

State of the Art: Lung Cancer in China

Li Houwen, MD

Lung cancer is the most common malignant tumor leading to death worldwide. The estimated incidence of new cases of lung cancer in the world every year is nearly 1,000,000, and with more than 800,000 estimated deaths from cancer. In China, about 300,000 new lung cancer patients (23/100,000) and more than 250,000 deaths from the disease are predicted each year. Among the new cases, adenocarcinoma accounts for equal amount of cases as squamous cell carcinoma. Tragically, 2/3 of the patients are inoperable when diagnosed. Among the patients who undergo surgical operation with overall 5-year survival rates of about 40%, nearly 40% belong to stage IIIA (N2) and a few to stage IIIB with a 5-year survival rate of about 20% which is in contrast to 50-70% for stages I, II (N0-1). Therefore, in order to improve the survival rate, surgeons have paid more attention to the dissection of N2 diseases for years. But should we take the approach of a systematic removal of mediastinal lymph nodes voluntarily or a selective removal of suspicious lymph nodes? It is controversial because neither proponents can persuade the other with statistical data, but more and more surgeons prefer the systemic dissection of lymph nodes with positive effects,^{1,2)} but mainly with T1-2N2M0. In T3N2, T4N2 patients, the prognosis is still poor. With the increasing occurrence of adenocarcinoma,³⁾ N2 disease is expected to account for more than half of the cases that need operation. And that is one of the reasons that the 5-year survival rate does not rise after systemic lymph node dissection in these years.

In the TNM staging system of Union International Contre le Cancer (UICC), both squamous cell carcinoma and adenocarcinoma are non small cell lung cancer (NSCLC), but surgeons will still take different treatment strategies. For example, they prefer to run the risk of performing a more extended resection for squamous cell

From Department of Thoracic Surgery, The First Affiliated Hospital of China Medical University, Shenyang, China

Address reprint requests to Li Houwen, MD: Department of Thoracic Surgery, The First Affiliated Hospital of China Medical University, No. 155, Nanjing North Street, Heping District, Shenyang City 110001, China.

carcinoma but stop where it should stop for adenocarcinoma when it cannot be resected radically.

In the past 20 years, chemotherapy has markedly improved the prognosis of SCLC, as it has done for NSCLC, especially for those with mediastinal lymph node metastasis. Preoperative radiotherapy and postoperative chemotherapy was once used 40 years ago to improve the curative effect of NSCLC, but the former increased both the difficulties of operations and postoperative complications. Moreover, the survival rate did not improve, so that "local control" was the main concern at that time.

In the 1970s, the development of molecular biology, especially genetic techniques, revealed the principles of initiation, development and metastasis of carcinoma. With the awareness of the subclinical stage and occult micrometastases of lung cancer, multidisciplinary treatment was introduced to surgery.⁴⁾ The TNM staging system is mainly based on the clinical findings. In fact, a patient in stage IA (cT1N0M0) may present with CK19 (cytokeratin 19, marker of micrometastasis)⁵⁾ in blood and bone marrow which produce a substantial difference with the clinical stage. What is more, hematogeneous dissemination of lung cancer cells during surgery can also be confirmed.⁶⁾ So the treatment of lung cancer certainly should be a multidisciplinary treatment, and the necessity of neoadjuvant chemotherapy has been accepted gradually, especially for those with NSCLC with mediastinal lymph node metastasis. Neoadjuvant chemotherapy will bring some side effects,^{7,8)} such as decline of performance status and immune function or even affecting postoperative recovery, but the risk will be far smaller than that of relapse and metastasis of tumor. Of course, we do not expect to extend the surgical indication without limits depending on the preoperative treatment. Although preoperative chemotherapy and/or concurrent radiotherapy can downstage the TNM staging and increase the resectable ratio, this approach often can not get a satisfactory result as it did in the case of most patients of cT3N2M0 and cT4N2M0, especially those with adenocarcinoma. Such cases are worth thinking carefully, not only in the respect of effect/cost ratio but also of short-

term mortality/long-term survival ratio. The global clinical feature of lung cancer is changing with an increase in adenocarcinoma, which is a multidisciplinary disease. There are many differences between adenocarcinoma and squamous cell carcinoma. For adenocarcinoma, the size of the tumor is less important for prognosis than the existence of lymph node metastasis, and in my own opinion extended resection is more important in squamous cell carcinoma than in adenocarcinoma.

Some new molecular targeted therapies have been developed recently. For example, ZD1839 (Iressa)⁹⁾ is an EGFR (HER-1) specific small molecular receptor tyrosine kinase inhibitor. Besides, trastuzumab (herceptin)¹⁰⁾ which is first used for breast cancer with EGFR-HER-2/neu overexpression has also been introduced in clinical trials of lung cancer based on its effect of interfering with the signaling pathway of tumor cells, inducing apoptosis, increasing the cytotoxicity of chemotherapeutic agents and enhancing the antibody-dependent cytotoxicity¹¹⁾ and improve the survival after multidisciplinary treatment. In a word, multidisciplinary treatment, especially including molecular targeted therapy, will give rise to the expectation of improving the postoperative survival of lung cancer.

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Remark by Editorial Board

Please note this survey addresses the present situation concerning lung cancer treatments in China, and there are certain differences when compared to Japan, the US, and other countries where evidence-based medicine (EBM) is greatly needed.