

Treatment of Peripheral Early Stage Lung Cancer

Harubumi Kato, Haruhiko Nakamura, Masahiro Tsuboi, Norihiko Ikeda, Takaaki Tsuchida, Yasufumi Kato, and Takashi Hirano

Introduction

Not only is the incidence of lung cancer increasing around the world, this disease has become the leading cause of cancer death. Since lung cancer kills 85% to 90% of its victims, it is recognized as one of the most difficult to cure diseases. Although the therapeutic results are quite unsatisfactory as a whole, earlier stages of lung cancer, stages IA and IB show better therapeutic results (Table 1).¹⁾ To improve the therapeutic results of lung cancer, efforts for early detection and treatment are essential. In our institution, the 5-year survival rate has gradually improved over the past five decades. These results could be due to improvement of therapeutic procedures including surgery, chemotherapy, radiotherapy, laser therapy and immunotherapy. Furthermore, the improvement of survival may be partially due to lung cancer mass screening made by the Health Insurance Act of 1987.

Lung cancer mass screening by chest computed tomography (CT) was begun in Japan 10 years ago and now is becoming subsequently used in the United States and Europe. Since large numbers of peripheral tiny lung shadows were detected in many of the CT screening pilot trials,^{2,3)} it is important to establish an internationally accepted definition of peripheral type early stage lung cancer.

In this editorial the authors describe the present status and prospects for the treatment of early stage lung cancer.

The Criteria of Early Stage Lung Cancer

Since there are no authorized international criteria of early

stage lung cancer, establishment of criteria is urgently required. According to the location of the tumor, early stage lung cancers are classified into two categories; central type and peripheral type.

In Japan, the criteria of early stage lung cancer were first proposed about 30 years ago, in 1975. Peripheral type early stage lung cancer was defined as a tumor located in an airway more peripheral than subsegmental bronchi, and the longest dimension of the tumor should be 2 cm or less and with no recognized lymph node and distant metastases. In central type early stage lung cancer, the tumor should be located in a segmental bronchus or more proximal airway, and the depth of tumor invasion should be limited to within the bronchial wall with no lymph node or distant metastases. These criteria of central type early stage lung cancer were first defined pathologically in a resected lung by Ikeda in a study supported by the Ministry of Health and Welfare in Japan. Now we have criteria of endoscopically diagnosed central type early stage lung cancer defined by the Japan Lung Cancer Society.⁴⁾

Therapeutic Guidelines of Early Stage Lung Cancer

In Japan, the therapeutic guidelines of lung cancer established on Evidence-based Medicine were made with the support of the Ministry of Health, Labor and Welfare in 2002. In these guidelines, surgical resection and PDT are recommended for treatment of central type early stage lung cancer.⁵⁾

The Possibility of Limited Resection by Video-assisted Thoracoscopic Surgery (VATS)

The standard therapeutic procedure for peripheral type early stage lung cancer is believed to be lobectomy with mediastinal lymph node dissection. However the question was raised whether lobectomy is really needed for tiny tumors, particularly those less than 1 cm in greatest

From Department of Surgery, Tokyo Medical University, Tokyo, Japan

Address reprint requests to Harubumi Kato: Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Table 1. Survival rates according to pathologic stages (n=7,047)

| p-stage | n | 1 year | 2 year | 3 year | 4 year | 5 year |
|---------|-------|--------|--------|--------|--------|--------|
| IA | 2,142 | 96.5 | 92.8 | 87.9 | 82.7 | 79.2 |
| IB | 1,488 | 90.2 | 80.3 | 72.4 | 65.6 | 60.1 |
| IIA | 261 | 90.7 | 78.6 | 68.4 | 62.9 | 58.6 |
| IIB | 785 | 81.3 | 64.5 | 52.7 | 47.6 | 42.2 |
| IIIA | 1,337 | 74.7 | 53.8 | 40.3 | 32.6 | 28.4 |
| IIIB | 759 | 64.6 | 40.2 | 28.4 | 22.5 | 20 |
| IV | 275 | 60.3 | 39.4 | 29.9 | 22.5 | 19.3 |

n: numbers of patients with lung cancer

dimension. There are several reports on limited resection of small lung cancer.^{6,7)} Some of these results showed satisfactory 5-year survival rates. Clinical trials to clarify the possibility of limited resection are needed for particularly small lung cancers showing ground glass opacity (GGO), or ground glass attenuation (GGA). Most of these lesions showed no lymph node metastases, and a 100% 5-year survival was obtained in such cases who underwent resection. A multi-center clinical trial sponsored by the Japan Clinical Oncology Group (JCOG) just started to examine the suitability of limited resection for peripheral small lung cancer. Wedge resection of small lung cancer by VATS without lymph node dissection is one type of the minimally invasive surgery. If some types of lung cancer could be shown to be resected by VATS without any increase of local recurrence, this method could become a future standard treatment for peripheral small lung cancer.

The Rate of Lymph Node Metastasis of Peripheral Small Nodular Cancer

In the past five years, 783 patients with lung cancer underwent surgery in our institution. Among them there were 150 patients with peripheral nodules less than 2 cm in diameter, including 135 adenocarcinomas. Lobectomy was performed in 93 cases and limited resection was performed in 42 cases. The pathological prognostic factors were investigated for the future selection of surgical procedures in the peripheral small nodules. Of cases less than 1 cm, 97.5% of cases showed no lymph node involvement, however even in such tiny tumors 2.5% of them already showed N2 disease. In the cases between 1 and 1.5 cm, 91.9% of cases showed no metastasis, however 8.1% showed either N1 or N2 involvements. In the cases between 1.5 and 2 cm, lymph node involvement was recognized in 12%. Therefore it seems that the tumor size does not have a large correlation with lymph node in-

volvement.

According to Noguchi's classification,⁸⁾ bronchioalveolar cell carcinoma showing findings of GGO on CT images did not have any nodal metastases.⁹⁾ The CT images of our cases were classified into four categories according to the percentages of areas of GGO findings in relation to the entire tumor; 100% GGO, between 50% and 100%, less than 50% and 0% GGO findings. According to these criteria, 16 cases consisted of GGO in 100% of the tumor area and 21 cases consisted of between 50% and 100% GGO. These two groups showed no lymph node metastases. Furthermore, in cases with GGO findings consisting of less than 50% or 0% of the lesion, cases with a tumor size of less than 1 cm showed no lymph node metastasis. However, two cases with a tumor size more than 1 cm had nodal metastases. In the cases with 0% GGO, the presence of lymph node metastases was not related to the sizes of the tumor. The overall 5-year survival rate in adenocarcinoma 2 cm or less in tumor size was 93.3%.

The survival curves according to the postoperative stage showed a 98.1% 5-year survival rate in stage IA, 54.7% in stage IIIA and no 5-year survivals in stages IIA and IV. Since the number is small in stages IIA and IV, it is necessary to increase the number for accurate evaluation. In the survival curves according to the tumor size, tumors less than 1 cm showed a 100% 5-year survival rate. In tumors between 1 and 1.5 cm the survival rate was 86.5%, and in cases between 1.5 and 2 cm, the 5-year survival rate was 92.4%. On the survival curves according to area of GGO finding, the cases consisting of more than 50% GGO showed 100% 5-year survival rate and the cases consisting of less than 50% GGO had 91.1% 5-year survival rate. From these data it seems that the proportion of GGO in the tumor may be related to prognosis. The survival rate was 100% in cases of limited operation and 91.5% in lobectomy cases. The better result of limited resection than lobectomy might be due to selection bias.

Future Surgical Procedures for Peripheral Early Stage Lung Cancer

Tumors with 100% GGO findings on CT images could indicate the suitability of surgical limited resection by VATS. Lesions consisting of between 50% and 100% of GGO in area may also be indication for limited resection in cases less than 2 cm in diameter, and also perhaps in cases consisting of between 10% and 50% GGO finding with a tumor size less than 1 cm in diameter.

The evaluation of limited resection for the small peripheral nodules were reported previously by several researchers,^{6,7,9)} however different opinions concerning these modalities have been reported.^{10,11)} There are still controversies concerning limited resection of peripheral small lung cancers. A randomized clinical trial by the Lung Cancer Study Group (LCSG) demonstrated disadvantages of limited resection for T1N0 tumors in relation to lobectomy.¹¹⁾ Therefore clinical evidence of the usefulness of limited resection for peripheral early stage lung cancers should be proven. The features of peripheral lung cancers suitable for limited resection without lymph node dissection should be clarified. That will make it possible to determine the optimal CT findings for limited resection.

In our experience, even if the primary lesion was less than 1 cm in size, nodal involvement was confirmed histologically in some cases. Prognostic factors may not solely depend on tumor size but also on the percentage of the area of GGO. It is necessary to clarify the findings of CT images of non-invasive cancer by a clinical multi-center study.

Acknowledgment

The authors are indebted to Prof. J. Patrick Barron of the International Medical Communication Center of Tokyo Medical University for his review of this manuscript.

References

1. Shirakusa T, Kobayashi K. Lung cancer in Japan. Analysis of lung cancer registry for resected cases in 1994. Japanese joint committee of lung cancer registry. *Jpn J Chest Surg* 2002; **16**: 757–68.
2. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201**: 798–802.
3. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; **351**: 1242–5.
4. The Japan Lung Cancer Society. Classification of Lung Cancer. Tokyo: Kanahara, 2000; pp 34–5.
5. Furuse K, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. The Japan Lung Cancer Photodynamic Therapy Study Group. *J Clin Oncol* 1993; **11**: 1852–7.
6. Jensik R, Faber L, Kittle C. Segmental resection for bronchogenic carcinoma. *Ann Thorac Surg* 1979; **28**: 475–83.
7. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. *J Thorac Cardiovasc Surg* 1997; **114**: 347–53.
8. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; **75**: 2844–52.
9. Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. *Ann Thorac Surg* 2002; **73**: 1071–5.
10. Miller D, Rowland C, Deschamps C, Allen M, Trastek V, Pairolero P. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg* 2002; **73**: 1545–50.
11. Ginsberg R, Rubinstein L. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995; **60**: 615–22.