Early Stage Lung Cancer: Progress in the Last 40 Years

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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).

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.

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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 cases[7] 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.[10–12] 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

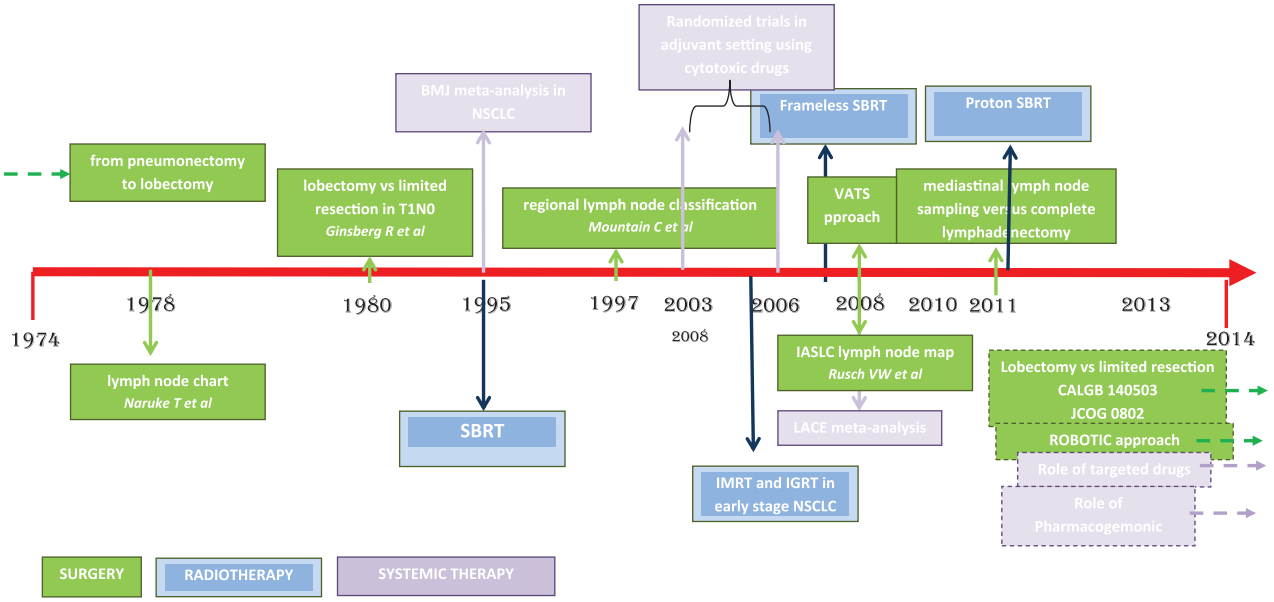

FIGURE 1. Early-stage non–small-cell lung cancer (NSCLC): overview of the scientific achievements characterizing this setting over the last 40 years.

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 al[15] 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.