Usefulness of sentinel lymph node biopsy for the detection of lymph node micrometastasis in early lung cancer

Kazuro Sugi*, Seiki Kobayashi, Ryuji Yagi, Takahisa Matsuoka

National Hospital Organization, National Sanyo Hospital, Chest Surgery, Higashikiwa 685, Ube, Yamaguchi, 755-0241, Japan

Received 19 December 2007; received in revised form 12 May 2008; accepted 21 May 2008

Abstract

The purposes of this study were to examine the usefulness of the biopsy of the sentinel lymph nodes (SNs) for the accurate and effective detection of lymph node micrometastasis in early lung cancer and to clarify the spread of lymph node micrometastasis. One hundred and thirty-three stage IA non-small cell lung cancer patients in whom SNs could be identified by radioisotope (RI) method were enrolled. All dissected lymph nodes were stained with cytokeratin AE1/AE3 for the examination of micrometastasis. A total of 1375 lymph nodes including 220 SNs were dissected from the 133 patients. From the 220 SNs, 35 (15.9%) were found to be positive for metastasis. Of the other 185 SNs negative for metastasis, 19 (8.6%) were positive for micrometastasis. When patients were limited to those with pN0, there were no lymph nodes positive for micrometastasis other than SNs. In pN1–2 patients, micrometastasis to non-SNs were observed in 2.3–13.2%. In patients with pN0, micrometastasis was limited to SNs, and the results of the examination of SNs for micrometastasis accurately represented those of the examination of all lymph nodes. With advancement of the stage, micrometastasis was not limited to SNs and showed an irregular distribution.

Keywords: Early lung cancer; Sentinel lymph node; Lymph node metastasis; Micrometastasis

1. Introduction

Lymph nodes (LNs) metastasis is an important prognostic factor in lung cancer. It is possible that LNs micrometastasis is also a significant prognostic factor. Wang, Gu and Dobashi et al. reported LNs micrometastasis detection rate of 27.6–45% and significantly poorer outcomes in patients positive for micrometastasis [1–3]. The total number of LNs examined in these studies was 242–480 (4.2–10.2/patient), showing that much labor is necessary for the detection of micrometastasis. Therefore, even if the usefulness of an examination for micrometastasis is recognized, this examination may not be widely performed.

Recently, the usefulness of the biopsy of the sentinel lymph nodes (SNs) has been evaluated mainly in breast cancer and skin melanoma. In lung cancer, Sugi, Nomori and Lipaty et al. attempted to identify SNs with a radioisotope (RI) and succeeded in SNs identification in 63–87% of lung cancer patients [4–6]. Based on these findings, we performed this study to confirm that LNs micrometastasis can be detected by SNs biopsy accurately and effectively.

In breast cancer and skin melanoma, the tumor is considered to metastasize to adjacent LNs, and the metastasis spreads by local extension. However, in lung cancer, mediastinal LNs metastasis in the absence of hilar LNs metastasis has been reported in 17–33% of patients positive for mediastinal LNs metastasis. Therefore, the secondary purpose of this study was to evaluate the spreading pattern of micrometastasis in early lung cancer.

2. Subjects and methods

A total of 170 patients with non-small cell lung cancer in clinical stage IA who underwent complete resection by lobectomy or segmentectomy with LNs dissection or sampling in our hospital between January 2001 and December 2004.

One hundred and thirty-three patients in whom SNs could be identified by our previously reported method were enrolled in this study. The SN identification method was briefly as follows [4]: 2–8 mCi technetium-99m tin colloid was percutaneously injected near the tumor under CT guidance. Dissected LNs radioactivity was measured extra-corporeally using a portable γ probe. LNs showing radioactivity five times the background activity or more were identified as SNs.

The dissected LNs were divided on the maximum cut surface into three sections, and the middle section was subjected to a rapid pathological examination or examination for metastasis by hematoxylin-eosin (HE) staining. The other sections were immunologically stained with cytokeratin AE1/AE3 (CK AE1/AE3) (1:50; DAKO Corp., Carpinteria, CA, USA) for examination for micrometastasis. When there were single tumor cells with appropriate tumor cell morphology or clusters (diameter ≤0.2 mm), a diagnosis of micrometastasis was made.

*Corresponding author. Tel.: +81-836-58-2300; fax: +81-836-58-5219. E-mail address: ksugi@sanyou.hosp.go.jp (K. Sugi).

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LNs metastasis shown by routine HE staining was expressed as p and LNs micrometastasis shown by immunostaining as i. For example, when HE staining showed no lymph node metastasis, but immunostaining showed mediastinal lymph node metastasis, the condition was expressed as pN0 (iN2).

Values were expressed as the mean ± standard deviation. Two groups were compared by associated generalized estimating equations method, and P<0.05 was regarded as significant.

The Institutional Ethics Committee approved this research and informed consent was obtained from all patients.

3. Results

The average age of the 133 patient was 63.8 years, with male and female patients being almost equal. The average of tumor diameter was 18.7±6.6 mm, and 86.5% of the tumors were adenocarcinoma.

A total of 1375 LNs consisting of 220 SNs and 1155 non-SNs were dissected from the 133 patients. LNs metastasis was positive in 24 patients (18.0%), and negative in 109 patients. From the 220 SNs, 35 SNs (15.9%) were found to be positive for metastasis. Of the other 185 SNs negative for metastasis, 19 SNs (8.6%) were positive for micrometastasis. From the 1155 dissected non-SNs, 52 (4.5%) were shown to be positive for metastasis by HE. Of the other 1103 non-SNs negative for metastasis, 13 (1.1%) were shown to be positive for micrometastasis. The metastasis-positive rates were higher for examination of SNs than non-SNs both by HE staining and immunostaining (P<0.001 for both).

Of the 109 patients with pN0, 101 patients were classified by micrometastasis examination as pN0 (iN0) and eight patients as pN0 (iN1). Of the 17 patients with pN1, 12 patients were classified as pN1 (iN1) and five patients as pN1 (iN2). As shown in Fig. 1, all LNs positive for micrometastasis were SNs in the patients with pN0 (iN1). Therefore, examination of only SNs for micrometastasis should have considerably reduced the labor requirement in patients with pN0. However, micrometastasis was observed in 2.3%, 13.2%, and 12.8% of non-SNs in the patients with pN1 (iN1), pN1 (iN2), and pN2 (iN2), respectively. Thus, with the advancement of the stage, the incidence of micrometastasis to non-SNs increased.

4. Discussion

The method for the detection of micrometastasis by RT-PCR or immunostaining is not a routine method because of the considerable labor costs involved. Even when the usefulness of, and necessity for examination for micrometastasis are shown, examination of all dissected LNs for micrometastasis is very difficult in clinical practice. We showed that the results of SNs biopsy for the detection of micrometastasis were comparable to those for the examination of all LNs for micrometastasis in patients with pN0, suggesting that the number of LNs examined for micrometastasis could be considerably reduced by SNs biopsy.

Multiple large-scale clinical studies have shown that postoperative chemotherapy for early lung cancer improves the 5-year survival rate by 10–15%. Kato et al. also successfully indicated that oral uracil-Tegafur for two years significantly improved the survival in patients with pathological stage I adenocarcinoma [9]. This suggests that the prognosis of pN0 (iN) patients might be improved by postoperative chemotherapy. Examination for micrometastasis by SNs biopsy might be useful for detecting patients who benefit by postoperative adjunctive therapy.

Micrometastasis was detected in LNs other than SNs with the advancement of the disease stage. SNs could not be identified because of the lack of RI inflow into the SNs when the metastatic lesion becomes large. Ludwig reported that the pattern in which lymphatic vessels bypass lymph nodes is often observed [10]. Once the tumor volume in LNs becomes large, lymph flow more often bypasses these LNs, flowing into adjacent LNs. In such cases, SNs identified with RI might be different from true SN.

In conclusion, in patients with pN0, the results of examination for micrometastasis by SNs biopsy were similar to those by biopsy of all metastasis-positive. Micrometastasis is limited to SNs in early lung cancer but tends to spread to LNs other than SNs with the progression of metastasis.

References

