'cutoff' as to how much volume is considered dangerous, it has been estimated that even 100 cc of blood within the lungs can impair gas exchange enough to be life-threatening [38]. Generally, a larger volume of blood over a shorter time period correlates with outcomes, including mortality, and could indicate a more urgent situation [39]. When in doubt, referral to the emergency department is a prudent option. Persistent hemoptysis, even in small amounts or with a normal CXR, should prompt concern for an endobronchial lesion [40].

Other signs of intrathoracic spread are the superior vena cava syndrome due to a primary mass or enlarged nodal metastasis in the mediastinum [41]. Dysphagia from compression of the esophagus can also occur [41]. Superior sulcus (Pancoast) tumors can affect the brachial plexus leading to arm and shoulder pain as well as the sympathetic chain causing Horner syndrome [42].

Symptoms due to distant metastases vary and are sometimes absent. Involvement of the liver and adrenal glands is not uncommon but these are rarely symptomatic; bone metastases, however, are often painful [41]. Indicators of spread to the brain are variable; metastasis can be incidentally found on imaging done for staging or other reasons however neurological signs and symptoms can be the first presentation of underlying primary lung cancer [41]. Certainly, any new symptoms in a patient with current lung cancer or a history thereof should raise concern for possible malignancy. Positron emission tomography (PET) scan is useful for the evaluation of most metastatic burden; MRI is the test of choice for the brain.

Finally, paraneoplastic syndromes can occur but these are most often in the setting of small cell lung cancer. With non-small cell lung cancer, hypercalcemia can result from bone metastases or secretion of parathyroid hormone-related protein, usually with squamous cell carcinoma; the syndrome of inappropriate antidiuretic hormone has also been reported [43-46].

Diagnosis and Staging

The optimal approach to the diagnosis and staging of non-small cell lung cancer depends on various factors including the histologic subtype, the size and location of the primary tumor, the likelihood of metastatic lesions, and the clinical status of the patient [47]. Additionally, minimizing the number of procedures that a patient must undergo is ideal as this reduces both the chances of complications and the time to institution of treatment. A full methodology of how to diagnose and stage lung cancer is beyond the scope of this article but we will review important concepts and details of which clinicians should be aware.

As recommended by current guidelines, any patient with known or suspected non-small cell lung cancer should have a thorough clinical evaluation and a CT scan of the chest with contrast [48]. If these are unremarkable aside from the primary lung lesion(s), a PET scan is recommended to evaluate for signs of metastases. A bone scan combined with abdominal CT are alternatives if PET is not available. Of note, barring any other suspicious findings, guidelines state that a PET scan is not required if the primary lung lesion is a ground glass opacity or a peripheral nodule 3 cm or less as these have a low likelihood of having spread [48]. These patients may be considered to go directly to treatment with curative-intent. Conversely, any sign of metastasis on clinical examination or imaging usually warrants a site-specific evaluation-unless the radiographic evidence for metastasis is overwhelming, in which case sampling may not be needed beyond that required for a diagnosis.

An important facet of staging is invasive staging of intrathoracic lymph nodes. These lymph nodes can be enlarged or even PET-avid due to non-malignant diseases (e.g. sarcoidosis, infection) so sampling is useful rather than assuming this to be due to regional metastasis. In terms of which approach, ultrasound-guided bronchoscopic/endoscopic biopsy is recommended over surgical staging (e.g. mediastinoscopy). Bronchoscopy with endobronchial ultrasound is as good as or better than surgical methods while also causing less complications [49-51]. However, surgical staging is recommended if suspicion remains after a negative bronchoscopy [48]. There are cases where invasive staging may not be needed. If the mediastinum is extensively infiltrated, this most likely represents malignancy and invasive staging is not considered necessary [48]. Similarly, clinical stage IA tumors have a low likelihood of spread and invasive staging is not required in this setting either [48].

An important technical concept here is that maximizing staging information while minimizing the number of invasive procedures-such as attempting to diagnose and stage with a single procedure. For example, if a patient with suspected lung cancer has a possible metastatic lesion, this should be sampled first rather than the primary lung mass [47]. The reason is that the finding of lung cancer in a metastatic site would both stage the patient and provide a diagnosis and so no further biopsy (i.e. of the primary lung mass) would be needed. More specifically, the highest stage should be sought; for example, findings of lung cancer in a mediastinal lymph node would make a patient stage III but if a pleural effusion is also present, the question of the presence of stage IV disease (e.g. pleural involvement) remains. Sampling of the pleural effusion first and finding cancer there would obviate the need for biopsy of mediastinal nodes for the purpose of diagnosis or staging. Further considerations would need to be made if a given biopsy is negative but suspicion for cancer remains high (i.e. a false negative result). Of course, an important caveat to all of the above is that clinical judgment must be exercised-some tests may be

more definitive but carry more risk; instead, less invasive sampling may suffice in certain patients [47]. Thus, a patient's plan will need to be devised on a case-by-case basis and should involve a multidisciplinary team.

Treatment

Surgery, radiation, and systemic therapy are the three modalities most commonly used to treat non-small cell lung cancer. They can be used alone or in combination-and to varying degrees of aggressiveness-depending on various factors including cancer subtype, stage of disease, and a patient's ability to tolerate therapy.

For stage I and II non-small cell lung cancer, surgical resection is the treatment of choice [52]. The extent of resection (e.g. wedge resection, segmentectomy, lobectomy, pneumonectomy) depends on various tumor characteristics such as location within the lung as well as patient characteristics like predicted post-operative lung function. Chemotherapy will often follow completely resected stage II NSCLC but not usually stage I. Post-operative radiation is not recommended for either unless there is a positive bronchial margin (R1 resection); chemotherapy may also be considered in these cases [52,53]. For those deemed to not be surgical candidates (or who refuse surgery), stereotactic body radiation therapy (SBRT) can be considered though there is current controversy as to whether this is equivalent to surgery (the gold standard) in terms of long-term outcomes; further studies are underway [54-57]. Also known as stereotactic ablative body radiotherapy (SABR), SBRT can be used for limited lung metastases as well. Newer technology includes tumor ablation via bronchoscopy and is currently in the experimental phase [58-60]. This may provide further options for non-surgical patients with early-stage disease.

Stage III non-small cell lung cancer is comprised of various permutations of tumor and nodal characteristics from the TNM classification. As such, specific treatment approaches also vary but nearly always involve a combination of chemotherapy and radiation [5]. Patients with limited nodal involvement may be candidates for resection though chemotherapy and/or radiation are usually given before or after surgery depending on the extent of nodal involvement [5,61]. Whether there is benefit from adding surgery to chemoradiation is unclear though it may help certain subgroups of patients [61]. Patients with a high degree of nodal involvement are not generally considered for surgical resection at any point. As mentioned previously, specific patient and tumor characteristics will need to guide therapeutic decisions. Patients that cannot tolerate treatment with curative intent may receive palliative radiation alone [61].

For stage IV non-small cell lung cancer, therapy is systemic given the metastatic nature of the disease. Chemotherapy treatments have typically been two-drug, platinum-based regimens but the last several years have witnessed the development of therapies directed at molecular targets that are specific to each patient [62]. As such, ideally at the time of diagnosis or invasive staging, sufficient tissue should be obtained for molecular studies. The presence or absence of specific genetic mutations predicts responsiveness to certain agents. These include the tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, osimertinib and crizotinib and other agents such as dabrafenib and trametinib [5]. Furthermore, testing for programmed death ligand-1 (PD-L1) expression levels can be used to prompt treatment with certain immunotherapies such as pembrolizumab and nivolumab [5]. These novel agents can boost antitumor immunity but may also cause immune-mediated side effects.

Regardless of stage, local treatment may also be needed if malignant burden is clinically significant [5,41]. For example, symptomatic airway obstruction can be relieved by a trained bronchoscopist. Notably, this may thereby improve a patient's candidacy for other therapies that would not otherwise have been offered when he or she was more debilitated by his or her airway tumor burden. Bone metastases may undergo radiation therapy or even surgical stabilization if needed to prevent a fracture. Brain metastases can also be treated with radiation or possibly resection [41]. Recurrent malignant pleural effusions are usually treated with tunneled pleural catheters or chemical pleurodesis. Other localized problems from metastases may include spinal cord compression, airway-esophageal fistulae, and superior vena cava syndrome among others. These should prompt referral to the emergency department and will require urgent evaluation by their respective specialists.

Conclusion

Lung cancer has firmly held its place as the predominant malignancy of our day. The new and growing use of lung cancer screening may be able to change this tide as lung cancer is detected at earlier and more treatable stages. Nevertheless, clinicians should consider lung cancer in any former or current smoker who presents with new symptoms. Thankfully, there has been significant progress in lung cancer therapeutics. This will hopefully continue and further improve lung cancer outcomes.

Disclosures

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