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UNIVERSITÀ DEGLI STUDI DI TORINO

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Early stage lung cancer:

progress in the last 40 years

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Early Stage Lung Cancer: Progress in the Last 40 Years

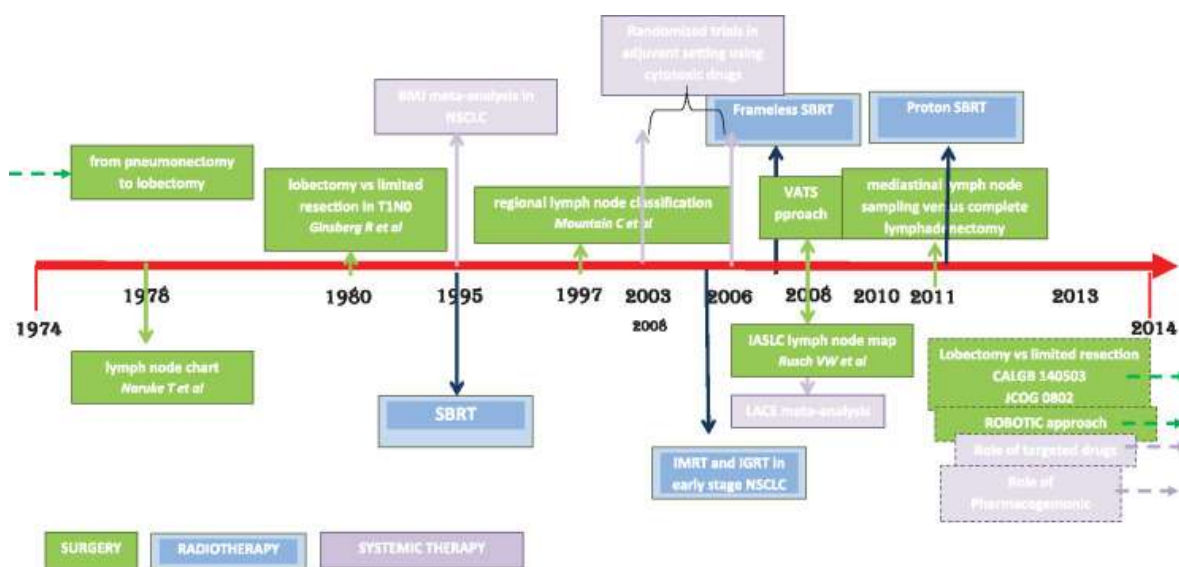
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Key Words

- Adjuvant setting;
- NSCLC;
- Early stage;
- Radiotherapy;
- Thoracic surgery

Surgery remains the cornerstone in the early-stage non-small-cell lung cancer (NSCLC) treatment, but a lot of efforts have been focused on the use of systemic therapy in this setting, on technological advances in thoracic surgery and radiotherapy, and on better application of local therapeutic approaches to improve the survival rates in these patients.

The aim of this article is to provide a synthetic overview of the scientific achievements characterizing this setting during the past 40 years (Figure 1).



Early-stage non-small-cell lung cancer (NSCLC): overview of the scientific achievements characterizing this setting over the last 40 years.

THORACIC SURGERY FOR EARLY-STAGE NSCLC

For early-stage lung cancer (mainly stages I and II), surgery has continued to be a mainstay treatment in the past 40 years or even longer period. However, there have been revision and improvement in many important procedures used for the complete resection of lung cancer. The present-day procedure for the curative resection is composed of the removal of lung parenchyma with primary tumor and sampling/dissection of locoregional lymph nodes. In relation to these, the determination of proper extent of parenchymal resection for lung cancer and assessment of prognostic significance of lymph node dissection have been two major issues. In addition to these, the management of earlier lung cancers and development of minimally invasive approach became the important challenge in the surgical community in the past 40 years.

EVOLUTION OF LUNG CANCER SURGERY: EXTENT OF PARENCHYMAL RESECTION

The history of lung cancer surgery is that of minimization of the extent of parenchymal resection. Lung cancer surgery started as pneumonectomy, a removal of one entire lung of either side, in 1930s by the giants in surgical history such as Graham, Nissen, and Overholt.¹ In late 1950s and 1960s, pneumonectomy was gradually being replaced by

lobectomy, and lobectomy became the standard by the mid-1960s.² The transition from pneumonectomy to lobectomy was based on the accumulation of surgeons' anecdotal but successful experiences. Further progress in lung-sparing resection was afforded by the development of "sleeve" resection in 1955.³ Since that time, bronchoplastic and angioplastic resections became more widely adopted, as evidence accrued that these lung-sparing operations combined lower perioperative mortality,⁴ better functional results,⁵ improved quality of life,⁶ and better long-term survival in suitable cases⁷ compared with pneumonectomy. Then, the next step toward lesser resection was attempted through scientific way of randomized trial by North American Lung Cancer Study Group in late 1980s.⁸ The trial compared the prognosis between lobectomy and limited resection for patients with T1N0 peripheral NSCLC, and the results indicated a 75% increase in recurrence rates and 30% increase in overall death rate. However, the data on postoperative pulmonary function were not given because of early funding termination, and the functional advantage of sublobar resection was not clearly demonstrated. It was concluded that lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1N0 NSCLC. However, especially in these days, we are more often encountering earlier and smaller lung cancers with predominantly ground-glass appearance on high-resolution computed tomography (CT), and their superb prognosis has been shown.⁹ Many case series that demonstrated the excellent prognosis after sublobar resection equivalent to that after lobectomy are accumulating, although these sublobar techniques were not novel.^{10, 11 and 12} The need of revision of randomized trial between lobectomy and sublobar resection has been evoked among thoracic surgeons. At present, two important randomized trials are actually underway across the Pacific Ocean. In the United States, the cancer and leukemia group B trial 140503 will randomize small peripheral tumors to lobectomy versus limited resection, wedge resection, or segmentectomy being allowed in the limited resection arm. In Japan, Japan Clinical Oncology Group (JCOG) 0802 study, a prospective randomized trial compares the prognoses between lobectomy and segmentectomy in a noninferiority setting.¹³ In cancer and leukemia group B trial, primary end point was noninferiority of disease-free survival (DFS), and secondary end points were noninferiority of overall survival (OS), local and systemic recurrence rates, and difference in spirometry at 6 months. Target accrual is 1297 patients. In Japan Clinical Oncology Group trial, the primary end point was noninferiority of OS, and secondary end points were difference in spirometry at 6 and 12 months, noninferiority of DFS, local recurrence rate, and others. Target accrual is 1100 patients. For both these trials, in case the prognosis after segmentectomy is not significantly inferior to that of lobectomy and pulmonary function after segmentectomy is significantly superior to that of lobectomy, segmentectomy is confirmed as a new standard.

Definitive answer to the question whether sublobar resection can replace lobectomy will be given soon. However, until then it is recommended that anatomical segmentectomy be reserved for the CT screening-detected pure ground-glass opacity lesions or part-solid lesions less than 2 cm located in the peripheral third of the lung, after frozen section of N1 and N2 lymph nodes has confirmed the T1aN0M0 status. In addition, frozen section or cytological evaluation of resection margins is recommended.¹⁴

LYMPH NODE DISSECTION FOR LUNG CANCER

Another important aspect of lung cancer surgery is the management of the locoregional lymph nodes, because we realize that metastasis to these lymph nodes is strongly prognostic. Naruke et al¹⁵ published a landmark article in 1978, in which so-called lymph node map (chart) was introduced for the first time. He analyzed the prognosis of patients with metastasis at the specific lymph node site and showed a prognostic importance to describe the site of lymph nodes. Owing to this nodal chart, surgeons became able to speak in the same language of lymph nodes. There have been several revisions in lymph node map. In United States, Mountain-Dressler American Thoracic Society map has been mainly used.¹⁶ However, the coexistence of different maps caused discrepancy in tumor-node-metastasis (TNM) staging worldwide. In 2009, the International Association for the Study of Lung Cancer (IASLC) map was promulgated as a part of IASLC staging project for the global use.¹⁷

An IASLC workshop in 1996 discussed the techniques available at that time for intrathoracic nodal evaluation.¹⁸ The participants, including Dr Naruke, agreed the term "systematic nodal dissection" (SND) and defined the minimum standards for such an assessment. These included the labeling of all excised nodes using an internationally accepted nodal map, the excision of a minimum of three mediastinal nodal stations, one of which should be the subcarinal node, station 7, and excision of hilar and intrapulmonary nodal stations in a centrifugal manner until the extent of resection required has been established. Subsequently, a proposal was made that the definition of a complete resection should accept SND as a requirement for an R0 resection with a minimum of three mediastinal and three N1 nodes/stations excised/sampled and examined by the pathologist.¹⁹ SND was shown to identify 18% "unexpected N2" disease after preoperative evaluation by CT scanning and selective mediastinal exploration.²⁰ The development of positron emission tomographic scanning may have reduced this incidence by as much as half, but the inaccuracy of preoperative nodal evaluation remains problematic.²¹ An alternative approach was suggested by Japanese colleagues, Lobe-Specific Nodal Dissection.²² The attraction of this technique was the demonstration that the subcarinal nodes in station 7 were rarely involved in the case of right upper lobe and left upper segment tumors if all other superior mediastinal nodal stations were clear of disease on frozen section. Although this may save time and a difficult

dissection of station 7 nodes during video-assisted thoracoscopic surgery (VATS) lobectomy, most surgeons find that that removing all mediastinal nodes by SND is expedient.

There has been much debate as to whether such extensive nodal evaluation contributes to cure after complete resection. One study showed that survival after resection for stage I, node-negative, NSCLC improved with the number of lymph nodes resected and examined, with a statistically significant cut point at six lymph nodes,²³ a surprising result given that all such nodes were thought to be clear of disease on pathological examination. However, such an effect could be merely a reflection of “stage migration.”²⁴ Studies confirmed that extensive nodal excision was more accurate in determining the correct nodal category compared with “sampling,”^{25, 26} and one randomized prospective trial showed a survival for SND compared with sampling.²⁷ To further evaluate the prognostic significance of systematic lymph node dissection in comparison with sampling, American College of Surgeons Oncology Group conducted a large-scale randomized trial with 1100 patients undergoing resection for T1-2, N0, or nonhilar N1 NSCLC, randomized between mediastinal lymph node dissection (MLND), roughly equivalent to systematic nodal dissection and an extensive systematic sampling (ACOSOG Z0030).^{28, 29} The results indicated that in 4% of N2 patients lymph node metastasis was overlooked in sampling and there was no difference in perioperative indicators such as blood loss and operative time between sampling and dissection. Most importantly, lymph node dissection did not improve OS or DFS in early-stage lung cancer. It was concluded that “MLND provides patients with the most accurate staging and the opportunity for adjuvant therapy if occult metastatic disease is present. Because current preoperative staging cannot definitively identify patients with mediastinal lymph node involvement and because patients with known hilar or mediastinal disease (N2) or with T3 or T4 tumors may benefit from MLND because the pretest probability of N2 disease is higher, we still recommend that all patients with resectable NSCLC undergo MLND because the procedure does not increase mortality or morbidity.” The discussion regarding the prognostic impact of SND has become superfluous since the finding that node-positive cases benefit from adjuvant chemotherapy.³⁰ In the adjuvant era, it is of paramount importance that the surgeon and pathologist collaborate to ensure that the determination of the postsurgical/pathological N category is conducted using the most rigorous techniques available. In the 7th edition of TNM for lung cancer, the IASLC lymph node map and table of nodal definitions were acknowledged as the recognized method for describing regional node involvement in lung cancer.²² The definition of an R0 resection has been expanded to incorporate the resection and pathological examination of the minimum number of lymph nodes proposed in the definition of SND.³¹

TREND TOWARD MINIMALLY INVASIVE SURGICAL APPROACH

Apart from the extent of parenchymal resection, surgeons used various types of chest wall incisions in the past few decades. Since the late 1990s, the VATS has been extensively used especially for early-stage lung cancers.³² Perioperative parameters in patients who underwent lobectomy by either open or VATS approach were extensively analyzed, and the consensus has been established that the VATS major lung resection is feasible and gives the shorter hospital stay, less morbidity, and less cost.^{33, 34} According to the retrospective, multinstitutional database analyses of 3961 patients who underwent either open lobectomy or VATS lobectomy, VATS procedure was significantly superior to open procedure in hospital costs, length of stay, and risk of adverse events. Only operative time was longer for VATS procedures.³² Similar results were reproduced by a propensity-matched analysis of Society of Thoracic Surgeons database regarding 5042 open thoracotomy lobectomy and 1281 VATS lobectomy. Again, VATS lobectomy was associated with lower incidence of arrhythmias, reintubation, blood transfusion, shorter stay (4.0 versus 6.0 days), and shorter chest tube duration. There was no difference in mortality between two surgical modalities.³⁵ However, it should be realized that the prognostic equivalency between VATS and open procedures has not been definitively proved especially in advanced lung cancers because the comparison between different modalities cannot be completely free from selection bias. Actually, surgeons prefer open procedures to VATS procedures in dealing with difficult, time-consuming, risky cases. Furthermore, the surgical robot is being introduced and applied for the resection of lung cancer recently. The robotic procedures are expected to facilitate the dissection phase of the resection by providing a high-resolution binocular view, wrist-like action of the instruments, and ease of fine dissection in a confined space. Some early reports addressed the low mortality, morbidity, and the advantage that it can achieve a good dissection in difficult situations.³⁶ However, the disadvantage that there is no tactile feedback to surgeons must be mentioned. The feasibility is to be evaluated from technical and economical viewpoints.³⁷

STAGING OF LUNG CANCER

Staging of lung cancer is the basis for clinicians to make treatment plans and anticipate the outcome. In the past, two great leaders played very important roles in revisions of recent staging systems: Mountain for 6th edition and Goldstraw for 7th edition. The IASLC decided to take responsibility for the revision of TNM staging system in lung cancer and initiated IASLC staging project in 1998.³⁸ Previous revisions of the TNM classification for lung cancer had been based on iterative analysis of a single institutional database in the United States. The cases had been accrued during a period of 40 years and were predominantly referred for a surgical opinion. The IASLC was able to develop a

data set of more than 100,000 cases, donated by 46 data centers from more than 20 countries around the globe, treated by all modalities of care and accrued during a 10-year period. Collection and analysis of these data were undertaken by Cancer Research and Biostatistics, a not-for-profit organization in the United States. Such a huge increase in the database available for analysis permitted validation, both internal and external, to a degree not possible previously,³⁹ more closely aligning stage with prognosis than ever before. The IASLC proposals for revision^{38, 40, 41, 42, 43, 44, 45, 46, 47 and 48} were accepted by the Union for International Cancer Control and the American Joint Committee on Cancer and formed the basis of the 7th edition of TNM for Lung Cancer.^{49, 50} The IASLC Staging and Prognostic Factors committee is presently working toward the 8th edition of TNM due to be published late in 2016. The project will be expanded to include other tumor sites in the thorax: malignant pleural mesothelioma, in collaboration with the International Mesothelioma Interest Group, and thymic malignancies, in association with the International thymic Malignancies Interest group. The proposals for the staging classification of lung cancer and these other tumor sites will be published in the *Journal of Thoracic Oncology* during the next 12 to 18 months.

Radiotherapy for Early-Stage NSCLC

Surgery remains the cornerstone in the early-stage NSCLC treatment, and concerning the role of radiotherapy in the adjuvant setting, there is no indication that postoperative radiotherapy (PORT) improves outcome in patients with completely resected N0 or N1 disease, with a meta-analysis in fact demonstrating a detrimental effect on survival in these cases. For patients in whom unsuspected mediastinal nodal metastases are discovered during surgery, PORT has not been shown to improve OS in prospective randomized studies.⁵¹ Ongoing trials (LUNGART, NCT00410683) are currently evaluating the contribution of PORT delivered through modern techniques in N2 resected patients.

A lot of efforts during the last four decades have been focused on technological advances in radiotherapy and on a better application of such an alternative local therapeutic approach to improve the survival rates in patients considered at risk for surgery.⁵²

The apparent reluctance to refer such patients for conventional radiotherapy was partly due to the requirement for 30 or more once-daily treatments, which is cumbersome for frail elderly patients. Moreover, outcomes of conventionally fractionated radiotherapy (CFRT) in early-stage NSCLC was poor despite treatment to doses ranging from 60 to 66–70 Gy because local tumor recurrences were seen in approximately 40% of patients, with OS at 3 years of approximately 20% to 30%.⁵³ Also, hyperfractionation and accelerated hyperfractionation, used to intensify radiation dose from a biological point of view, were ineffective in improving these outcome figures, even if not extensively studied in early-stage NSCLC.

When compared with observation, a Surveillance, Epidemiology, and End Results registry study demonstrated that CFRT alone leads to only modest improvements in outcomes (median OS = 1.7 years with CFRT versus 1.2 years with observation and 5-year OS = 15% versus 14%, respectively).⁵⁴

In the mid-1990s, the principles of cranial stereotactic radiosurgery were transferred to extracranial sites by pioneering work at the Karolinska Hospital in Sweden.⁵⁵ This so-called stereotactic body radiotherapy (SBRT) approach, also known as stereotactic ablative radiotherapy, was further developed by centers in Japan,⁵⁶ Germany,⁵⁷ and North America.⁵⁸ In the United States, preliminary results from Indiana University led to the Radiation Therapy Oncology Group 0236 trial, a phase II study that enrolled medically inoperable patients with T1-T2 (less than 5 cm), peripherally located NSCLC. All patients received 60 Gy (20 Gy × 3). Fifty-five patients were enrolled, and the results demonstrated a 3-year actuarial LC rate of 98%, with OS at 3 years of 56% (median OS of 4 years).⁵⁹

In subsequent years, encouraging results from both prospective and retrospective studies resulted in rapid adoption of SBRT for early-stage NSCLC.⁶⁰ The rationale of SBRT for early-stage NSCLC is that higher radiotherapy doses are more effective in locally controlling the tumor (local tumor control rates of 90% and higher are achieved, with rates of severe toxicity below 10%), which in turn translates into longer OS.

Due to large differences in single fraction and total doses between different studies, a comparison of physical doses is less meaningful. The current recommended tumor dose for SBRT of lung tumors is a minimum of 100 Gy BED, prescribed to the target volume encompassing isodose.^{61, 62 and 63} Total doses are typically delivered in between one and five fractions. Treatment of tumors in the proximity of critical normal organs has led to the used of so-called risk-adapted fractionation schemes that deliver the minimal required dose of 100 Gy BED in a larger number of lower treatment fractions.^{64, 65}

Fractionation appears especially valuable for centrally located tumors (tumors located either adjacent to the proximal bronchial tree or ≤ 1 cm from the heart or mediastinum) because it allows for radiobiological sparing of critical organs.

A higher incidence of complications has been initially reported after SBRT for central tumors.⁶⁶ However, a systematic review of the literature indicates that SBRT is a relatively safe and effective curative treatment, provided that appropriate fractionation schedules are used for central tumors.⁶⁷

A favorable therapeutic ratio of high local control and simultaneously low toxicity has been maintained even after a more widespread adoption of SBRT outside of clinical trials and specialized radiotherapy centers.^{32, 68} This finding of reproducible clinical outcome despite relevant variability and time trends in SBRT practice suggests that clinical SBRT outcomes are fairly robust. Safety profile of SBRT is certainly quite good; symptomatic radiation pneumonitis (RP) is uncommon after the treatment of peripheral lung tumors measuring 5 cm or less, irrespective of the presence of common findings of RP/fibrosis on follow-up CT scans.

SBRT is safely practiced also in patients with severe pulmonary comorbidities, in patients with and very poor pretreatment pulmonary function, and in patients older than 75 years. A higher incidence of severe RP has been reported only in patients with pre-existent idiopathic pulmonary fibrosis.

Milder and risk-adapted fractionation schedules have to be used in larger (more than 5 cm) and centrally located tumors. More uncommon toxicities reported after SBRT include chest wall toxicity such as rib fracture and/or neuropathic pain. At present, SBRT is the guideline-recommended nonsurgical treatment of choice for early-stage NSCLC.⁶⁹

Guidelines for SBRT have been reported by several professional groups: very shortly, SBRT is a technique for delivering external beam radiotherapy with a high degree of accuracy, using high doses of irradiation, which are delivered in one or few treatment fractions to an extracranial target.³²

SBRT can be adequately performed using either traditional linear accelerators equipped with suitable image-guidance technology or linear accelerators specifically adapted for SBRT and using dedicated delivery systems. The SBRT procedure was initially defined by the use of stereotactic frame-based patient set-up. However, frame-based stereotactic patient set-up has been replaced by image-guidance (frameless SBRT with image-guidance technologies). With nonframe-based patient set-up, external stereotactic coordinates are replaced by visualization of a patient's anatomy using images acquired on-table and subsequently compared with pretreatment planning images (image-guided radiotherapy). Several technologies for image guidance are commercially available, and superiority of one method over the other has not been demonstrated. Use of volumetric imaging (cone beam CT), as opposed to only implanted fiducials, has the advantage of enabling assessment of changes in target shape and position, relative to the position of organs at risk.

SBRT: SIMULATION, PLANNING, AND TREATMENT DELIVERY

Four-dimensional CT is the recommended technique for SBRT simulation, due to its ability to accurately target moving thoracic tumors and define patient's specific internal target volume.⁷⁰

For planning, all published prospective trials have used three-dimensional conformal treatment planning. Intensity-modulated radiation therapy (IMRT) and advanced rotational techniques such as volumetric modulated arc therapy (VMAT) have the potential to increase dose conformity and homogeneity and reduce treatment delivery times.⁷¹

VMAT is a form of IMRT in which the gantry continuously moves around the patient with a varying speed and rate of dose delivery. The maximal dose rate on some of the current linear accelerators (flattening filter free) using this approach is up to four times faster than the standard dose rates most often used.

When using IMRT planning, larger volumes of normal pulmonary tissue, including contralateral lung, can be exposed to low radiation doses (V_5); especially when treating larger tumors with VMAT-based approach, doses to the contralateral lung may predict for the risk of pneumonitis.⁷²

Regarding delivery phase and active motion management strategies, continuous irradiation in free breathing is performed using the internal target volume concept, the mean target position concept, or real-time tumor tracking. Noncontinuous irradiation of the tumor in a reproducible position is performed using gated beam delivery in predefined phases of the breathing cycle.⁷³

FUTURE DIRECTIONS

Currently, the safest dose and fractionation for SBRT in centrally located tumors are not known: some ongoing trials will certainly contribute to clarify this issue. The role of SBRT in so-called borderline operable patients will also be better clarified.

The use of proton radiotherapy is receiving increased attention as a modality that is just as effective as photon therapy, but with improved dose distribution in terms of better therapeutic ratio; the role of proton SBRT will be promptly evaluated, especially for centrally located tumors.

Finally, despite high rates of primary tumor control, the rate of distant failure remains consistently high; more work is needed to identify biomarkers that may predict those patients at risk of developing systemic failures such that these patients can be eventually offered adjuvant treatments.

SYSTEMIC TREATMENT FOR EARLY-STAGE NSCLC

At the end of the 1970s, it became clear that many early-stage NSCLC patients already had occult distant metastases at the time of surgery, which led to predominantly distant recurrence and death.⁷⁴ Effective adjuvant therapies thus might improve outcome, even if small studies with the available agents at that time were not effective to demonstrate a benefit.⁷⁵

In the 1980s, several randomized controlled trials (RCTs) further studied adjuvant chemotherapy. They were small (less than 100 patients per arm), and many used the so-called cyclophosphamide, adriamycin, cisplatin (CAV) regimen. Some effects on distant metastasis and DFS could be demonstrated, but side effects—emesis in particular—impeded delivery of doses that could affect long-term outcome.^{76,77}

In the 1990s, a landmark individual patient–based meta-analysis on the effect of chemotherapy in NSCLC reported the potential benefit of postoperative cisplatin-based chemotherapy.⁷⁸ In the adjuvant setting, the comparison of surgery alone versus surgery and chemotherapy gave a hazard ratio (HR) for (OS) of 0.87 (13% reduction in the risk of death, estimated absolute benefit of 5% in 5-year OS, $p = 0.005$). This meta-analysis was the basis for the statistical design of the International Adjuvant Lung Cancer Trial.

The landmark International Adjuvant Lung Cancer Trial results were reported in the 2000 decade and were the first to indicate the benefit of adjuvant cisplatin-based chemotherapy in 1867 patients with completely resected stage I to III NSCLC.⁷⁹ This trial, together with several others, both with positive^{80,81} and negative^{82,83} outcomes, was entered into the individual patient–based Lung Adjuvant Cisplatin Evaluation meta-analysis.²⁹ In this study of the five largest trials (4584 patients), the HR of death was 0.89 (95% confidence interval (CI) 0.82–0.96; $p = .005$), corresponding to a 5-year absolute benefit of 5.4% with chemotherapy. The benefit varied with stage and was documented in stage II, associated with N1 disease in the 6th edition of TNM used in these studies, and stage III, patients with N2 disease in these studies.

In the same decade, several RCTs examining the value of neoadjuvant cisplatin-based chemotherapy, started based on promising signals in very small-sized trials from the 1990s,^{84,85} were reported.^{86,87 and 88} These trials were in general of smaller size and could not demonstrate a significant improvement in OS. A recent meta-analysis on 2385 patients, however, reported a very similar HR compared with the adjuvant approach: 0.87 (95% CI 0.78–0.96, $p = 0.007$), with an absolute 5-year OS improvement of 5%.⁸⁹

In Japanese patients, several studies looked at adjuvant use of oral uracil-tegafur for 2 years, based on promising findings from the 1990s. In a RCT with 999 resected stage I adenocarcinoma patients, OS was significantly better with uracil-tegafur versus standard follow-up: HR 0.71 (95%CI 0.52–0.98, $p = 0.04$).⁹⁰

Postoperative cisplatin-based chemotherapy remains limited by toxicity because the most often used regimen of cisplatin-vinorelbine is not well tolerated by patients, which led to delivery of the planned number of cycles in only 50% to 75% of the patients in the phase 3 studies. Moreover, even if clearly significant, effect on OS remains limited. Several ways to improve are currently being studied. Ways to improve are depicted in [Figure 2](#). With surgery alone (left part), around 40% of the patients will be cured, around 40% will relapse and die of lung cancer, and around 20% will die of comorbidity (often smoking-related cardiovascular or lung disease). With adjuvant chemotherapy (right part), we have brought this to 45%, 35%, and 20%, respectively.

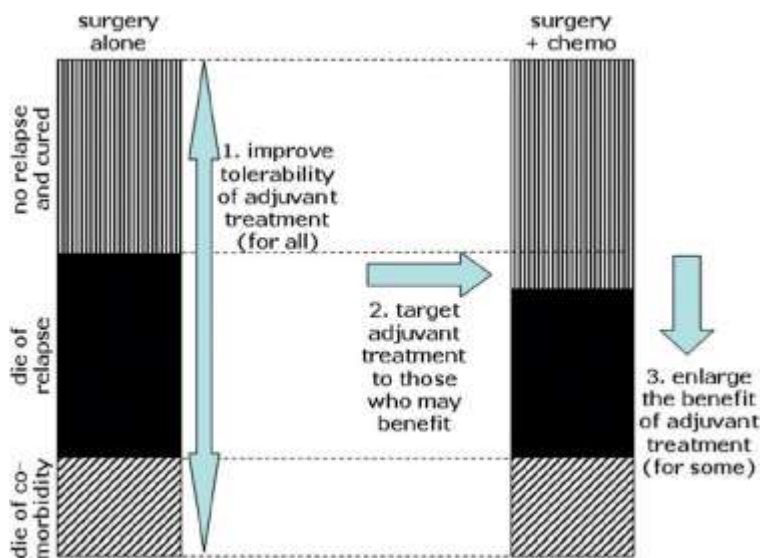


FIGURE 2.

Ways to improve adjuvant therapy for resected non–small-cell lung cancer (NSCLC). Adapted with permission from Spiro SG, Tanner NT, Silvestri GA, et al. Lung cancer: Progress in diagnosis, staging and therapy. *Respirology* 2010; 15: 44–50.

A first idea is to improve tolerability and thus drug delivery of adjuvant chemotherapy. Better anti-emetics such as the neurokinin-1 antagonists were an important step. Using better tolerated chemotherapy has been examined as well, and several trials reported a far lower toxicity and better drug delivery with, for example, cisplatin-pemetrexed.^{91, 92}

A second way is to use adjuvant therapy only in those who are more likely to benefit based on prognostic factors. Indeed, nowadays we administer adjuvant treatment to 100 patients to have an extra cure in 5% of these (number needed to treat 20). Examples are the 15-gene signature reported in the BR.10 adjuvant trial⁹³ or the 14 gene quantitative polymerase chain reaction –based assay.⁸⁹

A third strategy is enlarging the therapeutic ratio, that is, the risk-benefit profile, based on predictive factors. Several predictive factors for better activity of chemotherapy have been described in retrospective reports, such as expression of the excision repair cross-complementation 1 expression (ERCC1) for sensitivity to cisplatin,⁹⁴ thymidilate synthase expression for pemetrexed,⁹⁵ or ribonucleotide reductase M1 expression for gemcitabine.⁹⁶ This principle of so-called pharmacogenetic-driven adjuvant chemotherapy is currently being explored in several prospective trials. A recent report on the French study showed multicenter feasibility of such an approach, but further development was stopped because of unreliable ERCC1 readouts, due to different antibodies reacting with different isoforms.⁵⁹ Moreover, recent phase 3 confirmatory pharmacogenetic studies in the setting of advanced NSCLC were disappointingly negative.^{97, 98} So, albeit attractive, the principle of biomarker-driven adjuvant chemotherapy clearly needs further technical refinement before patient benefits can be expected.

The past decade has also seen the marked increase in the development of novel therapeutic strategies targeting signaling pathways, such as epidermal growth factor receptor (EGFR), angiogenesis, and, more recently, immunotherapy in stage IV NSCLC. The potential contribution of these strategies in the adjuvant setting is still a matter of debate. More than 1000 patients were included in a phase III trial (NCIC BR.19) originally designed to evaluate the efficacy of gefitinib versus placebo in unselected patients with resected stage IB to IIIA NSCLC disease; unfortunately this study was prematurely stopped because of the negative results of other gefitinib studies.^{99, 100 and 101} No overall survival benefit was detected with adjuvant gefitinib in the 503 patients included, and results were also inconclusive among EGFR mutant patients. Another phase III study (RADIANT) is comparing erlotinib with placebo in patients with resected stage IB to IIIA NSCLC after being treated with adjuvant chemotherapy (clinicaltrials.gov, NCT00373425). Eligible patients include those with EGFR mutation, gene amplification, or protein expression.¹⁰² Erlotinib did not prolong disease free survival in these NSCLC completely resected population.

The role of bevacizumab (added to cisplatin-based chemotherapy) in the same disease setting is currently under evaluation in Eastern Cooperative Oncology Group 1505 study, a randomized phase III trial in completely resected stage IB to IIIA NSCLC.

MAGE-A3 vaccine is a cancer immunotherapy that is being developed specifically in the adjuvant setting in patients with resected NSCLC, where MAGE-A3 antigen is expressed in 33% of the tumor samples. On the basis of a phase II

study in which patients who received MAGE-A3 vaccine had a nonsignificant improvement in DFS and OS compared with placebo, a large phase III trial was designed and 2270 patients were enrolled. Unfortunately, at the beginning of 2014 it was announced that the trial did not meet its first and second co-primary end points. There was no significant improvement in DFS compared with placebo in either the overall MAGE-A3-positive population (first co-primary end point) or in those MAGE-A3-positive patients who did not receive chemotherapy (second co-primary end point). Also a third end point based on a previously identified gene signature predicting efficacy of MAGE-A3 vaccine was not reached.

CONCLUSIONS

Surgery remains the standard treatment for early-stage NSCLC. In the past 40 years, a lot of improvements have been made in this setting with the introduction of modern surgical techniques and radiotherapeutic approaches, alternative treatments to sublobar resection—in patients with borderline medical criteria for surgery—based on SBRT, and the complementary role of systemic treatments has been definitively established.

Nevertheless, many issues are still a matter of debate, and OS improvements are clearly needed in this curative context ([Figure 1](#)). Here are only some of the topics that are under investigation in early stages: the extent of parenchymal resection, the role of robotic surgery, a better definition of the role of SBRT, the role of IMRT as adjuvant treatment, and an update of the PORT meta-analyses, which will include last-generation radiation techniques. In the area of systemic treatment, the impact of pharmacogenomic factors, definition of prognostic and predictive factors, and the role of targeted drugs and immunotherapy are only some of the main themes worth of investigation.

The IASLC is the only international association grouping together all the specialists involved in the early disease approach and, consequently, the only scientific association potentially able to promote and support initiatives devoted to implement knowledge in this field.

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