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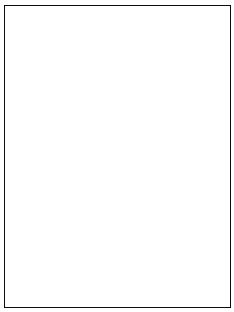

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Abstract

The landscape of care for early stage non-small cell lung cancer continues to evolve. While some of the developments do not seem as dramatic as what has occurred in advanced disease in recent years, there is a continuous improvement in our ability to diagnose disease earlier and more accurately. We have an increased understanding of the diversity of early stage disease and how to better tailor treatments to make them more tolerable without impacting efficacy. The International Association for the Study of Lung Cancer and the Journal of Thoracic Oncology publishes this annual update to help readers keep pace with these important developments. Experts in the care of early stage lung cancer patients have provided focused updates across multiple areas including screening, pathology, staging, surgical techniques and novel technologies, adjuvant therapy, radiotherapy, surveillance, disparities, and quality of life. The source for information includes large academic meetings, the published literature, or novel unpublished data from other international oncology assemblies.

Introduction

This is an exciting time for those who treat thoracic malignancies, with tremendous advances in lung cancer research and treatment over the past year. This annual report is in its third year, and this edition is more focused on specific disease stages. We are pleased to bring together leaders in early stage non-small cell lung cancer (NSCLC) to summarize recent major breakthroughs and significant advances in early detection, molecular diagnostics, pathology, minimally invasive techniques, sublobar resections, nodal evaluation, adjuvant therapy, radiotherapy, disparities in care and post-resection surveillance.

Smoking and Lung Cancer in Asia

Recent cancer statistics note that rates of NSCLCs are declining in males and increasing in females.[1-3] In Korea the male-to-female ratio of lung cancer surgery changed from 2.1:1 in 2010 to 1.6:1 in 2014.[3] Smoking is a major risk factor for lung cancer, but approximately 25% of NSCLCs occur in never-smokers,[4] and the incidence among females in Eastern Asia is increasing despite low smoking rates.[5-8] Air quality is an important issue in Asia with indoor pollution from unventilated coal-fueled stoves, cooking fumes,[9] asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons all recognized carcinogens.[10] Similarly, outdoor air pollution has also been associated with lung cancer development,[11] with > 50% of the lung cancer deaths in China and East Asian countries attributable to ambient fine particles.[12] However, evidence continues to suggest that non-smoking NSCLCs arise from a different carcinogenic process, unrelated to passive exposure and have mutational profiles that differ from tumors associated with tobacco exposure. Lung cancer susceptibility loci have been identified in Asian never-smoking females,[13, 14] which are distinct from those identified in smokers of European-ancestry, suggesting that the genetic susceptibility and etiology of lung cancer could differ between groups of distinct ancestral origin and more importantly by smoking status.[15] Comprehensive tobacco control programs, are helping to decrease the incidence of lung cancer

in smoking men. However, the oncogenic process seems to differ non-smoking females future studies focusing on this population are needed.

Lung Cancer Screening

Low-dose CT (LDCT) lung cancer screening (LCS) continues to evolve, and was an intense area of current discussion and debate in 2017. In contrast to the National Lung Cancer Screening Trial (NLST), the ITALUNG study failed to demonstrate significant reductions in either lung cancer specific- or overall mortality, compared to usual care.[16] Instead of standard criteria, Tammemagi et al. used the PanCan risk model to determine patient eligibility for screening.[17] Results demonstrated the incidence of cancers detected, as well as the proportion of early stage cancers, in the screened population was higher than in the NLST. Final outcome from the NELSON trial and pooled results that will include the UKLS participants are eagerly anticipated in the near future.

The importance of continued screening and follow-up was highlighted in two analyses of NLST data. For patients with positive screens and subsequent cancer diagnosis, 37% were diagnosed more than a year after the baseline screen.[18] After a negative baseline study, the incidence of new nodules was 2-3%, with cancer risk correlating with nodule size.[19] To this end, guidelines for the evaluation and management of new and progressive pulmonary nodules seen on screening exams may be useful,[20, 21] as optimal screening intervals and risk stratification continue to be investigated.[22-24]

Other studies provided valuable contributions to the understanding of risks and benefits of LDCT LCS. In the UK Lung Cancer Screening Pilot Trial, the odds of smoking cessation were higher in screened participants.[25] In addition, examination of the COSMOS study data

demonstrated acceptable radiation exposure in 5203 subjects over a 10-year period.[26] Cost effectiveness studies in Taiwan and Canada also support the use of LDCT LCS.[27, 28]

Despite demonstrated efficacy and availability, widespread implementation of screening continues to lag, and educational opportunities exist for both health care providers and patients. Several authors have identified knowledge gaps for health care providers regarding LCS, and these areas should be viewed as opportunities for future educational efforts.[29-34] With regard to patients, there are gaps in awareness of screening criteria and availability as well.[35] A pragmatic trial is currently underway to investigate the impact of patient navigation on screening adherence, patient-reported barriers, psychosocial concerns and smoking cessation.[36]

A general European position statement on lung cancer screening was published in Lancet Oncology in 2017[37] and for European centers starting a screening program, specific recommendations related to surgical management were recently published by a task force of the European Society of Thoracic Surgeons.[38]

Pathology and diagnostics

The 2015 World Health Organization classification of pulmonary adenocarcinoma,[39] recommends the performance of comprehensive histological assessment (CHA) to estimate the percentage of each histological subtype and to sub classify adenocarcinoma by the predominant histological pattern. The classification has a built-in prognostic grading system that allocates histological patterns into 3 tiers: lepidic pattern (low-grade); acinar and papillary (intermediate grade) and solid and micropapillary (high grade), which has been confirmed by several studies.[40-43] The inclusion of a number of additional histopathological features to further stratify risk of recurrence has been proposed such as secondary patterns,[44, 45] mitotic counts,[46] nuclear grade,[47] and spread through air spaces (STAS). STAS is defined as discrete cells clusters, within air spaces in the surrounding lung beyond the tumor edge. STAS has been shown to be associated with recurrence in limited resection of early stage lung

cancer,[48] and to be associated with high grade histological patterns such as solid and micropapillary.[49, 50] STAS however, is not universally accepted among pathologists, it has been shown that STAS could be an artifact seen in unfixed prosected cases,[51] caused by mechanical manipulation of the specimen. The prognostic effects of STAS warrant further investigation on whether it could be used to help further stratify recurrence risk in early stage lung adenocarcinomas.

The comprehensive histological assessment and its risk stratification have led to applications beyond subclassification of lung tumors. The consensus that lepidic pattern equates to adenocarcinoma in situ led to modifications in the pathological staging of lepidic predominant tumors. In the 8th edition of TNM classification for lung cancer, for subsolid lesions only the invasive histological component (non-lepidic) is to be used for determination of tumor size, thus leading to prognostic refinement.[52]

CHA has also been proposed to help in the separation between second primary pulmonary adenocarcinomas from intrapulmonary metastases.[53] A recent study involving members of the International Association for the Study of Lung Cancer (IASLC) pathology panel found a good reproducibility of CHA among pathologists for this purpose; it is also proposed that CHA alone is not enough in certain cases (similar histology) to separate synchronous/metachronous tumors from intrapulmonary metastasis. Thus suggesting that other parameters, such as molecular characterization of tumor may be necessary.[54, 55]

The College of American Pathologist, IASLC and Association for Molecular Pathology updated their guidelines for molecular testing. New recommendations include ROS1 testing for all adenocarcinoma patients; inclusion of ERBB2, MET, BRAF, KRAS, and RET for laboratories that perform next-generation sequencing; IHC as an alternative to fluorescence in situ hybridization for ALK and ROS1 testing; use of 5% sensitivity assays for EGFR T790M

mutations for secondary resistance to EGFR inhibitors; and use of cell-free DNA to ‘‘rule in’’ targetable mutations when tissue is limited or unobtainable.[56]

Diagnosis and Staging

The 8th Edition Lung Cancer Stage Classification was introduced in Europe and Asia on January 1, 2017 adopted worldwide on January 1, 2018, resulting in both new and reclassified stages of primary lung malignancies. While the most obvious change affecting early stage NSCLC is the subdivision of the T (tumor) component into additional 1 cm increments for T1 and T2 tumors, it is important to note that the N (node) classifications remained unchanged from the 7th TNM staging classification.[57] A needle technique (endobronchial ultrasound needle aspiration (EBUS-NA), endoscopic ultrasound needle aspiration (EUS-NA), or a combined procedure) remains the test of first choice for staging the mediastinum, as endorsed by the American College of Chest Physicians (ACCP), European Society of Thoracic Surgeons (ESTS), European Respiratory Society (ERS), and European Society of Gastrointestinal Endoscopy (ESGE).[58-60]

In 2017, the 2014 ESTS staging guideline, which suggests no preoperative mediastinal staging is necessary in patients with a peripheral tumor of non-adenocarcinoma histology, less than 3 cm in its longest axis, and without evidence of mediastinal metastasis on positron emission tomography (PET)-computed tomography (CT) scan, was corroborated in a retrospective study of 571 patients with NSCLC.[61]

Notably, intercontinental differences in node-stratified survival were observed in the analysis of patients included in the most recent IASLC staging database. Thoroughness of nodal sampling, as defined by number of nodes resected during surgery, was shown in a regional study to be associated with improved N-stratified survival in patients with early stage (pN0 and pN1) disease. In patients with pN1 disease, examination of 3 or more mediastinal nodes demonstrated the greatest improvement in survival. More accurate pN staging may identify

patients with pN2 disease that may benefit from adjuvant chemotherapy. Further quality measures may be included in future iterations of the staging guidelines.[62]

Novel Technologies for Lung Resections

The need to localize non-palpable lung nodules for surgical resection has stimulated a recent explosion in novel surgical technologies aimed toward achieving that goal. Small-nodule localization not only facilitates early-stage resection, it minimizes unnecessary loss of parenchyma for diagnostic resections, and allows for parenchymal-sparing surgery in patients with limited lung reserve. New technologies used for nodule localization broadly fall under one of four categories: 1) intraoperative imaging adjuncts, such as thoracoscopic ultrasound;[63] 2) physical markers, such as hookwires,[64] microcoils,[65] and iVATS fiducials;[66] 3) parenchymal dyes and “tattoos” used in conjunction with near-infrared (NIR) imaging;[67] and 4) molecular targets,[68] and synthetic fluorophores.[69]

Although lack of radiation is an advantage with thoracoscopic ultrasound, results have been moderate due to a steep learning curve, limited tissue penetrability, and variability in image quality.[63] In contrast, image-guided placement of markers such as microcoils, hookwires, and fiducials has met considerable success.[64, 65] One novel surgical technology, termed iVATS, leverages a hybrid OR for CT-guided fiducial placement at the same time and setting as surgical resection.[66] Intraoperative NIR imaging capitalizes on fluorescent properties of unique fluorophores to augment visualization of nodules marked via image-guided “tattoo” at the time of surgery.[67] NIR technology yields additional benefit by enabling lymphatic mapping and sentinel lymph node identification, which can markedly increase the prognostic and therapeutic value of resection for early stage lung cancers. Lastly, molecular targeting is the latest surgical innovation in lung nodule localization.[68] Systemically administered molecular constructs such as epidermal growth factor receptor (EGFR) analogs, folate receptor-targeted fluorophores, and

synthetic antibody conjugates accumulate within tumor cells, yielding high specificity and the unique potential to aid in intraoperative margin assessment.[69]

Although early in development, these novel surgical technologies show promise in the operating room. Further refinement will broaden their utility and will stimulate advancement of safer, more precise, and optimally effective operative techniques.

Minimally Invasive Lung Cancer Resections

The application of minimally invasive approaches for lung cancer resection, both by VATS and robotic techniques, continues to advance. In 2017, this was demonstrated by an increasing volume and breadth of publications describing more complex resections, alternative uniportal, subxiphoid, and microlobectomy approaches**,** and initial glimpses of comparative data.[70-72] Of note, Yang et al. reported a retrospective comparison of 470 patients (172 robotic, 141 VATS, and 157 open) with associated clinical parameters and 5-year survival data.[73] They concluded overall that minimally invasive approaches to lobectomy for clinical stage I NSCLC resulted in similar long-term survival as open thoracotomy. The use of VATS and robotic approaches were both associated with shorter length of stay, and the robotic approach appeared to result in greater lymph node assessment. In an analysis of recent US National Cancer Data Base data, Yang et al. reported an ongoing application of VATS to fewer patients than open lobectomy, despite VATS lobectomy being associated with shorter length of stay and non-inferior long-term survival when compared with open lobectomy.[74]

Given these retrospective data, many have argued that investing in prospective, randomized trials comparing different approaches to lobectomy would be redundant. The field however remains challenged by the lack of such data, with skeptics claiming the retrospective data that does exist is heavily biased by individual minimally invasive champions and industry influence. As evidence that it can be done, a prospective randomized trial by Long, et al. from China randomized 425 eligible patients to either a VATS or axillary thoracotomy for early stage

NSCLC resection.[75] The authors did not note any differences in length of hospitalization, lymph node yields, or rates of morbidity and mortality. Calls for further randomized trials continue to accumulate, however, are hampered by feasibility issues well known in randomizing patients to different procedural approaches. They may be necessary however to remove all doubt regarding the true extent of benefit for a minimally invasive resection.

Sublobar Resections

The elective use of sublobar resection for stage I NSCLC continues to be informed by the increased appreciation of the heterogeneity of stage I NSCLC. Accepted modifications to the lung cancer staging system further delineate T1 and T2 tumors into 1 cm increments, highlighting differential prognosis and treatment decisions for small node negative tumors.[76] In 2017 the Cancer and Leukemia Group B (CALGB) 140503 completed accrual and short-term surgical results are to be reported in 2018. This is the only randomized trial in North America since the Lung Cancer Study Group [77] to compare lobectomy to sublobar resection for stage I tumors.[78] Meanwhile the Japanese have completed a series of trials which stratify tumors by both size and density. JCOG 0201 helped to define ground glass nodules < 2.0 cm and < 0.25 consolidation as noninvasive lesions.[79] JCOG0804/WJOG4507L examined the use of wide resection for tumors with C/T ratio $\leq$0.25, and JCOG0802/WJOG4507L compared lobectomy to segmentectomy for tumors with C/T ratio >0.25, similar in design and inclusion to the CALBG trial. Short term outcomes from JCOG0802/WJOG4507L were reported this year. Mortality in the 1106 randomized patients was 0%. Postoperative complication (grade $\geq$2) occurred in 26% of lobectomy and 27 % of segmentectomy patients. Alveolar fistulas were more common following segmentectomy 6.5% vs. 3.8%.[80] The median change in FEV1 at 1 year was -0.5% and 5-year recurrence free survival was 99.7%.[81]

A National Cancer Database (NCDB) analysis confirmed the importance of basic quality measures in wedge resections for lung cancer. In >7000 wedge resections analyzed 92% had

negative surgical margins, but 46% had no lymph node evaluated, and only 17% had > 5 nodes examined. In propensity matched cohorts increased number of resected lymph nodes and negative margins were associated with improved survival.[82]

Intraoperative Lymph Node Evaluation

The pathologic nodal stage remains the most powerful predictor of prognosis in seemingly early-stage lung cancer, and a major guide to optimal postoperative management.[83] Patients with nodal metastasis (pN1-N3) benefit from additional adjuvant chemotherapy, [84-86] those with mediastinal nodal involvement (pN2,N3) probably benefit from adjuvant radiation therapy.[87, 88] Furthermore, patients with nodal metastasis are among the few groups of patients with incomplete resection who benefit from adjuvant radiation therapy.[89] To make more definite recommendations for completely resected pN2 disease, the results of the European randomized LungART trial are awaited.[90]

There was growing appreciation of the near-universality of the nodal staging quality gap, from preoperative to intraoperative staging.[91-96] Although the use of preoperative staging PET/CT scans has increased significantly (>80%), minimally-invasive nodal staging techniques (EBUS, EUS, TBNA, mediastinoscopy) and mediastinal lymphadenectomy remain heavily underused,[97] with major implications for the accuracy of staging, reflected in differences in pathologic nodal stage distribution, use of adjuvant therapy, and survival.[98, 99]

There was additional evidence for the inherent value of surgical lymphadenectomy, indicated by better survival in subsets of patients meeting more stringent definitions of nodal staging quality.[62] The more detailed was the requirement for nodal staging quality (such as criteria set by the National Comprehensive Cancer Network (NCCN), UICC/AJCC), the better was survival and the more discriminating was the nodal staging system (separating pN0 v pN1 v pN2).[62, 100] Linking the environmental structure of care delivery to outcomes, patients who received care within a structured multidisciplinary care program received more thorough staging, and

higher rates of stage-appropriate treatment (including surgery for early stage disease) than those whose care was provided in 'serial care' settings.[101]

2017 brought evidence that directly linked specific process measures (attainment of the NCCN-recommended quality of resection [anatomic resection, negative margins, examination of N1 lymph nodes and examination of a minimum of 3 mediastinal nodal stations] and the ratio of the observed-to-expected rate of incomplete resection) to survival: two readily-measured surgical quality benchmarks.[102, 103]

Adjuvant and Neoadjuvant Therapies

Treatment with 4 cycles of cisplatin-based chemotherapy following complete surgical resection in patients with stage II-IIIA NSCLC remains the standard of care in the adjuvant setting, offering an approximately 5% overall survival (OS) benefit.[26, 104] Patients with stage I disease and tumors > 4cm likely also derive benefit from adjuvant chemotherapy. [85, 105] Comparing chemotherapy doublets, results from the E1505 trial showed no OS or disease free survival (DFS) difference between cisplatin plus either vinorelbine, gemcitabine, docetaxel, or pemetrexed, as well as no difference in OS or DFS with the addition of bevacizumab, the study's primary aim.[106, 107] The ongoing adjuvant JIPANG trial is directly comparing cisplatin plus vinorelbine to cisplatin plus pemetrexed.[108] Carboplatin is a feasible option in patients unable to tolerate cisplatin.[105, 109]

Adjuvant EGFR inhibitors in patients with an exon 19 deletion or exon 21 (L858R) missense mutation shows promise, though a survival benefit has yet to be demonstrated. In the RADIANT trial of adjuvant erlotinib, the subgroup of patients with EGFR mutations had a non-statistically significant DFS benefit, but no OS benefit.[110] The ADJUVANT trial was the first phase III trial to show a significant DFS benefit using 2 years of adjuvant gefitinib versus 4 cycles of cisplatin plus vinorelbine in resected stage II-IIIA NSCLC. Survival data however remains immature.[111] Several targeted trials are ongoing, the largest being the ALCHEMIST trial, investigating

adjuvant erlotinib, crizotinib, or nivolumab in patients with EGFR mutations, ALK translocations, or neither, respectively.[112]

Multiple ongoing trials are exploring PD-1/PD-L1 checkpoint inhibitors in the adjuvant and neoadjuvant setting with exciting preliminary phase I results from a neoadjuvant trial in 22 patients who received 2 doses of pre-operative nivolumab with a 43% major pathologic response rate.[113]

Lastly, the use of circulating tumor DNA (ctDNA) to better select and identify patients for adjuvant therapy is promising. Two trials have shown that NGS technology can detect ctDNA in NSCLC patients with high specificity and sensitivity, and those with positive post resection ctDNA had higher rates of recurrence that preceded detection with standard imaging.[114, 115]

Advances in SBRT

Stereotactic body radiotherapy (SBRT) is the standard-of-care for early stage, medically inoperable NSCLC patients. The American Society for Therapeutic Radiation Oncology published guidelines for SBRT use in NSCLC.[116] Strong recommendations were made for altered fractionation for central tumors and for surgery over SBRT in standard-risk medically operable patients with early-stage NSCLC. Conditional recommendations were made on SBRT for tumors >5 cm, following a pneumonectomy, T3 tumors invading the chest wall, synchronous multiple primary lung cancer, and as a salvage therapy after prior radiation.

Two prospective trials addressed the widely-held assumption that SBRT provides superior disease control as compared to conventional radiation. SPACE, a randomized phase II trial for medically inoperable stage I NSCLC, reported no difference in OS and PFS despite an imbalance in prognostic factors favoring conventional radiation and noted improved quality of life and decreased toxicity in the SBRT cohort.[117]The randomized phase III CHISEL trial, presented in abstract form, identified superior freedom from local failure (HR 0.29) and overall

survival (HR 0.51) as compared to conventionally fractionated radiation.[118] As SBRT is evaluated in trials among the operable population, long-term (>3 year) follow-up data is crucial. Videtic et al. presented long-term outcomes from RTOG 0915, a randomized comparison of two SBRT fractionation schemas for early stage, peripheral NSCLC, with a median follow-up of 5.1 years for living patients. They identified median overall survival of 4.1 and 4.0 years for the two arms, and progression-free survival of 19.1 and 31.8%. In-field control remained in excess of 90% at 5 years.[119]

Several novel prognostic markers have shown early promise as adjuncts in predicting clinical outcomes for patients treated with lung SBRT. Zheng et al. presented data evaluating post-treatment immune parameters from peripheral blood as predictors of post-SBRT failure, and found that elevated post-treatment cytotoxic CD8+ T cell level at 4 weeks was an independent prognostic factor for recurrence.[120] As the patient numbers were small, further validation will be required. Several preliminary studies have evaluated higher order CT and PET/CT texture characteristics, or radiomic signatures, to predict outcomes.[121, 122] Although preliminary, these studies suggest that integration of radiomic signatures with clinical characteristics may improve patient risk stratification.

Although SBRT, particularly for peripheral tumors, is typically well-tolerated, increased risks have been identified for tumors adjacent to the structures of the central chest. Cardiac toxicity is a frequent focus, following publication of RTOG 0617 which identified a marked survival decrement with increasing cardiac dose for locally advanced disease.[123] Several studies found correlations between maximum dose to specific sub-structures and survival, including the bilateral ventricles,[124] the left atrium, and the superior vena cava.[125] Further studies that build on these findings are needed to clearly define cardiac dose guidelines for lung SBRT.

Access to Care

Access to specialty care remains an obstacle for lung cancer patients, particularly for minority groups, women, and the uninsured.[126] These subgroups are particularly prone to delays in the diagnosis and/or treatment of lung cancer, including access to and the utilization of lung cancer screening across the United States.[127] It has been 6 years since the 2011 NLST reported a cancer-specific survival benefit for the use of LDCT in select high-risk patients[128] Although these recommendations have been endorsed by the U.S. Preventive Service Task Force and the Center for Medicare and Medicaid, physician compliance with guideline concordant recommendations remains low.[129] Lack of familiarity with guidelines,[130] and challenges associated with implementation of a systematic screening program are thought to be the main culprits.[131] In a survey from a large academic institution with a large smoking population, <55% of physicians had full knowledge of existing screening guidelines, and < 45% believed CT screening was effective to reduce lung cancer mortality.[130] These findings are not isolated to a particular geographic region and are present even in the most comprehensive healthcare systems. Improving access to recommended screening for these vulnerable subgroups may facilitate closure of this disparity gap and improve survival for early-stage lung cancer patients.[132]

Disparity issues persists past diagnosis, the receipt of surgery for early stage NSCLC continues to differ by race in the US, with 47% non-Hispanic blacks not receiving surgery compared to only 38% of whites in a recent SEER analysis.[132] Unfortunately survival following curative surgery also differed between blacks and whites,(HR 1.05), with the majority of the difference attributed competing cause of death such as cardiovascular and other cancers. The racial disparity did not extend to Hispanics and Asians, who received surgery at similar rates to whites and experience and higher overall survival.[132]

Surveillance and Quality of Life

Post-treatment surveillance is imperative to sustain survival benefits associated with early detection by CT screening. Most major medical societies involved with lung cancer care have surveillance guidelines. These vary significantly although most support frequent imaging in the first two years, corresponding to peak incidence for recurrence, and favor chest CT over CXR.[133-135] The NCCN guidelines are the most widely referenced and were updated in 2017, moving from “one-size-fits-all” to a tailored strategy that varies according to stage and treatment.[136] The panel recommends more frequent surveillance (CT every 3-6 months) for patients with Stage III or IV disease or treated with radiotherapy versus every 6 months for Stage I or II disease or those treated with chemotherapy.

The highly anticipated Intergroupe Francophone de Cancerologie Thoracique (IFCT 0302) trial was presented at ESMO 2017.[137] This was the first large-scale prospective randomized trial of imaging surveillance. 1775 patients were randomized to CXR vs CT scan every 6 months for 2 years then annually for a median 8.7 years follow-up. The study included Stage I-IIIA patients, including those receiving adjuvant and neoadjuvant therapies. The authors reported a trend towards earlier diagnosis of recurrence and second primary lung cancers (SPLC) with CT, but no significant survival benefit. They concluded that CT surveillance offered no benefit within the first two years for Stage III patients and postulated that these patients have a tendency for early recurrence with poor outcomes independent of time of detection, this lies in conflict with new NCCN guidelines supporting more frequent surveillance for Stage III disease. The authors recommend annual CT surveillance for all stages of disease. Limitations of the IFCT include heterogeneity of the cohort and the extended length of follow up required to reach its clinical endpoint. Clinicians acknowledge the lack of high-level evidence regarding surveillance, but most believe routine follow-up testing results in diagnosis of recurrence (70%) or SPLC (84%) early enough to institute potentially curative treatment.[138]

Future Directions

The era of personalized medicine will continue to impact NSCLC care for both early and advanced disease. Increased understanding of the genetic diversity of early stage disease will allow us to more appropriately tailor treatment and follow up to the individual patient and tumor. There is promise for biologic markers to help better identify appropriate individuals for CT screening, to differentiate benign nodules from early cancers, and recognize indolent from aggressive malignancies. Simultaneously all of our interventions are becoming less invasive and more tolerable; improving short term outcomes, quality of life and integration with other therapies.

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