Clinical Issues in the Surgical Management of Screen-Identified Lung Cancers

This review outlines the diagnostic and therapeutic challenges associated with the increased number of screen-identified indeterminate lung nodules, highlighting currently recommended follow-up and management algorithms, as well as the various methods of nodule localization, tissue diagnosis, and definitive local therapeutic modalities.

Introduction

The confirmation that screening by computed tomography (CT) significantly reduces mortality in lung cancer is one of the major recent advances in thoracic oncology. In 2011, the National Lung Screening Trial (NLST) investigators reported that CT screening resulted in a 20% reduction in lung cancer-specific mortality compared with screening by plain chest radiography.[1] The results of this trial were the basis for the endorsement of CT screening for lung cancer by the US Preventive Services Task Force (USPSTF). The USPSTF gave screening a Level B recommendation, indicating that the benefits of lung cancer screening exceeded potential harms. Low-dose CT (LDCT) screening for lung cancer was subsequently approved by the Centers for Medicare and Medicaid Services (CMS) as a reimbursable preventive health service.

Despite these seminal events, legitimate concerns remain about the potential harmful effects of lung cancer screening. The USPSTF and other organizations have outlined these potential harms, which include excessive or unnecessary testing, patient anxiety about a cancer diagnosis, increased radiation exposure, and the potential for excessive invasive interventions and associated complications in otherwise healthy persons.[2,3] Clearly, national dissemination of lung cancer screening programs must be accompanied by thoughtful strategies embedded in such programs in order to mitigate potential risks.

In the United States alone, it is estimated that approximately 8 million people are candidates for screening based on the eligibility criteria applied in the NLST.[4] This number would likely increase if the strict risk profile used by the NLST is relaxed to include persons older than 75 years of age (as recommended by the USPSTF), those with a less extensive smoking history, persons with occupational exposures, and those with a history of lung cancer (Table). In either scenario, the large number of indeterminate pulmonary nodules anticipated to be encountered during the course of screening will pose diagnostic and therapeutic challenges. These challenges will be met against a backdrop of critical views, some of which contend that lung cancer screening will result in a 10-fold increase in surgical procedures.[5] If true, such an inordinate increase in invasive procedures could erode the efficacy of screening and unfavorably alter the risk/benefit assumptions.

In addition to their strong endorsement of lung cancer screening, thoracic surgical organizations have moved swiftly to address such concerns. In 2013, the Society of Thoracic Surgeons (STS) Workforce on General Thoracic Surgery established the Task Force on CT Screening.[6] The Task Force was composed of expert thoracic surgeons from around the world who were charged with defining the role of the thoracic surgeon in CT screening programs for lung cancer, as well as identifying the surgical issues relevant to the screened population. In this review, we will focus on some of the specific challenges faced as we move toward national and possibly international implementation of LDCT screening programs.

Role of the Surgeon in the Multidisciplinary Team

Both the STS Task Force and the Surgical Experts Group of the International Association for the Study of Lung Cancer (IASLC) consider it essential that thoracic surgeons be involved early in the design and structure of screening programs. They also highly recommend that surgeons participate in the crafting of the diagnostic protocol and the therapeutic algorithms. The success of the
The Diagnostic Challenge

A major risk of LDCT screening is the detection of a large number of indeterminate pulmonary nodules that may require further diagnostic imaging or invasive interventions. In the setting of lung cancer screening, inappropriate invasive interventions pose a greater risk to the screened population than that encountered in other cancer screening programs, given the small but real risk associated with invasive thoracic procedures. The optimal mitigating strategy against the risk of excessive testing or inappropriate intervention is the prior development and strict implementation of a detailed diagnostic protocol. Deviations from the prescribed diagnostic algorithm should occur only after input from the multidisciplinary team.

A number of radiologic diagnostic protocols are available, including those from the Fleischner Society, the American College of Chest Physicians, and the International Early Lung Cancer Action Program (I-ELCAP), as well as the diagnostic protocol employed by the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) investigators. It is notable that despite the availability of a companion diagnostic protocol for the NLST, the participating sites were allowed to apply their institutional standards of care. More recently, the American College of Radiology released its first edition of the Lung Imaging Reporting and Data System (Lung-RADS™) for the standardized management and reporting of screen-detected nodules.[7] A recent study retrospectively applied the Lung-RADS criteria to the NLST and found that these criteria were associated with a substantial reduction in the false-positive rate, but at the expense of a corresponding reduction in sensitivity.[8] Nearly all diagnostic protocols use nodule size, shape, and density, as well as rate of growth, to differentiate between benign and malignant nodules. Among these variables, nodule growth—determined by either unidimensional or volumetric assessment—is generally considered the critical determinant for proceeding to invasive testing. The NELSON investigators reported on the efficacy of nodule volume and volumetric changes as important predictors of malignancy and consequently the need for invasive testing.[9,10]

It is important to recognize that the overwhelming majority of nodules found by screening are not cancer. In the NLST, baseline scans led to a confirmed diagnosis of lung cancer in 0.5% of 4- to 6-mm nodules and in 1.6% of 7- to 10-mm nodules.[11] Even in larger (11- to 20-mm) nodules, lung cancer was confirmed in only 12%. In the I-ELCAP data, 11.6% of patients with positive baseline CT scans were found to have cancer.[12]

Suspicious nodules detected by CT may be further investigated with positron emission tomography (PET) scanning. Veronesi et al reported that the sensitivity and specificity of PET for screen-detected lung nodules were 89% and 93%, respectively, but the median nodule size was 14 mm in their cohort of patients.[13] PET likely has a lower sensitivity in subcentimeter nodules and in pure ground-glass lesions.

Obtaining a Tissue Diagnosis

Fine-needle aspiration

When a nodule is suspected to be malignant based on baseline characteristics, positive PET scan findings, or the demonstration of growth, obtaining a tissue diagnosis is the next important step. The Surgical Experts Group of IASLC encourages the use of transthoracic fine-needle aspiration (FNA) and suggests that in many cases it will facilitate surgical decision making.[14] FNA is particularly useful in patients with nodules deeply seated in the lung parenchyma, where a diagnostic surgical approach might entail a significant parenchymal resection. FNA is also valuable in small subcentimeter nodules or nonsolid nodules, in which difficult intraoperative localization may limit the surgical diagnostic options. In such instances, a nondiagnostic FNA should not automatically trigger a surgical biopsy, since the small size of the nodule or its indolent nature may permit safe continued observation until there is evidence of interval nodule growth. FNA performed at high-volume centers can be extremely accurate, with a sensitivity of 82% to 99% and a diagnostic accuracy of up to 97%.[15]

Bronchoscopy

If expertise in FNA is not readily available, other invasive diagnostic approaches include...
bronchoscopic or surgical biopsies. The NELSON investigators evaluated the role of white-light bronchoscopy in 308 persons with 318 suspicious lesions.[16] The sensitivity of bronchoscopy was 13.5%, and the specificity was 100%. The positive and negative predictive values were 100% and 47%, respectively. Notably, bronchoscopy found less than 1% of all detected cancers. The investigators concluded that conventional bronchoscopy should not be routinely recommended in persons with a positive result in a lung cancer screening program. Nonetheless, bronchoscopy remains one of the more commonly used diagnostic modalities in patients with lung nodules. For example, in the NLST, approximately 39% of all invasive procedures performed in patients with positive CT scan results were bronchoscopy with or without a biopsy.[1] Although novel bronchoscopic techniques, such as endobronchial ultrasonography and navigational bronchoscopy, are useful in the traditional clinical setting, their diagnostic role in the context of a CT screening program has not been investigated.

**Surgical biopsy**

When surgical biopsy is necessary, minimally invasive approaches such as video-assisted thoracic surgery (VATS) and robotic-assisted techniques are strongly recommended over open thoracotomy approaches. Excisional wedge biopsies are usually straightforward with minimal morbidity and negligible mortality when performed in otherwise healthy patients. Data from the STS General Thoracic Surgery Database show that hospital mortality and major morbidity in more than 3,700 patients who had wedge resections were 1.2% and 4.5%, respectively.[17] Similarly, Altorki et al reported that in a screened population, there were no hospital deaths among 53 patients with screen-detected cancers treated by limited resection alone.[18] Most patients in whom a diagnostic wedge resection is performed can proceed directly to lobar resection at the same time if a frozen section examination confirms the diagnosis of lung cancer.

When a nodule is smaller than 1 cm or is nonsolid, surgical localization can present a challenge that demands intimate knowledge of pulmonary segmental anatomy and its correlation with the CT images. Several techniques have been developed to facilitate the intraoperative localization of small or subtle lung nodules. These techniques are briefly discussed below.

**Preoperative CT-guided localization**

Transthoracic dye injection directly adjacent to the tumor has been used for lung nodule localization for many years, with minimal morbidity. Because diffusion of the dye away from the nodule site can occur in the interval between injection and surgery, dye injection should preferably be done as close to surgery as possible. In addition, pulmonary embolism may rarely occur with the use of non–water-soluble dyes. A major drawback of this technique is the lack of information about the depth of the tumor, which increases the possibility of missing the tumor or having a positive parenchymal resection margin. Therefore, a new technique has been developed, virtual-assisted lung mapping (VAL-MAP), which uses multiple dye markings guided by three-dimensional CT virtual images to delineate the borders of the tumor and to serve as a reference for the subsequent biopsy/resection.[19]

Another technique for CT-guided localization, metal wire localization, facilitates the intraoperative detection of nodules, but at the expense of increasing the incidence of procedure-related complications, including bleeding, pneumothorax, air embolism, and wire dislodgement.[20] The wire used in localization should be cut flush with the chest wall to prevent dislodgement upon lung collapse intraoperatively. Another common method of localization is microcoil insertion.[21] Microcoils are usually inserted within 1 cm of the tumor and can be detected intraoperatively by manual palpation. This technique has gained wide popularity in recent years and carries a much lower risk of dislodgement than wire localization. Typically, microcoil insertion and dye localization are used together to increase the accuracy of nodule detection.

**Radiotracer localization**

The technique first described in 2000 by Chella et al uses a radionuclide (technetium-99m) that is placed under CT guidance in or near the lung nodule and is detected intraoperatively with a radio probe.[22] The VATS radiotracer localization technique has a success rate of 92% for nodules with a median size of 8 mm.[23] This technique can be applied to all pleural surfaces, including interlobar regions with complete fissures, and enables rapid and predictable intraoperative localization. The procedure uses readily available technical components with minimal additional cost.

**Intraoperative ultrasonographic localization**
Intraoperative ultrasonographic localization spares the patient from undergoing additional procedures, with their associated complications, and it also reduces the risks associated with repeated radiation exposure.[24] However, it is a time-consuming, operator-dependent procedure that requires adequate training. Moreover, this technique is not suitable for patients with extensive emphysema or with deep or nonsolid nodules. Because of these limitations, it is rarely used compared with other localization techniques.

**Navigational bronchoscopy**

Two navigational bronchoscopy systems have been developed to facilitate the endobronchial localization of peripheral lung nodules: electromagnetic navigational bronchoscopy (ENB) and virtual navigational bronchoscopy (VNB).\[25,26\] ENB uses a sensor device to detect location within a magnetic field created around the patient. Three-dimensional CT reconstruction images are superimposed on the real anatomy using the magnetic field and the site of the sensor within; the system thus helps guide an instrument through the bronchial tree to localize or biopsy the nodule. VNB uses preprocedural CT images to create a three-dimensional bronchial tree and a roadmap that can be followed to reach the nodule, which makes it easier to biopsy or localize peripheral nodules and minimizes the duration of the procedure and associated complications. We have used VNB to localize subcentimeter and nonsolid nodules by navigating as close as possible to the nodule and injecting methylene blue at the site to aid the visual localization of the nodule at the time of surgical exploration, which is carried out during the same session. One advantage of this method over transthoracic injection of methylene blue is the significant reduction in dye diffusion throughout the lung parenchyma with bronchoscopic administration. Regardless of the method of localization, it is essential that an expert pulmonary pathologist be available to readily identify the lesion, particularly a nonsolid lesion, and to confirm the diagnosis.

**Resection of Screen-Detected Lung Cancer**

To date, lobectomy remains the standard of care for the management of non–small-cell lung cancer (NSCLC). However, the past decade has witnessed a resurgence of interest in sublobar resection for small, peripheral, early-stage lung cancers, as well as for nonsolid nodules that are the radiologic manifestations of adenocarcinoma in situ and minimally invasive carcinoma. These lesions are currently detected with higher frequency owing to the more widespread use of CT scanning and the enhanced resolution of CT scanning devices. Their detection will likely continue to increase once CT screening programs are more widely implemented. The rationale for sublobar resection in such instances is supported by the results of a number of retrospective case series, mainly from Japan, showing that overall and disease-free survival are comparable to those achieved after lobar resection.[27-30]

Recently, Altorki et al reported the overall and cancer-specific survival for 347 patients with clinical stage IA NSCLCs manifesting as solid nodules in the I-ELCAP screening program.[31] Ten-year survival was 85% for 53 patients treated by sublobar resection and 86% for 294 patients treated by lobectomy. Cox survival analysis showed no significant difference between sublobar resection and lobectomy when adjusted for propensity scores or when using propensity quintiles. For those with cancers 20 mm or less in diameter, the 10-year rates were 88% and Cox survival analysis showed no significant difference between sublobar resection and lobectomy. Despite these results, the majority of lung cancers detected in the context of screening continue to be treated by lobar resection, which remains the standard of surgical care worldwide.
What Is New Here?
Kamel et al from Weill Cornell Medical College in New York City (the birthplace of computed tomography screening for lung cancer with Henschke’s article in the *Lancet* in 1999) point out that the diagnosis and treatment of screen-detected lung nodules/cancers differ importantly from our traditional algorithms for evaluating lung nodules. We must be aware of these differences and update our practices accordingly if we are to provide our patients with the benefits of screening while minimizing the very real risks. The authors highlight both new and well-described methods of localizing these small tumors, note instances in which standard techniques (eg, white-light bronchoscopy) fall short, and reemphasize the well-accepted benefits of minimally invasive surgical resections.

How Will Clinical Practice Be Affected?
As surgeons, Kamel et al credibly remind other thoracic surgeons of the need to participate in the development of diagnostic algorithms based on the expertise available in one’s own hospital, to cultivate a working knowledge of lung segmental anatomy, to be able to comfortably perform sublobar resections, to evaluate lymph nodes intraoperatively for solid cancers, and to obtain appropriate parenchymal margins, all while using minimally invasive approaches (video-assisted thoracic surgery or robotic-assisted techniques). This sets the surgical bar fairly high—where, of course, it should be.

What Still Needs to Be Addressed?
Currently, we need better methods of localizing screen-detected nodules and of identifying potential cancers. We also need to determine the role of alternative therapies (for example, does radiation play a role in the treatment algorithm?), and to fine-tune our imaging abilities. In the future, other means of detecting lung cancer in high-risk persons (eg, blood tests, exhaled breath analysis) may resolve some of these issues.

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Currently, two randomized noninferiority trials are testing the hypothesis that lobar and sublobar resections are associated with comparable disease-free survival in patients with solid clinical stage IA NSCLC. The Japanese trial (Japan Clinical Oncology Group [JCOG] 0802) randomized 1,100 patients with clinical stage IA cancer to either lobectomy or anatomic segmentectomy. Accrual was completed in September 2014. The North American trial (Cancer and Leukemia Group B [CALGB] 140503) continues to randomize patients with clinical stage IA cancer to either lobectomy or sublobar resection (wedge resection or segmentectomy). Target accrual is 692 patients, of whom 511 patients have been randomized. The results of these two important trials, expected within the next 5 to 7 years, will determine the standard of care for decades to come.

The role of sublobar resection in nonsolid nodules is also being evaluated in a Japanese phase II trial (JCOG 0804) in which 330 patients with either nonsolid ground-glass nodules or part-solid nodules with a solid component of ≤ 25% were treated with wide wedge resection. Accrual was completed in March 2012, and mature follow-up data on survival and recurrence are awaited.

In the meantime, sublobar resection is slowly emerging as a viable alternative to lobectomy,
particularly in patients with nonsolid nodules that may represent indolent cancers, namely preinvasive or minimally invasive adenocarcinoma. The challenge in localizing such lesions intraoperatively has already been discussed, and the application of sublobar resection in such cases requires careful planning. An important aspect of such planning is the participation of an expert pulmonary pathologist who will be able to confirm on frozen section examination the diagnosis of cancer and the adequacy of the resection margins.

The role of sublobar resection in solid lesions is more controversial and should probably be limited to patients with reduced cardiopulmonary reserve until the results of the randomized trials are available. However, when sublobar resection is attempted, the surgeon must ensure the absence of nodal metastases in the mediastinal and major hilar lymph nodes. The presence of metastases should prompt conversion to lobectomy. Particular attention should also be directed to obtaining a satisfactory resection margin that is at least equivalent to the greatest diameter of the tumor and is confirmed to be free of disease on the frozen section examination. Such examinations can be challenging for pathologists, particularly for preinvasive and minimally invasive adenocarcinoma. In the absence of a qualified pathologist, an attempt should be made to obtain a wider margin around the tumor. Most thoracic surgeons emphasize the role of mediastinal nodal dissection or systematic mediastinal nodal sampling in the treatment of clinical stage IA NSCLC that manifests as a solid nodule. The merits of mediastinal nodal dissection in the case of nonsolid nodules are less clear, since nodal metastases are rarely found in such instances.

Regardless of the extent of parenchymal resection and nodal dissection, minimally invasive approaches are strongly encouraged. Multiple studies have shown that video-assisted lobectomy and segmentectomy are oncologically equivalent to open thoracotomy approaches and are associated with significantly lower cardiopulmonary morbidity, less need for blood transfusion, and shorter length of hospital stay.[32-34] In addition, data suggest that in the context of screening, the use of minimal access surgery would be associated with improved cost-effectiveness.[35]

Surgical Qualifications

Nearly all recommendations made by surgical and nonsurgical organizations emphasize that surgeons who participate in LDCT screening programs should be adequately trained in thoracic surgery and either be eligible for or have received the requisite certification by the American Board of Thoracic Surgery or its equivalent international credentialing body.[6,14,36] Participating surgeons should also have expertise in the management of lung cancer and the radiologic interpretation of pulmonary nodules, as well as a good grasp of surgical and nonsurgical diagnostic and therapeutic options. Expertise in minimally invasive thoracic surgery, such as conventional video-assisted or robotic-assisted procedures, is highly desirable given the documented superiority of minimal access surgery in perioperative outcomes and length of stay compared with open thoracotomy procedures. It is also our personal view that the management of screen-detected nodules requires additional expertise not generally provided during the course of conventional training programs. Accordingly, surgeons with an interest in screening are encouraged to attend continuing medical education programs or visit established screening programs to gain some familiarity with issues relevant to the topic.

Quality Metrics

Surgical quality assurance is likely to emerge as an important component of any screening program and may in fact be monitored by CMS and other third party payers, since it will be a major determinant of cost-effectiveness. Quality metrics that require monitoring include the frequency with which surgical biopsies result in a benign diagnosis. While the exact acceptable rate is currently unknown, the frequency of benign diagnosis after surgical resection was 11% in the I-ELCAP program and 12% in the NELSON trial. This is significantly lower than the rate of benign diagnosis reported in clinical case series, which ranges from 25% to 50%. Another metric of surgical quality will be the proportion of patients treated by minimal access techniques. The superiority of these techniques over conventional open approaches has been well documented.

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