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Early Stage Non-Small Cell Lung Cancer: Advances in Thoracic Oncology 2018

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Abstract

2018 was a banner year for all thoracic oncology, but especially for early-stage non-small cell lung cancer (NSCLC). Three seminal events occurred in the approximately 18 months from mid-2017 to the end of 2018: in June 2017 at the American Society of Clinical Oncology Annual Meeting a small, relatively unheralded study from Max Diehn's group at Stanford University reported on the use of a novel 'cancer personalized profiling by deep sequencing' circulating tumor-DNA technology to identify minimal residual disease in patients after curative-intent radiation or surgery for NSCLC; in April 2018 at the American Association for Cancer Research Annual Meeting, Drew Pardoll presented a small pilot study of 21 patients who had received 2 doses of preoperative Nivolumab; in September 2018, at the 19th World Conference on Lung Cancer, Harry J. De Koning presented the long-awaited results of the Dutch-Belgian Lung Cancer Screening Trial (NELSON). These three seminal studies, along with others which are reviewed in this paper, promise to accelerate our progress towards a world in which lung cancer is identified early, more

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patients undergo curative-intent treatment that achieves the promised cure, and those at risk for failure after treatment are identified early, when the cancer remains most vulnerable. The day is round the corner when lung cancer is de-fanged and no longer the worldwide terror it currently is. We herein present an overview of the most recent body of work that moves us inexorably towards that day.

Introduction.

Although lung cancer remains the oncologic public health challenge of our age, with a worldwide estimate of 2.1 million new diagnoses and 1.8 million deaths annually,[1] exciting developments over the past year promise to transform the stage distribution more towards the curative treatment end, increase the effectiveness of curative treatment options, while minimizing the morbidity of treatment and improving the patient experience. In 2018, at the 19th World Conference on Lung Cancer, the exciting results of the Dutch-Belgian lung cancer screening trial, NELSON, were presented.[2] This long-awaited trial corroborated the findings of the United States (US) National Lung Screening Trial and will stimulate widespread engagement of the opportunity represented by the challenge of implementing national lung cancer screening programs.[3]

The 2018 Nobel Prize for medicine or physiology was awarded to James P. Allison and Tasuku Honjo for their seminal work leading to the development of immunotherapy.[4] How fitting then that one of the most exciting developments in lung cancer in 2018 was emerging evidence of the powerful role adjuvant and neoadjuvant immunotherapy can play in increasing the success of curative-intent surgery and radiation therapy.[5,6] If two doses of Nivolumab administered preoperatively can induce major pathologic response in 9 of 20 non-small-cell lung cancer (NSCLC) patients, we have much to be excited about (Fig 1)! Advances in pre-surgical care, surgical techniques and immediate postoperative care are decreasing treatment-related morbidity, thereby expanding the role of surgery where once deemed unsafe. Concurrently, the role of curative-intent nonsurgical options such as stereotactic body radiation therapy (SBRT), continues to be defined.

Although surgery provides the pathway to cure for most long-term survivors, ongoing efforts to increase the quality of surgical resection, improve pathologic nodal staging and, importantly, improve our ability to accurately predict failure of curative-intent treatment, early, when the opportunity for salvage is most likely, continue apace. The potential for circulating tumor DNA (ct-DNA) analysis to predict disease recurrence or progression shortly after curative-intent treatment is an exciting new possibility.[7]

These developments, and more, are covered in this update by an international team of clinician scientists, experts who are also the drivers of some of these advances. Our objective was to highlight and contextualize the main emerging developments in early-stage NSCLC over the 18 months from mid-2017 to the end of 2018. We have culled information from recent publications, as well as abstracts presented at major academic meetings such as the World Conference on Lung Cancer, the American Association for Cancer Research, American Society of Clinical Oncology, and European Society of Medical Oncology Annual Meetings.

Lung cancer screening and prevention.

Recent developments in lung cancer prevention promise to be game-changers. Large epidemiological studies indicate that high serum interleukin-6 and C-reactive protein are associated with increased lung cancer risk.[8] In a recent large double-blind randomized trial, the treatment groups received the monoclonal antibody Canakinumab to reduce interleukin-1beta activity. In the group receiving 300 mg, incidence (HR 0.33, 95%CI 0.18–0.59) and mortality (HR 0.23, 95%CI 0.10–0.54) were significantly reduced (p=0.0002),[9,10] suggesting that Canakinumab should be further investigated, most obviously in targeted prevention trials nested within screening programs.

In Europe, the scientific community has only recently pronounced in favor of mass screening for lung cancer,[11] notwithstanding the 20% mortality reduction demonstrated by the National Lung Screening Trial.[3] The change coincides with 10-year mortality results for the NELSON trial, Europe's largest: the low-dose CT (LDCT)-screened arm had a 26% (95%CI 9–41%) reduction in mortality in men and a 39–61% reduction in women.[2] Europe is now poised to introduce screening. However high-risk populations need to be better defined. The INTEGRAL consortium recently showed that circulating proteins can improve lung cancer risk assessment and may be useful for defining screening eligibility.[12] A combined blood test assessing the levels of circulating proteins and mutations in cell-free DNA was shown to detect eight common cancer types, including lung cancer, with good sensitivity and very high specificity.[13]

Furthermore, since the population eligible for screening is large, screening has enormous potential for the primary prevention of cardiovascular events (CVEs). A recent systematic review concluded that LDCT-evaluated coronary artery calcification score has the potential to predict CVEs, reduce cardiovascular morbidity and mortality, and hence increase the cost-effectiveness of screening.[14] European cost-effectiveness analyses revealed LDCT screening was associated with very favorable Incremental Cost-Effectiveness Ratio (the yearly incremental costs of saving a patient's life), likely acceptable to the relevant health authorities: £6325 in the United Kingdom;[15] €2943 in Italy.[16] Thus screening can be implemented at relatively low cost.

Advances in diagnostics, clinical staging, clinical prognostic markers.

Besides the exciting results of the NELSON trial which should stimulate development of a screening strategy in most countries,[2] the widespread use of chest CT scans in the workup of different diseases means a growing number of solitary pulmonary nodules are being found.[17,18] At present no reliable biomarker or imaging technique is available to determine whether a lesion is, or will become, malignant in an individual patient within a clinically meaningful time-frame. The implementation of volume doubling time or radiomics to determine whether a lesion is malignant remains unvalidated, pathological diagnosis based on tissue biopsy is still the gold standard in patients with undetermined nodules. The choice between radiologic surveillance for high-risk imaging features and invasive diagnostic procedures for histological or cytological confirmation of the nature of a lesion remains difficult for patients and their clinicians. The complication rates of invasive procedures and

the potential inaccuracies of imaging techniques necessitate thorough discussion with the patient.

With the increasing prevalence of small malignant lesions and growing awareness of the prognostic implications of tumor size, size was more deeply incorporated in the 8th edition TNM staging system, which was implemented in Asia and Europe in 2017 and in the US in 2018. T1 was split into 3 subgroups: (T1a< =1cm, T1b>1cm to≤2cm, T1c>2cm to≤3cm); T2 into 2 subgroups (T2a>3cm to ≤4cm, T2b>4cm to ≤5cm); tumors >5 to ≤7 cm are now designated as T3; and those ˃7 cm as T4.[19] Although size, distinct from lymph node metastasis, is appreciated as a risk factor for NSCLC recurrence, more exact biomarkers for predicting recurrence are needed.

Two potential such biomarkers are ct-DNA[7] and the Tumor Mutation Burden (TMB).[20] In a study of 40 patients with stage I-III lung cancer who had curative-intent surgery or radiation therapy, a ‘cancer personalized profiling by deep sequencing (CAPP-seq)’ ct-DNA analysis of the first post-treatment blood sample identified 94% of patients whose disease recurred, preceding radiographic progression in 72%, by a median of 5.2 months (Fig 2).[7] We may now have the technology to reliably identify minimal residual disease in lung cancer. Re-analysis of specimens from the Lung Adjuvant Cisplatin Evaluation-Bio-II study suggested that high non-synonymous TMB (>8 mutations/megabase) was favorably prognostic and adjuvant chemotherapy mostly benefited patients with low TMB (≤4 mutations/megabase).[20] If corroborated, these biomarkers will guide clinicians in the choice of adjuvant treatment.

Recent results of immunotherapy in advanced and early-stage NSCLC have reinvigorated the question whether the intra-tumoral immune infiltrate has prognostic or predictive value to establish indications for (neo)adjuvant treatment, and which treatment may be best. Early evidence suggests the prognostic and potential predictive capabilities of immune gene signatures in early-stage NSCLC but further prospective validation is necessary before use in clinical practice.[21] After neoadjuvant treatment with the Program Death (PD)-1 checkpoint inhibitor Nivolumab, the number of major pathological responses was related to the TMB.[5] With only 9 relevant patients in this study, firm conclusions must await future validation.[5] In addition, technical requirements to perform the kinds of genomic tests, whole-exome sequencing and neo-antigen prediction assays, used in this study must be simplified for wide use in clinical practice. Although most focus is currently on the pretreatment composition of the tumor tissue, the effect of treatment on the tumor must be taken into account. For instance, it was recently shown that SBRT in early-stage NSCLC induces a beneficial immune activation which may also be predictive of the effect of a PD-(ligand [L])1 checkpoint inhibitor.[22]

Surgery for early-stage NSCLC.

Except for ‘medically-inoperable’ patients, the prevailing belief is that surgical resection offers the best chance of cure for early-stage NSCLC,[23] but oncologically sound resection is imperative for optimal prognosis. Maximal reduction of the risk and trauma of surgery is also important, which is the potential advantage of minimally-invasive surgical techniques. The rising proportion of surgical resection candidates with smaller ground-glass nodules

(GGNs) raises a dilemma: malignant GGNs have a more indolent nature than solid nodules.[24]

In a prospective multicenter trial including 795 patients with 1238 GGNs, only 1.2% pure GGNs developed into heterogeneous GGNs (with the solid component appreciated only on lung windows) and 5.4% into part-solid nodules in a mean time of 3.8 years. Among 81 heterogeneous GGNs, 20% developed into part-solid nodules after a mean of 2.1 years. All resected pure GGNs and heterogeneous GGNs were pre-invasive lesions. Even among the 49 part-solid nodules resected, only 12 turned out to be invasive adenocarcinomas.[25] These results reinforce the 2017 Fleischner Society Guideline recommendations for extended follow-up.[26] It was recently suggested that automated interpretation of the radiological characteristics by deep learning techniques might improve diagnostic accuracy in GGNs.[27] Currently, a conservative approach remains the best strategy for such patients, to avoid over-hasty surgery upon initial detection and in the absence of significant change on CT surveillance.

Increased detection of smaller and ground-glass containing early-stage lung cancers has led to revival of sublobar resections that were once reserved for functionally compromised patients. Limited resection, especially anatomical segmentectomy, may carry similar oncological outcomes as standard lobectomy. However, even if this non-inferiority in oncological outcomes is proven by the two ongoing trials (JCOG 0802 and CALGB 140503), the benefit of segmentectomy may still be relative. Unlike wedge resection, segmentectomy is technically more demanding than lobectomy, and it may be necessary to first demonstrate its superiority in peri-operative outcomes and/or pulmonary function preservation.

Initial results of JCOG0802 showed that segmentectomy was associated with increased blood-loss and air-leak.[28] A post-hoc analysis of CALGB 140503 revealed no difference in either perioperative morbidity or mortality between lobectomy and sublobectomy in good-risk patients, even though 59% of the sublobectomies were actually wedge resection.[29] As to function preservation, in good-risk patients pulmonary function loss after video-assisted thoracoscopic surgery (VATS) segmentectomy was indeed significantly less than after VATS lobectomy.[30] But average loss per-segment resected was almost doubled after segmentectomy, probably due to distortion of the remaining lobe after dividing the intersegmental plane.[30] All these should be taken into account when selecting appropriate procedures for individual patients.

Lymph node dissection is an integral part of lung cancer surgery. The purpose of systematic lymphadenectomy is to assure accurate staging and complete disease removal. A recent metaanalysis found improved survival but also higher morbidity after lymphadenectomy than after sampling.[31] This seems to contradict ACOSOG Z0030, which found only 4% nodal upstaging after dissection than after systemic sampling and no difference in post-operative complications, survival or recurrence rates in patients with clinical T1–2, N0 and non-hilar N1 tumors.[32] But it is important to recall that patients were randomized after invasive mediastinal staging. Thus the ACOSOG Z0030 results may not be generalizable to patients staged radiographically or those with higher-stage tumors.

Z0030 notwithstanding, the importance of high quality intraoperative nodal staging in early-stage NSCLC continues to receive significant attention. Dissection of less than 15 nodes was associated with risk of under-staging, less than 6 nodes with worse survival.[33] Thus, either rigorous preoperative mediastinal staging or systematic intraoperative dissection or sampling are still recommended. A recent multi-institutional prospective study showed that the introduction and compliance with basic quality measures for lymph node evaluation by surgeons and pathologists (examination of at least 1 N1 lymph node, at least 10 total lymph nodes, and at least 3 mediastinal nodal stations) significantly increased lymph node yield,[34] improved survival, and better stratified post-operative stage-specific survival curves.[35] The authors also implicated variations in the quality of intraoperative nodal staging for the intercontinental differences in post-operative survival.[35]

With the increasing use of sub-lobar resection for small GGNs, which seem to have a low risk of nodal involvement, the extent of required nodal evaluation is an emerging controversy. Noticeably no lymph nodes were examined in 49% and 23% of wedge and segmental resections for stage I tumors ≤ 2cm, and the number of nodes examined was revealed as an independent risk factor for survival while the extent of resection was not.[36] However for GGNs, mediastinal dissection may not have significant impact on either staging or survival.[37] In a propensity-matched study comparing mediastinal or hilar-only dissection for stage I NSCLC appearing as mixed GGN, mediastinal nodal involvement was found in only 9 of 329 patients (2.7%) with solid-dominant lesions but in none with part-solid lesions. The extent of nodal dissection was neither a risk-factor for survival nor predictive of nodal involvement.[37]

Minimally-invasive approaches.

Thoracic surgery is becoming less invasive while procedures are becoming more sophisticated.[38,39] A 2018 study used spontaneous-ventilation VATS to perform tracheal and carinal resections in 18 awake patients, achieving anastomosis in 22–40 minutes, mean duration of surgery of 162 minutes, and low postoperative morbidity and mortality.[39] A recent multi-national study showed that robotic surgery could be safely extended to selected stage III NSCLC cases with acceptable complication and conversion rates, satisfactory long-term survival, and low local recurrence rates.[40] Similarly, a multi-institutional retrospective review of 1339 robotic lobectomies showed encouraging results particularly for N2 disease.[41]

Despite the success of robotic thoracic surgery, costs remain higher than for VATS,[42,43] except in the study of Musgrove et al. where robotic and VATS segmentectomy had similar costs, with a trend to shorter length of stay and fewer complications in VATS cases.[44] In over 1600 propensity-matched cases, conversions and postoperative complications were fewer in robotic than VATS cases after excluding learning-curve robotic cases.[45] Conversion from minimally-invasive to open surgery may not raise postoperative morbidity or mortality risk.[46] On the other hand, as robotic thoracic surgery is increasingly adopted, awareness of the risks inherent in this complex new technology has grown, and a group of European thoracic surgeons recently proposed a standardized training curriculum for young doctors.[47] Although robotic and other innovative surgical approaches such as uniportal or subxyphoid

VATS are receiving more attention, their additional functional benefit is questionable, as traditional VATS incisions cause loss of only 5% of pulmonary function.[30] Although these procedures are shown to be safe and feasible, their cost-effectiveness remains to be demonstrated. Well-designed studies are needed to better assess their advantages.

Enhancing surgical outcomes.

Novel protocols aimed at increasing the efficacy and tolerability of lung cancer resections now expand beyond minimally-invasive incisions, extending throughout the peri-operative setting. Pre-operative assessment is focusing on frailty measures, which is a more significant marker of operative risk than age. Multiple investigators have demonstrated the ability to preoperatively identify frail thoracic surgery patients.[48,49] A recent analysis used a combination of grip strength, gait, weight loss, and self-reported exhaustion and activity to identify 12% of thoracic surgery patients as frail and 57% as prefrail.[48] Ongoing trials are evaluating the ability of “prehabilitiation” to mitigate increased rates of operative morbidity in frail patients.

Pulmonary rehabilitation is a cornerstone of chronic obstructive pulmonary disease management, but not routinely used in preparation for NSCLC resections, due to the urgency between diagnosis and resection. Traditional endurance therapy (ET) requires daily sessions over 6–12 weeks, but recent evidence suggests that high-intensity interval training (HIIT) over 2–4 weeks provides meaningful rehabilitation for high-risk frail surgical patients. HIIT increases respiratory muscle strength and aerobic capacity similar to ET,[50] and significantly improves $V02_{max}$, dyspnea and fatigue compared to baseline.[51] Prospective studies of HIIT in NSCLC patients demonstrate measurable improvements in pulmonary function within the interval needed for cancer resections. Patients with poor pulmonary function had better short-term surgical outcomes after undergoing pre-operative HIIT.[52] Standard-risk patients did not see similar reductions in peri-operative morbidity following HIIT in one study,[53] but HIIT helped to prevent decline after surgery in all patients in another study.[54]

Similarly, Enhanced Recovery After Surgery (ERAS) protocols, are revolutionizing perioperative thoracic surgery care. The European Society of Thoracic Surgeons published ERAS guidelines that include 45 evidence-based care recommendations throughout the peri-operative experience emphasizing minimally-invasive surgery, decreased fasting, opioid-sparing analgesia, early mobilization, and increased patient education.[55] The thoracic surgeons from MD Anderson Cancer Center are leaders in ERAS use in the US, and reported decreased length of stay and cardiopulmonary complications,[56] and an increased compliance with adjuvant chemotherapy with implementation of their ERAS program.[57]

New adjuvant therapies and neo-adjuvant immunotherapy in early-stage NSCLC.

Disease recurrence remains the bane of curative-intent surgical resection.[58] Therefore, novel treatments are needed beyond the current standard adjuvant (or neoadjuvant) cytotoxic chemotherapies. In the advanced-disease setting, molecular targeted therapy with tyrosine kinase inhibitors (TKIs) and immunotherapy with immune-checkpoint inhibitors have shown

superior efficacy and lower toxicity compared to cytotoxic chemotherapy.[59] This experience has stimulated many clinical trials using TKIs or immune checkpoint inhibitors in the neoadjuvant and adjuvant settings. Most of the phase III trials were still ongoing in 2018, but some have presented preliminary data.

Advances in adjuvant therapies in surgically resected NSCLC.

Experience with treatment of stage IV NSCLC informs adjuvant therapy trials. Epidermal growth factor receptor (EGFR)-TKIs (Gefitinib, Erlotinib, Afatinib, Dacomitinib, and Osimertinib) are the most potent drugs against NSCLC with activating mutations of *EGFR*. Failure of 2 years of Erlotinib therapy to produce a survival benefit over placebo in the international randomized trial, RADIANT, did not cool interest in exploring the role of adjuvant EGFR-TKI therapy because in the 16.5% of patients with known activating mutations of EGFR, disease-free survival (DFS) was 46.4 v 28.5 months (HR 0.81 (0.38 – 0.98; p= 0.039, impressive, but not significant in the hierarchical testing procedure used in this trial).[60] In a single-arm phase II trial (SELECT), two years of Erlotinib after standard adjuvant chemotherapy showed an improved 2-year DFS compared with historic genotype-matched controls.[61] A randomized study, ADJUVANT, compared Gefitinib (24 months) versus Vinorelbine/Cisplatin in patients with pathologic Stage II - IIIA (N1–N2) EGFR-mutated NSCLC.[62] DFS, the primary endpoint of this study, was significantly longer with Gefitinib than with Vinorelbine/Cisplatin (HR 0.60, 95% CI 0.42–0.87; p=0.0054). In the safety population, the Gefitinib group had reduced toxicity and improved quality of life. However, overall survival (OS) data of ADJUVANT, together with results of other ongoing studies, including IMPACT/WJOG6410L (Gefitinib), ALCHEMIST (Erlotinib or Crizotinib based on driver mutation), ADAURA (Osimertinib), and ALINA/BO40336 (Alectinib), are essential before adjuvant TKIs (EGFR-TKIs or TKIs targeting other drivers) can become standard of care. Given the superior outcomes with Osimertinib over Gefitinib and Erlotinib therapy in patients with untreated EGFR-mutated advanced NSCLC (DFS 18.9 months v 10.2 months; HR for death, 0.63 [0.45 – 0.88], p=0.007),[63] results of ADAURA are eagerly anticipated.

Patients re-challenged with Erlotinib after recurrence in SELECT experienced durable response.[61] Recurrence patterns after adjuvant EGFR-TKIs may be spatially and temporally unique: Central Nervous System metastasis was frequent as the first site of recurrence in the Gefitinib group and the highest peaks were delayed in that group (e.g. the first peak of extracranial metastases appeared during 9 – 15 months and 24 – 30 months after surgery in the Vinorelbine/Cisplatin and Gefitinib groups, respectively).[64] Clinical trials are also evaluating the roles of PD-1 / PD-L1 immune checkpoint inhibitors in the adjuvant setting. Within these trials, patients receive immune checkpoint inhibitors, usually for up to 1 year, after or without adjuvant chemotherapy, such as in EA5142- Adjuvant Nivolumab in Resected Lung Cancer (ANVIL).

Use of TKIs and immune checkpoint inhibitors as neoadjuvant therapy.

Neoadjuvant chemotherapy is considered equivalent in survival impact to adjuvant chemotherapy.[65] Effective neoadjuvant therapy may also reduce the risk of incomplete resection or enable avoidance of pneumonectomy. In a randomized study for clinical stage

IIIA (N2) EGFR-mutated NSCLC, Erlotinib administered for 42 days neoadjuvantly and 12 months adjuvantly, was associated with significantly longer PFS and lower grade 3/4 toxicity compared with Gemcitabine/Cisplatin.[66] Early reports on neoadjuvant immune checkpoint inhibitor monotherapy (Nivolumab, Atezolizumab, or Pembrolizumab) or combination therapy (Atezolizumab plus chemotherapy) suggest relatively high efficacy (major pathologic responses 21 – 45 % in monotherapy and 50% in combination), acceptable toxicity, without enhanced surgical complications.[4,67–69]

Considering the regression bed (the area of immune-mediated tumor clearance), "Immune-Related Pathologic Response Criteria" were proposed by one of these study groups.[70] Currently, several randomized trials evaluating the roles of neoadjuvant immune checkpoint inhibitors are underway and expectations for these trials are high based on the idea that earlier administration may provide better outcomes. From a translational research aspect, neoadjuvant treatment is also important because it will provide a great opportunity to explore molecular mechanisms of inherent resistance or drug tolerant states.[71]

Non-surgical treatment.

SBRT has become standard-of-care in patients with medically inoperable early-stage NSCLC. The phase III CHISEL trial compared SBRT with conventional radiotherapy for inoperable stage I NSCLC, showing better OS and freedom from local failure in the SBRT arm,[72] with no differences in quality-of-life measures,[73] further supporting SBRT. There are no well-powered prospective studies comparing SBRT with surgery in early-stage NSCLC. A pooled, albeit severely under-powered, analysis of two randomized phase III trials, STARS and ROSEL (both prematurely closed due to slow accrual), comparing SBRT with surgery in patients with operable stage I NSCLC, showed better 3-year OS for SBRT (95%) versus surgery (79%, p=0.037), with fewer grade 3–4 adverse events with SBRT.[74] This analysis should provide equipoise for clinicians to support much-needed randomized trials in this setting.

Retrospective comparisons of SBRT versus surgery should be interpreted with great care, because of the risk of unmeasured confounding factors, including co-morbidities, that may influence the results. Nevertheless, a retrospective study demonstrated improved cancer-specific survival with lobectomy compared to SBRT in stage I NSCLC (HR 1.45), although no difference between sub-lobar resection and SBRT (HR 1.25).[75] In a meta-analysis, OS was better after surgery compared to SBRT in stage I NSCLC, however, lung cancer–specific survival was similar, indicating comparable treatment efficacy.[76]

Further investigation of the effectiveness of SBRT in operable patients includes updated 4-year results from RTOG 0618 with SBRT (54Gy/3 fractions) showing a high rate of primary tumor and local control (both 96%), and DFS and OS of 57% and 56%, respectively.[77] Another retrospective study found no significant differences between operable and inoperable patients in 5-year local control (93.1% vs. 96.7%), cancer-specific survival (80.6% vs. 91.0%), but a trend for worse OS (34.2% vs. 45.3%; P = .068), most likely due to more co-morbidities.[78] The true pathologic complete response (pCR) rate after SBRT is unknown. The phase II trial MISSILE-NSCLC with SBRT in the neoadjuvant setting found

the pCR rate after SBRT to be 60%, although this may be an underestimation because surgery was performed at 10 weeks and pCR to SBRT may take longer time.[79]

With the recent advances in treatment with immune checkpoint inhibitors, the combination of SBRT and immunotherapy is the focus of several ongoing clinical trials. One study of 3 single-institutional phase I/II trials concluded that combined treatment is safe in the short term, with no patients having grade ≥4 events and 9 pulmonary-specific grade 3 events (4 patients), encouraging further combination studies.[80]

Imaging after SBRT for early-stage NSCLC can detect recurrences, but may also be difficult to interpret. Recommendations for surveillance after SBRT were established by an international expert group, which identified a number of high-risk features for local recurrence: infiltration into adjacent structures; bulging margins; sustained, mass-like, spherical, or cranio-caudal growth; and loss of air bronchograms.[81,82]

SBRT of ultra-central tumors (in which the planning target volume touches or overlaps the central bronchial tree, esophagus, or pulmonary artery) may pose a higher risk of serious toxicity. Tekatli and colleagues found significant predictors for ≥grade 3 toxicity to be a planning target volume overlapping the trachea or main stem bronchus (P = .005), chronic obstructive pulmonary disease (P = .034), and the total volume receiving an ‘equivalent dose of a 2 Gy per fraction treatment of 130 Gy’ (P = .012).[83] Additional studies are needed to better understand toxicity for ultra-central tumors.

Alternative non-surgical treatment methods besides SBRT include radiofrequency ablation (RFA). Previous studies have demonstrated poorer local tumor control rates and a higher risk of adverse events, including pneumothorax, with RFA compared to SBRT.[84] Recently, two studies of RFA, one a retrospective analysis,[85] the other a single arm prospective phase II trial,[86] reported OS rates comparable to SBRT, but with considerable risk of pneumothorax in the prospective study.[86] These results should be interpreted with care because of the retrospective or indirect comparisons. Validation of this invasive approach to the care of medically inoperable patients needs prospective comparative-effectiveness studies.

Future developments.

The exciting developments reviewed in the preceding sections illustrate dynamic progress in management of early-stage NSCLC, where lung cancer is a survivorship story. Accelerating that progress mandates timely completion of the many rigorous studies already ongoing or in development. Ultimately, progress must be measured by our ability to deploy the emerging array of diagnostic, staging, treatment and surveillance options within the clinical arena, where lives are saved or lost. Immunotherapy will expand the candidate pool of patients for curative-intent treatment, while transforming long-term outcomes of recipients of such treatments, whether surgery, radiation therapy or other emerging alternatives.[5,6,87]

Equally exciting is the prospect of accurately gauging post-treatment risk by using biologic markers. Illustrating the need, the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee reported that 56% of 14,712 NSCLC resections in their database had ‘R-uncertain resections’, defined as resections with negative

margins which nevertheless have high risk of residual disease (indicated by failure to perform systematic or lobe-specific nodal dissection, involvement of the highest mediastinal lymph node, carcinoma in-situ at the resection margin or positive pleural lavage cytology).[88,89] A population-based cohort corroborated the IASLC finding (Fig 3)[89] that such patients have significantly worse survival than those meeting the new definition of complete resection.[90]

In this molecular age, the possibility that ct-DNA might accurately identify patients at risk for disease recurrence with a high degree of specificity, serial measurements might identify radiologically inevident recurrence, and also accurately categorize recurrence risk in patients with radiologically ambigious lesions (such as after radiation therapy with the usual scar-like changes), is definitely something to look forward to (Fig 2).[7] Admittedly not yet ready for primetime,[91] this emerging technology will transform our thinking about patient selection for adjuvant treatments, increase transparency in evaluating the likelihood of success after attempted curative-intent treatment and will significantly improve our ability to conduct comparative-effectiveness trials between treatment modalities and methodologies.

Arguably, the 3 most important developments in the 18 months up to 2018 are the publication of the NELSON trial results (there can now be no doubt about the need to implement lung cancer screening programs);[2] the emergence of neoadjuvant immunotherapy;[5] and the potential utility of ct-DNA for evaluating residual disease status and monitoring for treatment failure.[7] Successful implementation of these 3 technology-based opportunities will transform lung cancer into a routinely curable disease within our lifetimes.

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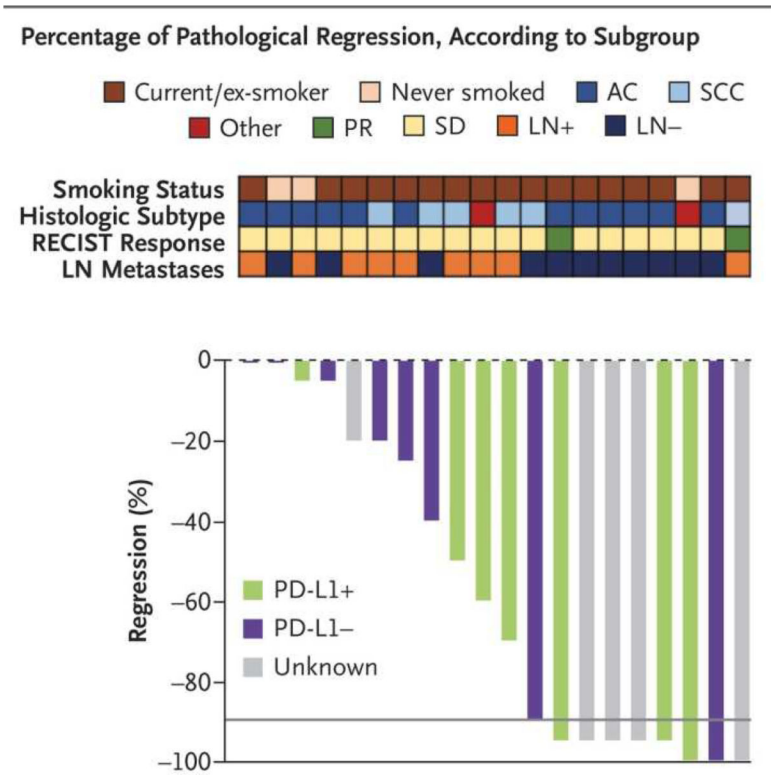

Figure 1.

Pathologic regression of tumor in 20 non-small cell lung cancer resection specimens following neoadjuvant blockade of Programmed Death 1 (PD-1) with 2 doses of Nivolumab. The gray horizontal line indicates the threshold for major pathologic response (90% regression). AC= adenocarcinoma, LN= lymph node, PD-L1= Programmed Death Ligand 1, PR= partial response, RECIST= Response Evaluation Criteria in Solid Tumors, SCC= squamous cell carcinoma, SD= stable disease.[5]

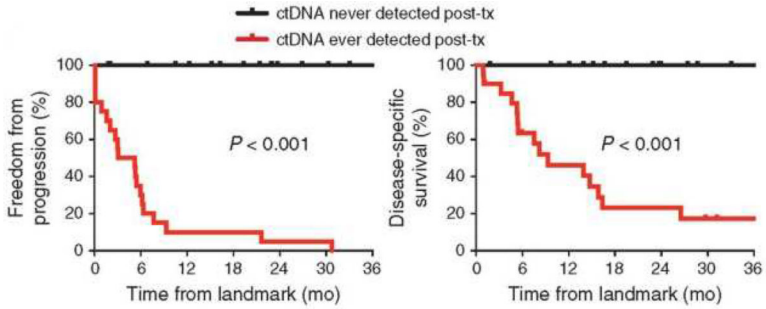

Figure 2.

Kaplan-Meier analysis for freedom-from progression (left) and disease-specific survival (right) stratified by circulating tumor DNA (ctDNA) detection status during posttreatment surveillance; ever positive (n=20) versus never positive (n=17). Landmark analysis was performed from the first post-treatment blood draw. Tx= treatment.[7]

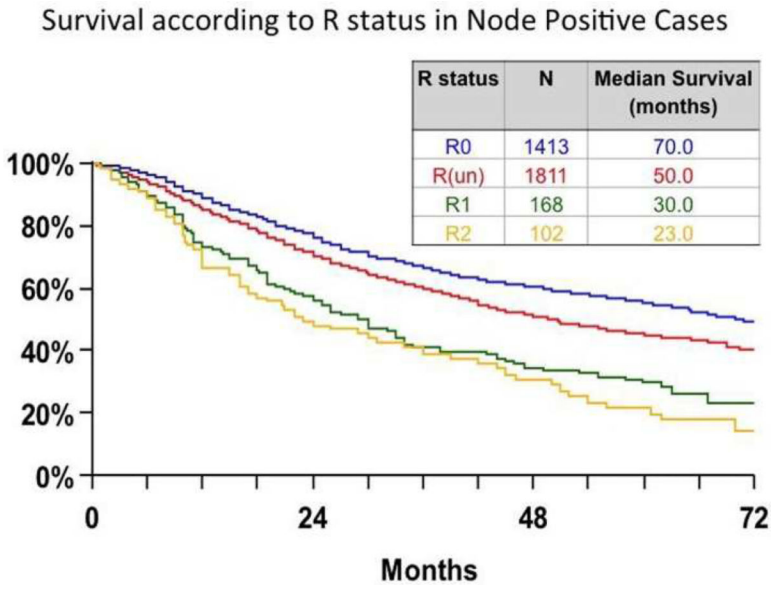

Figure 3.

Survival according to residual disease ('R') status in the International Association for the Study of Lung Cancer international lung cancer staging database. R0= complete resection, R(un)= uncertain resections (defined as resection with microscopic negative margins but residual risk features including any combination of intraoperative lymph node evaluation less rigorous than systematic or lobe-specific nodal dissection, positive highest mediastinal lymph node, carcinoma in-situ at the bronchial margin, positive pleural lavage cytology), R1= microscopic tumor involvement at the resection margin, extracapsular extension of tumor in lymph nodes removed separately or present at the margin of the main lung specimen), R2= macroscopic evidence of residual disease including positive pleural or pericardial effusions and nodes known to be positive but not removed.[83,84]