

# Current Status and Future Direction of Surgical Treatment for Non-Small Cell Lung Cancer

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Lung cancer in Japan has been a leading cause of cancer-related deaths since 1998, though therapeutic outcomes have gradually improved. Better prognoses have resulted from an increase of female adenocarcinoma (i.e., well-differentiated papillary adenocarcinoma or a nonmucinous type of bronchiole-alveolar carcinoma), which is known to have a low potential of malignancy and to be frequently detected at an early stage,<sup>1)</sup> and from the development of cytotoxic agents and molecular-targeted medicine.<sup>2)</sup> Several clinical trials concerning nonsurgical modalities conducted by medical oncologists have produced more and more “medical evidence,” and the role of surgery in the treatment of lung cancer has thus become slightly obscure in the era of “evidence-based medicine.” In this study I examine the concept of surgery and the role of surgeons in the treatment of lung cancer.

## Limited Operation with a Curative Intent: Catch Up with Evidence-Based Surgery

The purpose of lung cancer surgery is to clear macroscopic lesion from the thorax, and a cure is achieved in about half of the operations when the lesion is actually limited. One of the issues is the selection of true local disease that is expected to be cured by surgery or other local therapies. A central type of early lung cancer is defined by a histological type as squamous cell carcinoma and bronchoscopic findings, whereas a peripheral type is possibly defined by histological type as an adenocarcinoma, the size (less than 2 cm) and proportion of ground glass attenuation (GGA) in thin-slice computed tomography. Early lung cancers make up only a small percent of the entire lung cancer

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population; however, less-invasive treatments would cure such early diseases, i.e., photodynamic therapy or brachytherapy for central types<sup>3)</sup> and sublobar resection or stereotactic radiotherapy for peripheral types of early disease.<sup>4,5)</sup> Two clinical trials of sublobar resections are now ready to start in Japan. One is Japan Clinical Oncology Group (JCOG) 0804/West Japan Oncology Group (WJOG) 4507L (phase II), which investigates the feasibility of wedge resection for peripheral early disease defined as 2 cm or less adenocarcinoma with more than 75% of GGA portion. The other is JCOG0802/WJOG4607L (phase III), which investigates noninferiority of segmentectomy in comparison with lobectomy for relatively early disease defined as 2 cm or less adenocarcinoma with less than 25% of GGA portion. Fifteen years later, our textbook will have been revised according to the results of these two trials.

## Adjuvant Chemotherapy for Completely Resected Patients: Evidence or Illusion?

The most reliable parameter of postoperative recurrence is pathological determination of lymph node metastasis, pleural invasion, vascular permeation, and size of tumor. Once clinical stages I and II non-small cell lung cancer (NSCLC) has been well indicated for initial surgery, systemic adjuvant chemotherapy follows if the stages are pathologically proven to be IB–IIIA. Especially, adjuvant oral uracil/tegafur for stage I adenocarcinoma is established in Japan, and the survival benefit for IB cases is so large as to decrease 50% of lung cancer deaths.<sup>6)</sup> The survival benefits obtained by platina-based adjuvant chemotherapies for stages II–III NSCLC are still limited, with an approximate hazard ratio of 0.8 in comparison with surgery alone.<sup>7)</sup> Moreover, a late onset adverse effect is strongly suggested.<sup>8)</sup> Cancer and Leukemia Group B (CALGB) 9633, which was a phase III study to compare adjuvant therapy with carboplatin/taxol and surgery alone for completely resected stage IB NSCLC, showed significant survival benefits of adjuvant therapy after 2.8 years

of median follow-up; however, the benefit is no longer present after 4.5 years of follow-up. International Adjuvant Lung Cancer Trial, which proved the positive effect of adjuvant cisplatin-based combination chemotherapy in resected stages I–III NSCLC after 4.7 years of follow-up, showed negative results after 7.5 years of follow-up with an increased risk of noncancer death in the adjuvant group. Since such chemotherapy owns significant toxicities, and a considerable proportion of patients who receive surgery need no adjuvant therapy, adjuvant chemotherapy with platina-based regimens should not be a routine practice. Therefore it is mandatory to investigate a tailor-made modality such as a selection of candidates for adjuvant chemotherapy by tumor characteristics or individual difference of sensitivity to agents.<sup>9,10</sup> Such research is performed using surgical specimens; therefore the role of surgeons as investigators, coordinators, or cooperators, would be important.

### **Multimodal Treatment for Clinical IIIA-N2 NSCLC: Is Surgery Required?**

Clinical stage IIIA-N2 NSCLC is an old but still unresolved issue concerning lung cancer surgery. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans the alarm existence of hidden metastatic disease, and endobronchial ultrasonography enables pathological nodal staging prior to treatments with an accuracy rate of more than 96%.<sup>11</sup> Such a progression of diagnostic modalities may present several IIIA-N2 NSCLCs curable by surgery. From the lessons of former trials, how to regulate the local tumor burden safely is the key to success. Induction chemoradiotherapy followed by surgery exhibited more-effective local control than radical concurrent chemoradiotherapy did, though treatment-related death is experienced more in cases undergoing trimodality.<sup>12</sup> The power of induction chemotherapy is seemingly inadequate. Another point of the treatment of stage IIIA-N2 NSCLC is the occurrence of a latent systemic spread of cancer cells in most patients, but there is no reliable marker for the indication of microscopic metastasis. In such a condition, we thoracic surgeons would bravely challenge trimodality treatment for cases of this kind while hoping that no distant metastases occur; otherwise the surgical option should be abandoned. However, current platinum-based combination chemotherapy is still powerless and cannot completely eliminate even

microscopic metastasis. Therefore the role of surgery in the treatment of resectable IIIA-N2 disease would be enhanced by the development of novel effective agents, or of a detection system of microscopic distant metastasis. Recently, circulation tumor cells can easily be detected in a clinical setting; however, their significance in the management of lung cancer remains to be clarified.<sup>13</sup> If the existence of microscopic metastasis is diagnosed clinically, indications of surgery, surgical adjuvant therapy, and multimodal strategy, including surgery, can be determined.

### **References**

1. Yoshino I, Baba H, Fukuyama S, Kameyama T, Shikada Y, et al. A time trend of profile and surgical results in 1123 patients with non-small cell lung cancer. *Surgery* 2002; **131** (1 Suppl): S242–8.
2. Takano T, Fukui T, Ohe Y, Tsuta K, Yamamoto S, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. *J Clin Oncol* 2008; **26**: 5589–95.
3. Usuda J, Kato H, Okunaka T, Furukawa K, Tsutsui H, et al. Photodynamic therapy (PDT) for lung cancers. *J Thorac Oncol* 2006; **1**: 489–93.
4. Suzuki K, Koike T, Shibata T, Kusumoto M, Asamura H, et al. Evaluation of radiologic diagnosis in peripheral clinical IA lung cancer—a prospective study for radiological diagnosis of peripheral early lung cancer (JCOG 0201). *J Clin Oncol* 2006; **24** (18 Suppl). (abstr.)
5. Onishi H, Shirato H, Nagata Y, Hiraoka M, Kotaro G, et al. Stereotactic brachytherapy (SRT) for operable stage I non-small cell lung cancer: is SRT comparable to surgery? *J Clin Oncol* 2007; **25** (18 Suppl). (abstr.)
6. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350**: 1713–21.
7. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; **26**: 3552–9.
8. Besse B, Le Chevalier T. Adjuvant chemotherapy for non-small cell lung cancer: a fading effect? *J Clin Oncol* 2008; **26**: 5014–7.
9. Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006; **355**: 983–91.
10. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, et al. Vinorelbine plus cisplatin vs.

- observation in resected non-small cell lung cancer. *New Engl J Med* 2005; **352**: 2589–97.
11. Yasufuku K, Nakajima T, Fujiwara T, Chiyo M, Iyoda A, et al. Role of endobronchial ultrasound-guided transbronchial needle aspiration in the management of lung cancer. *Gen Thorac Cardiovasc Surg* 2008; **56**: 268–76.
  12. Albain KS, Swann RS, Rusch VR, Turrisi AT, Shepherd FA, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): outcomes update of North American Intergroup 0139 (RTOG 9309). *J Clin Oncol* 2005; **23** (16 Suppl). (abstr.)
  13. Wu C, Hao H, Li L, Zhou X, Guo Z, et al. Preliminary investigation of the clinical significance of detecting circulating tumor cells enriched from lung cancer patients. *J Thorac Oncol* 2009; **4**: 30–6.