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REVIEW ARTICLE

Advances in thoracic surgery: from diagnosing nodules to treating locally advanced lung cancer

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ABSTRACT

The field of thoracic surgery has seen tremendous advances over the last decade with substantial progress over just the last several years. In this review, we discuss changes to lung cancer screening guidelines in the United States, briefly review ongoing trials and current screening programs in Europe and discuss the promising role of artificial intelligence (AI) in lung cancer screening. Additionally, we discuss new diagnostic techniques, including image-guided video-assisted thoracoscopic surgery (iVATS), robotic bronchoscopy, and the use of biomarkers. We review current trends towards thoracic surgery becoming increasingly minimally invasive with the evolution of uniportal VATS (U-VATS) and uniportal robotic surgery (U-RATS). Lastly, we summarize the latest immunotherapy trials, which have revolutionized both neoadjuvant and adjuvant treatment for lung cancer and have demonstrated promising potential to improve the lives of our patients. These advancements have dramatically changed the landscape of thoracic surgery in patients with lung cancer.

Keywords: Artificial intelligence. Early detection of cancer. Image-guided biopsy. Immunotherapy. Lung neoplasms. Minimally invasive surgical procedures.

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INTRODUCTION

Lung cancer is a deadly disease and accounts for approximately 25% of all cancer deaths despite an overall decrease by ~27% in lung-cancer–related deaths in the last two decades[1]. Furthermore, although the median age of diagnosis of lung cancer in the United States is 71 years, lung cancer is not *only* a disease of the elderly. Younger patients, many of whom are often non-smokers and women, are increasingly being diagnosed with lung neoplasia[2,3]. Therefore, continual assessment of lung cancer screening guidelines is necessary to ensure that the population of patients considered to be at high risk and therefore eligible for screening according to the guidelines reflects the contemporary population afflicted with the disease. Expansions to screening guidelines and improvements in screening modalities translate to increased detection of smaller lung nodules, which then mandates improved diagnostic techniques to biopsy these nodules. Advancements in minimally invasive techniques allow for removal of these smaller nodules while preserving as much lung parenchyma as possible. All this combined with the latest immunotherapies and an expanding role for artificial intelligence (AI) has truly changed the thoracic surgery landscape when caring for patients with lung cancer.

9TH EDITION TNM LUNG CANCER STAGING SYSTEM

In September 2023, the 9th edition tumor, node, metastasis (TNM) staging system for lung tumors was introduced at the World Lung Cancer Conference in Singapore. Its primary revisions include reclassification of the N descriptors for lung cancer to add N2a (involvement of a single lymph node station) and N2b (multiple involved lymph node stations) subdivisions and subdivision of the T1 category for thymic tumors into T1a (≤ 5 cm) and T1b (> v5 cm). The 9th edition is expected to be published in early 2024[4].

LUNG CANCER SCREENING

The National Lung Screening Trial (NLST), published in 2011, and the Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) trial, published in 2020, were two landmark trials that forever changed lung cancer screening practices[5,6]. They established the importance of lung cancer screening by demonstrating improved survival in eligible patients who underwent regular screening. They also established that low-dose computed tomography (LDCT), rather than chest x-rays, should be employed as the primary screening modality. The ITALUNG randomized controlled trial, an Italian trial, also identified benefits of LDCT screening on reducing disease-specific and overall mortality[7].

Changes to the screening guidelines

In 2021, the United States Preventive Service Task Force (USPSTF) broadened their lung cancer screening guidelines to recommend that patients 50–80 years of age with at least a 20-pack-year smoking history who are current smokers or who quit smoking within the last 15 years should be screened with LDCT. Their previous guidelines had put forth a minimum age of 55 years and a 30-pack-year smoking history[8]. In November 2023, the American

Cancer Society removed the 15-year "quit rule" from their screening guidelines[9,10]. This decision was based on careful review of several published studies that had challenged this rule. For instance, Meza and colleagues[11] used validated lung cancer natural history models to assess the advantages and disadvantages that would result from employing different thresholds for the "quit rule" (i.e. 5, 10, 20 years versus no quit rule). They found that abandoning the 15-year quit rule would result in fewer deaths overall. To balance the inevitable overdiagnosis that would occur from expanding screening, the authors proposed factoring in life expectancy when deciding who may benefit from screening[11]. The weight of life expectancy when making screening decisions is still an ongoing discussion.

The current guidelines are by no means perfect, especially considering race and ethnicity-based disparities with fewer minority individuals meeting the eligibility criteria[12]. However, the aforementioned changes show that the guidelines are always in flux and can always be improved to reflect the changing population and new, evidence-based findings.

Lung cancer screening in Europe

Although lung cancer screening with LDCT has been established and widely utilized in the United States, formal screening programs are still lacking in many countries in Europe. The International Early Lung Cancer Detection Program (I-ELCAP) in Spain and ITALUNG in Italy are two of the largest programs in Europe[7,13,14]. However, this might change based on the findings of the 4-IN-THE-LUNG-RUN project (4-IN THE LUNG RUN: towards <u>in</u>dividually tailored <u>in</u>vitations, screening <u>in</u>tervals, and <u>in</u>tegrated co-morbidity reducing strategies in lung cancer screening), a multicenter randomized controlled trial at centers in five European countries with 24,000 participants who are at high risk for developing lung cancer. This trial began in 2020 and is expected to be completed at the end of 2024[15].

Role of artificial intelligence in screening

Changes to the screening guidelines to include more individuals who are potentially at risk for developing lung cancer and improvements in LDCT will result in increased detection of lung nodules, but not all the nodules detected will be malignant. With this increased detection, it is becoming imperative for providers to accurately interpret and triage the findings. Deep machine learning and AI might enable this type of precision medicine.

Research studies have demonstrated the potential for AI programs to accurately identify nodules and predict the likelihood that the identified nodules are malignant[16]. For example, a recently developed AI program named Sybil accurately predicted one-year lung cancer risk based on the findings of a single LDCT. Sybil was validated on LDCT data sets from the NLST, from Massachusetts General Hospital, and from Chang Gung Memorial Hospital[17]. (AI also has potential to decrease discrepancies in the interpretation of LDCT scans and in management recommendations for patients with pulmonary nodules by improving inter-reader agreement among radiologists[18].

DIAGNOSTIC TECHNIQUES

Increased and improved detection of pulmonary nodules means that small, often non-palpable, nodules with a "ground-glass" component are being identified more frequently and mandates the need for techniques that allow for accurate diagnosis of this type of nodule. Robotic bronchoscopy (RB) and image-guided video-assisted thoracoscopic surgery (iVATS) are two major technologies that greatly facilitate diagnosis. Peripheral nodules can be diagnosed via RB during endobronchial procedures. RB has better sensitivity (88–97%), navigational success (88–97%), and safety as compared with percutaneous biopsy techniques. The risk of adverse events, such as pneumothorax and major bleeding, is less than 1% with RB[19,20].

iVATS is another revolutionary, minimally invasive technique that permits localization and resection of these small, often non-palpable, pulmonary nodules in a single procedure. iVATS is performed in a hybrid operating room and contrasts with the two-stage procedure that is performed during traditional CT-guided biopsy, where the nodules are marked preoperatively under CT guidance, and then the patient is transferred to the operating room for resection. Indications for iVATS include the presence of screening-detected, subsolid lung nodules < 30 mm in diameter located in the outer third of the lung parenchyma. iVATS has a reported success rate of 97% for resection of nodules that are difficult to palpate[21]. The iVATS technique also improves surgical precision, helping surgeons optimize resection margins during segmentectomy[22]. It can also be used to improve lesion localization during uniportal VATS[23].

Single-anesthesia biopsy and robotic resection (SABRR) is another emerging technique, which is similar to iVATS, that can be used to localize and resect pulmonary nodules during a single anesthetic event. SABRR can reduce the time from identification to intervention in patients with early-stage lung cancer[24].

In addition to improvements in surgical diagnostic techniques, other methods for diagnosis have gained traction in recent years. These include assays to detect biomolecules via liquid biopsy. One key biomarker is circulating tumor DNA (ctDNA), which harbors mutations that reflect the genetic alterations of lung cancers. Easily collected via peripheral blood sampling, ctDNA can be analyzed in a time-dependent manner to assess response to treatment and monitor for recurrence[25,26]. Micro-RNA (miRNA) might also be helpful for fast and minimally invasive detection of early-stage lung cancers[27]. As assays and liquid biopsy techniques continue to advance, future analyses of promising biomarkers might facilitate screening and diagnosis of early-stage lung cancers via blood samples alone.

ADVANCEMENTS IN MINIMALLY INVASIVE THORACIC SURGERY

Transition from multiportal VATS to uniportal VATS

VATS approaches have evolved from being performed mainly for minor procedures, such as pleural biopsy, lung biopsy, and bullectomy, to now being routinely used for anatomic lung resection. One of the landmark trials demonstrating the feasibility and safety of the VATS lobectomy was Cancer and Leukemia Group B

(CALGB) 39802, a prospective, multi-institution feasibility study. One hundred eleven patients underwent minimally invasive surgery for stage T1N0 non-small cell lung cancer (NSCLC). A successful VATS lobectomy was performed in 96 patients (86.5%), the median surgical time was 130 minutes (range, 47 to 428 minutes), and median chest tube duration was three days (range, 1 to 14 days). This study showed that VATS lobectomy is feasible with a low complication rate and short chest tube duration[28]. Other studies have shown the superiority of VATS as compared with open approaches. When compared with open lobectomy, patients who underwent VATS surgery for early-stage lung cancer showed superior physical function five weeks post-surgery, improved general quality of life one year after surgery, less perioperative pain, shorter hospital stays, and fewer readmissions[29,30]. Current practice guidelines recommend minimally invasive surgery, either VATS or robotic surgery, as the standard approach for patients with resectable early-stage lung cancer[31].

Over the years, surgeons from major centers have promoted the evolution of VATS techniques by using fewer ports. In 2006, Onaitis et al.[32] reported the feasibility and safety of VATS lobectomy using only two ports in a cohort of 500 patients who had a lobectomy for lung cancer. They experienced a 1.6% conversion rate to open lobectomy[32], which was consistent with the conversion rate reported in other VATS series with > 2 ports[28,33]. Rocco and colleagues[34] described a single-port, or uniportal, approach for wedge pulmonary resection, either for diagnosis of interstitial lung disease (10 patients) or for treatment of primary spontaneous pneumothorax (five patients). In 2011, the first uniportal (U-VATS) lobectomy was reported, and since then, this technique has gained adepts worldwide[35-37].

In a retrospective analysis of lobectomy performed at a single institution from 2014 to 2017, 722 patients underwent VATS lobectomy for clinical stage I or II NSCLC. Of this cohort, 62% had the surgery performed by multi-port VATS and 38% by U-VATS. The uniportal approach was associated with a shorter duration of chest tube drainage, less intraoperative bleeding, faster surgery, less postoperative pneumonia, and shorter hospital stays[38].

With the development of new technologies, robotic approaches have been increasingly utilized by thoracic surgeons, and uniportal robotic thoracic surgery (U-RATS) is the natural evolution of U-VATS. Gonzalez-Rivas and colleagues[39] have detailed their operative techniques for U-RATS resections, including lobectomy, segmentectomy, sleeve resection, and tracheal and carinal resections, which were refined while performing 150 entirely robotic resections through a single port starting in September 2021. They went on to retrospectively compare U-VATS and U-RATS outcomes using propensity-matched data[40]. The number of resected lymph nodes was higher with U-RATS as compared with U-VATS (17.6 versus 13.7, $p = 0.007$), but the number of nodal stations explored was similar. The complication rate was lower in the U-RATS group (9% versus 28%, $p = 0.004$), but the severity of the postoperative complications was equivalent between the two techniques. This is one of the first studies to show that U-RATS is a safe and feasible approach for performing a minimally invasive lobectomy[40]. Further trials are necessary to confirm these findings.

Role of segmentectomy in NSCLC

In the last few years, the role of sublobar resection in treating patients with early lung cancer has been discussed extensively, especially with the advent of lung cancer screening programs that have resulted in the increased detection of smaller lesions. Lobectomy was established as the standard treatment for early-stage NSCLC in 1995 when the Lung Cancer Study Group published a randomized controlled trial demonstrating a 2.4-fold increase in local recurrence after a segmentectomy as compared with lobectomy[41]. However, over the next 20 years, there has been growing evidence in favor of sublobar resection, particularly for peripheral NSCLC smaller than 2 cm. For example, a retrospective study of 69 propensity-score–matched patients published by Kodama and colleagues[42] in 2016 showed no significant difference in overall survival ($p = 0.442$) or local-regional recurrence-free survival ($p = 0.717$) between segmentectomy and lobectomy. In this study of patients with clinical stage T1aN0M0 NSCLC, the oncologic outcomes of segmentectomy and lobectomy were similar.

The publication of the long-term results of two clinical trials (CALGB 140503 and Japan Clinical Oncology Group [JCOG] 0802), further changed the paradigm regarding sublobar resection. In 2022, Saji and colleagues[43], on behalf of the JCOG, reported the findings of a randomized controlled trial in patients with clinical stage IA NSCLC. In total, 1106 patients were enrolled to receive lobectomy or segmentectomy. Their five-year overall survival was 94.3% in patients who underwent segmentectomy and 91.1% in patients who underwent lobectomy ($p < 0.0001$ for non-inferiority; $p = 0.0082$ for superiority), and five-year relapse-free survival was 88% after segmentectomy and 87.9% after lobectomy ($p = 0.99$). These findings suggested that segmentectomy should be the standard surgical procedure for stage I NSCLC[43]. Altorki and colleagues[44] conducted a multicenter, phase 3 trial in patients with T1a N0 NSCLC with 697 patients randomized to receive either a sublobar (wedge or segmentectomy) or lobar resection. Sublobar resection was non-inferior to lobar resection when assessing disease-free survival, and overall survival was also similar between the two study groups. The applications of segmentectomy continue to be explored, but currently, segmentectomy is accepted as an adequate resection for patients with peripheral, early-stage (stage I) NSCLC that is < 2 cm.

IMMUNOTHERAPY FOR THE TREATMENT OF NSCLC

Treatment options for locally advanced NSCLC have improved significantly in the last two years with the establishment of neoadjuvant chemoimmunotherapy. Prior to the immunotherapy era, adjuvant or neoadjuvant chemotherapy for NSCLC only slightly improved five-year overall survival as compared with patients with resected locally advanced NSCLC without any neoadjuvant or adjuvant chemotherapy. When the NSCLC Meta-analyses Collaborative Group compared surgery plus adjuvant chemotherapy versus surgery alone in 8447 patients from 34 clinical trials, they found a small benefit of adding adjuvant chemotherapy after surgical resection with an absolute increase in survival of 4% at five years[45]. When the collaborative group assessed the effect of preoperative chemotherapy in patients with resectable NSCLC in 15 randomized controlled trials encompassing 2385 patients, they confirmed a small benefit of adding preoperative chemotherapy with an absolute increase in survival of 5% at five years[46]. In contrast, the introduction and growth of immunotherapy has changed the landscape for managing locally advanced NSCLC with improvements in survival of ~20%. The following is a brief overview of some of the recent landmark trials.

IMpower010

In 2021, the results of the IMpower010 trial were published. This was a randomized, multicenter, phase 3 trial comparing adjuvant atezolizumab versus best supportive care after adjuvant chemotherapy for patients with completely resected stage IB (tumors ≥ 4 cm) to IIIA NSCLC. Immunotherapy after adjuvant chemotherapy improved disease-free survival as compared with the best supportive care in this population, especially in patients whose tumors expressed PD-L1 on ≥ 1% of the cells[47]. The risk of recurrence, a new primary NSCLC, or death was reduced by 21-34% depending on tumor PD-1 expression (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50-0.88; $p = 0.0039$ for tumors with PD-L1 on ≥ 1% of the cells; HR, 0.79; 95% CI, 0.64–0.96; $p = 0.020$ for all tumors).

Checkmate 816

The Checkmate 816 trial evaluated the efficacy and safety of neoadjuvant nivolumab plus chemotherapy as compared with chemotherapy alone in patients with resectable stage IB to IIIA NSCLC. The median event-free survival (EFS) in the immunotherapy arm was 31.6 months (95% CI 30.2 – not reached) versus 20.8 months (95% CI 14.0 – 26.7) in the chemotherapy alone arm (HR for disease progression, disease recurrence, or death, 0.63; 97% CI, 0.43 to 0.91; $p = 0.005$). In the intervention arm, 24% of patients had a pathological complete response (pCR) (95% CI, 18.0 to 31.0) as compared with 2.2% in the control arm (chemotherapy alone) (95% CI, 0.6 to 5.6) (odds ratio, 13.94; 99% CI, 3.49 to 55.75; $p < 0.001$). This trial demonstrated that neoadjuvant chemo-immunotherapy had better EFS and pCR than chemotherapy alone[48]. Based on these results, on March 4, 2022, the United States Food and Drug Administration (FDA) approved neoadjuvant nivolumab with chemotherapy for patients with resectable NSCLC.

KEYNOTE-671 AND AEGEAN

Two papers detailing phase 3 clinical trials that investigated the role of perioperative immunotherapy (neoadjuvant + adjuvant) for resectable stage II to IIB (N2 node involvement) NSCLC were published in 2022. The KEYNOTE-671 trial evaluated perioperative pembrolizumab as compared with placebo in 797 patients. The 397 patients in the intervention group received neoadjuvant pembrolizumab plus chemotherapy followed by surgery followed by adjuvant pembrolizumab, while the 400 patients in the control group underwent neoadjuvant chemotherapy plus placebo followed by surgery followed by adjuvant placebo. EFS at 24 months was 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR for progression, recurrence, or death, 0.58; 95% CI, 0.46 to 0.72; $p < 0.001$). The pCR was 18.1% in the intervention group and 4% in the control group (a difference of 14.2 percentage points; 95% CI, 10.1 to 18.7; $p < 0.0001$; threshold, $p = 0.0001$). The relative benefit in the pembrolizumab intervention group increased with increasing PD-L1 expression. In all cases, the HR favored the intervention group[49]. In October 2023, the FDA approved pembrolizumab plus chemotherapy as neoadjuvant treatment with the continuation of single-agent pembrolizumab as post-surgical adjuvant treatment for resectable NSCLC that is ≥ 4 cm or node-positive.

The AEGEAN trial analyzed chemotherapy plus durvalumab before surgery followed by adjuvant durvalumab as compared with a control group (chemotherapy plus placebo before surgery followed by placebo). A total of 802 patients were enrolled (402 in the durvalumab arm and 400 in the placebo arm). At 24 months, EFS was 63.3% in the patients who received durvalumab (95% CI, 56.1 to 69.6) and 52.4% in patients in the placebo group who received only chemotherapy (95% CI, 45.4 to 59.0) (HR for disease progression, recurrence, or death was 0.68; 95% CI, 0.53 to 0.88; $p = 0.004$). The pCR was 17.2% in the durvalumab group and 4.3% in the control group (a difference of 13.0 percentage points; 95% CI, 8.7 to 17.6; $p < 0.001$)[50].

These recent studies focusing on neoadjuvant immunotherapy showed notable improvements in EFS, pCR, and overall survival as compared with chemotherapy alone. Neoadjuvant or perioperative immunotherapy has been proven to be an effective treatment for NSCLC and has a safety profile in these patients that is similar to chemotherapy alone. This data strongly supports the use of immunotherapy in the neoadjuvant and adjuvant settings in patients with locally advanced NSCLC. Further studies will be necessary to understand the optimal timing of adjuvant, neoadjuvant, and perioperative immunotherapy.

CONCLUSIONS

Recent advancements have dramatically changed care for patients with NSCLC. We must be willing to learn, stay up-to-date and adapt our practices. When thoracic surgeons familiarize themselves with rapidly evolving surgical techniques, immunotherapies, and screening and surgical recommendations, our patients ultimately benefit.

DISCLOSURES

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