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Review Article

Comprehensive Invasive and Noninvasive Approach to Diagnosis and Management of Non-small Cell Lung Cancer

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Abstract

In the United States, lung cancer is currently the leading cause of cancer mortality, with nearly 160,000 deaths estimated in 2014. Of newly diagnosed lung cancers, approximately 85% are non–small cell lung cancers (NSCLCs). Small cell lung cancer (SCLC) and NSCLC can often be distinguished based on clinical presentation and imaging findings. When SCLC is suspected, the diagnosis is typically established using noninvasive or minimally invasive means, and treatment is dictated by a dichotomous disease characterization: limited stage versus extensive stage disease

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Introduction

In the United States, lung cancer is currently the leading cause of cancer mortality, with nearly 160,000 deaths estimated in 2014.1 Of newly diagnosed lung cancers, approximately 85% are non–small cell lung cancers (NSCLCs) [1,2]. Small cell lung cancer (SCLC) and NSCLC can often be distinguished based on clinical presentation and imaging findings [3]. When SCLC is suspected, the diagnosis is typically established using noninvasive or minimally invasive means, and treatment is dictated by a dichotomous disease characterization: limited stage versus extensive stage disease [2,3].

The diagnosis and workup of suspected NSCLC, however, is more complicated because a thorough staging evaluation must be conducted to ascertain the tumor, nodal, and metastasis (TNM) designations that determine prognosis and guide treatment planning [2]. To that end, comprehensive clinical practice guidelines have been developed by several organizations, including the American College of Chest Physicians (ACCP) and the National Comprehensive Cancer Network (NCCN), but adherence to guidelines appears to be low [4,5]. For example, a recent retrospective study that included data from more than 15,000 patients with lung cancer and mediastinal lymphadenopathy but no metastatic spread found that only 21% of cases received an evaluation according to recommended best practices [6]. Nearly one half of cases (44%) did not undergo mediastinal sampling before treatment, and without pathologic confirmation of mediastinal nodal status, patients may be under staged and may not receive the optimal treatment for their disease [6]. These gaps in care are concerning and underscore the need for continued education and training to ensure appropriate and thorough work ups, which are the foundation for optimizing therapy and maximizing the potential for long term survival and—in some cases-cure.

This publication discusses the optimal management of patients with NSCLC and explores strategies for incorporating patient and disease related factors into treatment selection; it also discusses the role of the multidisciplinary care team.

Diagnostic and Staging Approaches in NSCLC

The diagnosis and staging of lung cancer are often intertwined to minimize the number of tests that a patient must undergo and to facilitate the prompt initiation of optimal therapy. In fact, the ACCP recommends that the process of stage evaluation begin before a definitive diagnosis is pursued, given the direct relationship between disease stage, treatment choice, and prognosis [7].

Many different noninvasive and invasive techniques can be used, all of which have advantages and limitations. The selection of the most appropriate test(s) should therefore be made by a multidisciplinary team that includes— at a minimum—a pulmonologist, chest radiologist, thoracic surgeon, and pathologist [3]. For example, in some cases, a single invasive test, such as endobronchial ultrasound (EBUS) guided biopsy of mediastinal lymph nodes or mediastinoscopy, performed in the same sitting as a planned surgical resection, can provide simultaneous diagnostic and staging information [5]. In other cases, a sequential workup is appropriate because of patient comorbidities and/or the potential for a non–lung cancer diagnosis [5].

Improper test selection and sequencing increases costs, delays time to treatment, and may increase the risk of complications [5,6]. It is therefore critical for team members to have a solid understanding of how to select and sequence the various tests in the current clinical armamentarium.

Table 1 Clinical Finding Suggestive of Metastatic NSCLC

INITIAL EXAMINATION	FINDINGS
Patient history	• Unintentional weight loss (> 10 pounds) • Anorexia • Fatigue • Focal skeletal pain • Headaches • Syncope • Seizures • Weakness in extremity(ies) • Recent change in mental status
Physical examination	• Supraclavicular lymphadenopathy • Hoarseness • Superior vena cava syndrome • Bone tenderness • Hepatomegaly (> 13-cm span) • Focal neurologic signs • Papilledema • Soft-tissue mass
Laboratory tests	• Hematocrit < 40% for men, < 35% for women • Elevated alkaline phosphatase, gamma-glutamyltransferase, aspartate transaminase, or calcium levels

Adapted from Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e211S-250S

Noninvasive Approaches

When NSCLC is strongly suspected, one of the first steps is to determine whether disease is limited to the chest or has spread to distant sites; this information determines whether the treatment approach will be aimed at potential cure or palliation [7]. Information obtained from an expanded clinical evaluation can suggest metastatic disease, such as abnormal findings on routine laboratory tests or symptoms associated with bone or central nervous system (CNS) involvement (Table 1). Nonspecific signs and symptoms such as fatigue, anorexia, and weight loss also suggest advanced disease. For patients with localized signs and symptoms of metastatic disease, directed tests such as plain bone films or needle aspiration of a palpable lesion may confirm the diagnosis. Other cases require imaging studies such as CT and/or positron emission tomography (PET) scans to aid in diagnosis and staging

[7].

Chest CT is an essential component of the workup for all patients suspected of having lung cancer, regardless of whether suspicion is due to an abnormal chest x ray or the presence of symptoms [7]. Chest CT facilitates determining the T stage of the lesion because it reveals the three dimensional size of the primary tumor as well as its location with respect to critical structures [2]. Although not absolutely required, intravenous contrast may be helpful for distinguishing vascular structures from lymph nodes and highlighting mediastinal invasion by central tumors [7]. When disease is limited to the chest (or if distant metastatic sites are difficult to biopsy), assessing the mediastinum becomes the focus of the workup [3,7]. Information gleaned from the CT scan can assist in determining how to proceed [7]. According to the ACCP, patients can generally be separated into the following four categories based on chest CT findings[7]:

- Group A, Mediastinal Infiltration: discrete lymph nodes are not visible or measurable due to mediastinal infiltration that encircles vessels and airways
- Group B, Enlarged, Discrete Mediastinal Nodes: nodes are enlarged but discrete and measurable
- Group C, Clinical Stage II or Central Stage I Tumor: mediastinal nodes are normal, but central tumor location and/or suspicion of N1 disease increases the likelihood of N2,3 nodal involvement
- Group D, Peripheral Clinical Stage I Tumor: mediastinal nodes are normal, and peripheral tumor location makes advanced disease unlikely

Group A patients are generally believed to have mediastinal involvement based on CT findings alone, and tissue sampling to distinguish between SCLC and NSCLC should be performed with the easiest method possible [7].

For patients in Group B, mediastinal involvement must be confirmed by tissue sampling, and for patients in Group C who have normal mediastinal nodes, tissue confirmation is recommended because of the elevated risk of N2,3 involvement. Staging of the mediastinum is not generally recommended for Group D patients because of the relatively low risk of mediastinal involvement [7].

Although chest CT provides anatomic detail, identifies the location of a tumor and its proximity to local structures, and aids in assessing the mediastinal lymph nodes, its ability to distinguish between benign and malignant conditions is low [7]. PET imaging provides less anatomic detail than CT scanning, but should be used in the evaluation of patients with lung cancer because of its higher sensitivity and specificity for identifying mediastinal node involvement and its ability to detect extrathoracic disease. It is not, however, a definitive test, and tissue confirmation is still required. Overall, studies of PET scanning have found that its benefit is greatest when the risk of advanced disease is high, such as in patients with symptoms suspicious for metastatic disease or in those with enlarged mediastinal nodes [7]. In these situations, PET scanning increases the preoperative detection of metastatic disease and, therefore, reduces the number of futile surgeries [2,7]. In fact, population based studies suggest that the increasing use of PET scanning has resulted in stage migration as a greater proportion of clinical Stage III patients today are upstaged to Stage IV disease [8,9]. Nonetheless, tissue confirmation of PET scan findings is still required because of the risk of a false positive result[7]. In randomized trials, as many as 42% of patients were incorrectly upstaged by PET scan [7]. These patients might have missed the opportunity for a potentially curative surgical resection if tissue confirmation had not been required in these studies.

Currently, the ACCP recommends the use of PET scanning for patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on CT scan in order to assess for non CNS metastases, with subsequent tissue sampling of an identified abnormal site to avoid incorrect upstaging [7]. The NCCN guidelines are similar, although they recommend use of combined PET/CT because this test is more sensitive [5]. If PET scanning is unavailable, bone scan and abdominal CT should be considered to evaluate for extrathoracic disease. In the case of overwhelming evidence of metastatic disease in multiple sites, tissue sampling of a distant site is not necessary, and sampling of the mediastinal nodes may not be needed [7]. Notably, PET scanning is not accurate for the evaluation of CNS involvement due to high glucose uptake and utilization by normal brain cells [2]. Contrast Enhanced MRI is the preferred imaging test for the brain and is recommended for patients with neurologic symptoms, patients with clinical Stage III or IV NSCLC who are asymptomatic, and all patients with SCLC [2,7].

Minimally Invasive Techniques

Invasive tests complement the results of noninvasive tests and should be selected based on imaging results, anatomic factors, and the expertise of the physicians who are available to perform the tests [7]. In general, the biopsy site is chosen to establish the higher stage of disease, such as an N3 node rather than primary tumor, unless the procedure is deemed too risky or would be unlikely to yield sufficient material for subsequent biomarker testing (eg, bone metastases) [2]. Given the variety of minimally invasive techniques currently available for diagnosis and staging, multiple disciplines may be involved, including a pulmonologist/bronchoscopist, an interventional radiologist, and/or an endoscopist.

Biopsy techniques for diagnosing lung cancer include CT guided transthoracic needle aspiration (TTNA; also known as percutaneous needle biopsy) and transbronchial needle aspiration (TBNA) [7]. TTNA can be used to sample a parenchymal mass for diagnosis [7]. Complications are relatively frequent, and approximately 10% of patients require chest tube placement for pneumothorax [2,7,10]. Given these limitations, this technique is most applicable when evaluating a peripheral nodule, confirming the diagnosis in patients with extensive or bulky mediastinal disease [2,3,7].

Flexible bronchoscopy (FB) (and variations thereof) is a useful tool for accessing centrally located tumors and mediastinal lymph nodes [3]. Visible central lesions can be sampled with a brush, needle, or forceps, although sensitivity is highest for direct forceps biopsy. Endobronchial needle aspiration can be performed simultaneously to obtain cytology or histology samples in cases of submucosal tumor spread or peribronchial disease [3].

The sensitivity of FB is relatively low for diagnosing peripheral lesions, which cannot be directly visualized with the bronchoscope [3]. Fluoroscopy Guided TBNA increases diagnostic accuracy for peripheral lesions, although other complementary tools are increasingly being used in this situation. For example, radial EBUS, performed by inserting a rotating ultrasound transducer through the working channel of the bronchoscope, produces a 360 degree image of surrounding structures [3]. After the target lesion is localized, the transducer is removed from the working channel and replaced with a sampling tool, such as forceps [11]. Fluoroscopy can be used to confirm the position of the forceps before sampling [11]. Navigational bronchoscopy, which uses computer guided imaging and navigation, may also increase the diagnostic accuracy of bronchoscopic tumor biopsy, especially for more peripheral lesions.

To date, most radial EBUS studies have been small or lack generalizability because of patient selection criteria, but the results of a contemporary meta-analysis suggest that radial EBUS is a safe

and relatively accurate tool for evaluating peripheral lung lesions [12]. Pooled sensitivity and specificity were high in this analysis (73% and 100%, respectively), although diagnostic yield was greatest for larger lesions (> 20 mm). Currently, radial EBUS has not been shown to be superior to CT guided TTNA of a peripheral lesion, but it appears to be safer, with a pooled pneumothorax rate of approximately 1% and chest tube rate of 0.4% [12]. The ACCP recommends radial EBUS as an adjunct imaging modality for patients with a peripheral lung nodule, noting that it facilitates real time identification of the ideal location for bronchoscopic sampling and increases diagnostic yield over conventional bronchoscopy [3]. They note, however, that additional well designed studies are needed to further quantify accuracy and identify patients most likely to benefit from this approach [3].

Minimally invasive, ultrasound guided techniques are also used to stage the mediastinum [13]. EBUS TBNA and endoscopic ultrasound guided fine needle aspiration (EUS FNA), which accesses mediastinal nodes through the wall of the esophagus, are outpatient procedures that can be used alone or together and provide a viable alternative to surgical staging. With appropriate patient selection and operator skill, these techniques may yield results equivalent to mediastinoscopy for detecting N2 or N3 disease. In contrast to mediastinoscopy, however, these procedures are sometimes performed by physicians who do not necessarily manage a large number of lung cancer patients as part of their routine clinical practice, underscoring the need for multidisciplinary collaboration to ensure an optimal workup that meets the needs of all team members [13]. Although research is needed in this area, experts generally recommend an approach similar to that used by thoracic surgeons during mediastinoscopy: at least [3], and ideally [5], distinct nodal stations should be assessed, and the largest nodes should be sampled when ultrasound guided staging is performed by a bronchoscopist or endoscopist [2,7,13].

The diagnostic sensitivity of EBUS TBNA and EUS FNA can be increased when the procedures are combined because this approach provides access to nearly the entire mediastinum [13,14]. EBUS TBNA provides access to the paratracheal, peribronchial, and hilar nodes, but not the aorto-pulmonary window (APW) nodes or low periesophageal nodes, whereas EUS FNA is particularly useful for reaching the inferior pulmonary ligament and esophageal and subcarinal nodes (Figure 1) [7,13]. EUS FNA can also be used to detect tumor invasion into the mediastinum (T4 disease) and metastatic disease in the adrenal glands, celiac and retroperitoneal lymph nodes, and liver [2,7,13]. Although a combined approach is feasible and highly sensitive, it is logistically complicated because two procedura lists and different instruments are required [2]. Thus, although appealing, this approach may not yet be available in many community oncology settings because combined endoscopic and bronchoscopic expertise may not be available [7].

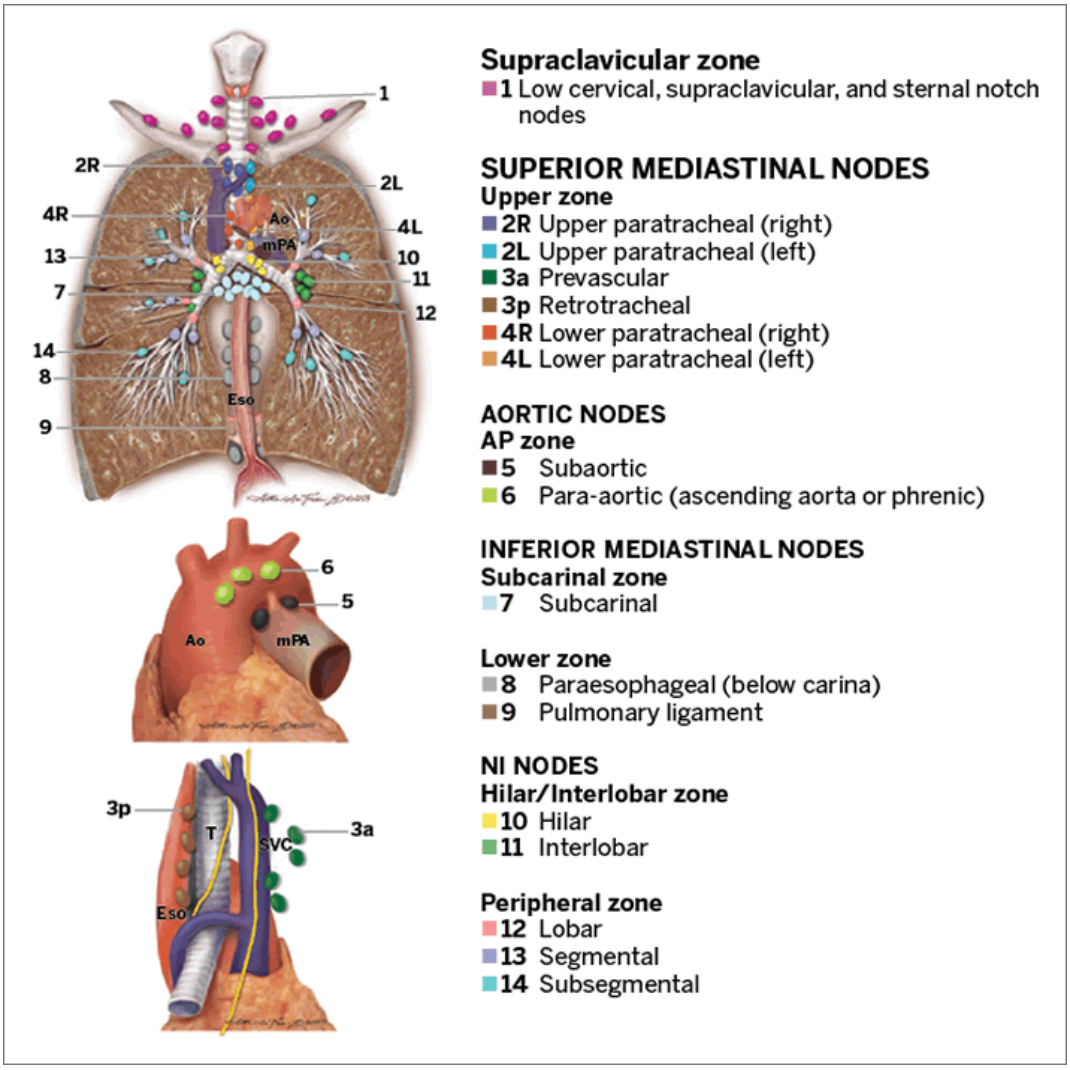

Figure 1 Nodal Chart With Stations and Zones

Reprinted with permission from Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami Porta R, Goldstraw P; members of IASLC Staging Committee. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol. 2009;4(5):568577.

Invasive Staging Techniques

Despite the increasing availability and use of minimally invasive staging procedures, there is still a role for traditional and advanced surgical staging in NSCLC. Mediastinoscopy and thoracoscopy (also known as video assisted thoracic surgery, or VATS) are the primary invasive techniques in use today. Mediastinoscopy is a surgical procedure that requires general anesthesia, although the vast majority of patients are discharged the same day [7].

To perform traditional cervical mediastinoscopy, the mediastinoscope is inserted through a surgical incision just above the suprasternal, or jugular, notch and extended in the plane anterior to the trachea [7,13]. The paratracheal, pretracheal, and anterior subcarinal nodes are accessible with this approach, and the use of a video mediastinoscope increases access to the posterior subcarinal nodes [7].

Videoassisted thoracic surgery can also be performed to evaluate mediastinal nodes, including the APW nodes [7]. As with mediastinoscopy, general anesthesia is required; however, VATS provides a more limited assessment than mediastinoscopy because only one side of the mediastinum can be assessed. Right sided procedures are generally straightforward, but access to the left paratracheal nodes can be challenging; left VATS is an alternative to extended mediastinoscopy for accessing the AP window nodes [7].

Although both mediastinoscopy and VATS are sensitive staging tools, a less invasive needle technique (EBUS TBNA or EUS FNA) is now recommended as the best first test when there is intermediate or high suspicion of N2 or N3 disease, assuming the availability of an experienced and skilled operator to perform the less invasive procedure [7]. However, surgical staging techniques are appropriate and should be performed if clinical suspicion of nodal involvement remains high after a negative result from a needle technique [7].

Recent Treatment Advances

Surgical resection offers patients with early stage NSCLC the best chance for cure and long term survival. For patients with Stage II/IIIA disease, survival is further improved with the use of adjuvant chemotherapy [5,15]. Lobectomy is the preferred approach for patients with T1b and larger tumors; greater resections are conducted as appropriate to obtain an R0 resection. Minimally invasive, or thoracoscopic lobectomy, has significantly improved the surgical care of patients with lung cancer. Compared with thoracotomy, significant benefits have been demonstrated for patients undergoing VATS lobectomy, including shorter hospital stays, fewer perioperative complications, and at least equivalent oncologic efficacy [16,17]. As such, VATS lobectomy can be successful in patients who might not otherwise be considered operative candidates, including the elderly and those with marginal pulmonary function.

Although VATS lobectomy has greatly expanded the utility of surgery in patient populations previously considered to be marginal for resection, not all patients are surgical candidates, and not all patients consent to surgery [15]. Moreover, the ACCP reports that approximately 30% of patients with potentially curable, early stage NSCLC receive no definitive treatment at all. Given the benefits of treatment in this setting, it is important that patients be evaluated by a multidisciplinary team that includes a thoracic surgical oncologist and radiation oncologist to ensure that all reasonable options are considered [15].

A growing body of evidence supports the practice of referring patients with known or suspected early stage NSCLC to higher volume centers and providers who focus on lung cancer for evaluation, treatment planning, and surgery [18,19]. Results from a recent meta analysis demonstrate that the improvements in surgical outcomes, such as reduced perioperative mortality and improved long term survival, are even greater than the improvements associated with established treatments like adjuvant chemotherapy [20]. Because the surgical treatment setting has a major influence on outcomes, the ACCP strongly recommends that medically fit patients with Stage I/II disease be evaluated by a certified thoracic surgeon [15]. Lobectomy remains the treatment of choice, and a minimally invasive approach such as VATS is recommended over thoracotomy if the surgery is performed at a higher volume center with VATS expertise. For patients who are unable to tolerate lobectomy, sublobar resection is a reasonable option and is preferred over nonsurgical therapy [15]. Those with early stage NSCLC who cannot or should not undergo surgery may be candidates for radiation therapy (RT)

[15,21]. Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), is an appropriate nonsurgical treatment for patients with clinical Stage I NSCLC who refuse surgery or who are inoperable because of comorbidities such as emphysema and heart disease [15,21]. Compared with conventional fractionated RT, which is typically administered over 20 to 30 outpatient sessions, SABR delivers higher dose radiation more precisely over a shorter period of time, ranging from only 1 to 5 treatment sessions [21,22]. Although several different commercial platforms are available to deliver SABR, all share the ability to deliver image guided conformal radiation with compensation for respiratory tumor motion [22]. As a result, there is minimal damage to surrounding healthy lung tissue.15 Updated results from the phase 2 RTOG 0236 trial, which evaluated SABR for high-risk, inoperable patients with biopsy proven peripheral NSCLC, were recently presented at the American Society for Therapeutic Radiation and Oncology Annual Meeting and revealed a 5 year survival rate of 40% [23]. Treatment related grade 3/4 adverse events were reported for 17 patients, and there were no treatment related deaths [23]. Although SABR is an effective option for select patients, questions remain about its optimal use; several clinical trials are currently examining this issue (see ClinicalTrials.gov).

Adjuvant chemotherapy is an established standard of care for patients with completely resected Stage II NSCLC with N1 node involvement [15]. The role of adjuvant chemotherapy for patients with Stage IB disease has been less clear. The randomized JBR10 and CALGB 9633 studies initially supported its use in this population, and the NCCN guidelines support at least the consideration of adjuvant chemotherapy in these patients. However, recent studies demonstrate that the survival benefit seems to have disappeared with longer follow up and was limited to patients with Stage II disease [24,25]. Exploratory analyses of both studies suggested a survival benefit for Stage IB patients with a tumor at least 4 cm in size, but this finding should be interpreted with caution. Nonetheless, the seventh edition of the IASLC TNM criteria has upstaged certain Stage I patients with primary tumors greater than 5 cm to Stage II disease, for which chemotherapy is generally recommended [15].

Unlike in the metastatic disease setting, targeted therapies are not yet recommended for use in early stage NSCLC [5,15]. A targeted therapy approach, however, is attractive, given its success in the treatment of advanced disease, and a number of phase 3 clinical trials of targeted therapies are underway.

Collaborative Care in NSCLC

As discussed, the diagnosis, staging, and treatment of NSCLC is increasingly complex. Because of this, many types of clinicians across a wide variety of disciplines collaborate with one another to provide patient care. This includes:

- Primary care physicians, who first suspect the disease
- Pulmonologists, endoscopists, and interventional radiologists, who may be asked to perform certain diagnostic tests
- Thoracic surgeons, who determine resectability and perform surgical staging and potentially curative resections
- Pathologists, who determine tumor histology and molecular phenotype
- Radiation oncologists, who determine and plan RT when appropriate
- Medical oncologists, who choose when and how to use systemic therapies based on disease stage and pathologic findings

It is key for these members of the oncology care team to work together to efficiently determine the diagnosis and treatment plan, avoid unnecessary tests and procedures, and maximize the opportunity for optimal therapeutic outcomes for all patients with suspected lung cancer. Indeed, professional organizations are increasingly recognizing that coordinated, multidisciplinary care underlies quality cancer care [26,27]. Multidisciplinary clinics, which allow patients the opportunity to be seen by the requisite specialists on the same day, and multidisciplinary conferences, which provide physicians the opportunity to review cases together prospectively and coordinate treatment plans, provide a structured process for collaborative care [27]. Traditional face-to-face conferencing can be challenging in the community, particularly in rural areas; however, telemedicine, via video or internet conferencing, can help extend collaborative care to these areas and increase access to university based specialists [28]. Although data have not yet clearly demonstrated improved clinical outcomes for patients who receive multidisciplinary thoracic oncology care, surrogate outcomes, including more complete staging evaluation, increased adherence to national care guidelines, and shorter time from diagnosis to treatment, suggest benefit [29,30]. Access to lung cancer clinical trials and palliative care may also be improved with a multidisciplinary approach [29,30].

Conclusion

The diagnosis, staging, and treatment of NSCLC are a complex undertaking that involves many different types of clinicians, from those who identify and stage the disease to those who treat it. Comprehensive clinical practice guidelines provide a roadmap for these elements of care, but adherence to guideline recommendations is lower than ideal. By working together to ensure appropriate workups and therapeutic interventions and applying the latest techniques and guidelines recommended approaches, these gaps in care can be reduced to maximize the potential for long term survival in patients with NSCLC.

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