# 学 位 論 文 の 要 旨

氏名　　沖本　民生

学 位 論 文 名　Immunohistochemical Comparison of Biomarker Expression in Biopsy and Surgical Specimens of Non-Small Cell Lung Cancer
発 表 雑 誌 名　Anticancer Research
（巻，初頁～終頁，年）　34, 2755-2762, 2014
著 者 名　Tamio Okimoto, Yukari Tsubata, Akihisa Sutani, Hiroshi Fuchita, Naoya Koba, Takamasa Hotta, Megumi Hamaguchi, Kiyotaka Miura, Shunichi Hamaguchi, Miki Ohe, Takashige Kuraki, Yuji Harada, Riruke Maruyama, Nobuhiro Miyamoto, Koji Kishimoto and Takeshi Isobe

# 論 文 内 容 の 要 旨

## INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide, and the incidence has continued to increase over the last few decades. The standard chemotherapy for non-small-cell lung cancer (NSCLC) is the combination of a platinum-based and a third-generation anticancer drug.

Although researchers have identified a number of predictive and prognostic biomarkers of NSCLC, most were identified using resected tumors. Resected tumor samples cannot be obtained from patients with advanced lung cancer, however, assessment in these cases is performed using small biopsy samples. While several reports have suggested that the assessment of biomarker expression in biopsy samples is useful, it is unclear whether biomarker expression correlates with resected samples and diagnostic biopsy samples, and only a few reports have confirmed correlations in expression between surgical and biopsy samples.

In the present study, to confirm the reliability of assessment of Excision repair cross-complementing gene 1 (ERCC1), Ribonucleotide diphosphate reductase M1 (RRM1),

Thymidylate synthase (TS), and Class III beta-tubulin (BT) biomarkers by immunohistochemistry (IHC), we retrospectively reviewed lung cancer patients who were diagnosed by diagnostic biopsy and underwent surgery and evaluated these four biomarkers in resected tissue and diagnostic biopsy samples with IHC.

## MATERIALS AND METHODS

The study population consisted of patients with operable and resectable NSCLC who underwent diagnostic lung biopsy and surgical resection between January 2007 and October 2010 at Shimane University Hospital, Shimane, Japan. Patients who had received chemotherapy or radiotherapy before surgery were excluded. We retrospectively identified 32 patients.

Immunohistochemical staining in both biopsy and surgical specimens was evaluated independently by four physicians who were blind to clinical data (TO, YT, AS, and TI). For ERCC1, RRM1, and TS evaluation, staining intensity was graded on a scale of 0 to 3, with higher numbers indicating higher intensity. A proportion score was assigned in four categories (0 if 0%, 0.1 if 1% to 9%, 0.5 if 10% to 49%, and 1.0 if 50% or more). This proportion score was multiplied by the staining intensity score to obtain a final semiquantitative H score. For BT evaluation, cytoplasmic expression was classified into five categories: score 0, no staining at all; score 1+, faint/barely perceptible partial cytoplasmic expression in <10% of tumor cells; score 2+, weak-tomoderate staining of the entire cytoplasm in >10% of tumor cells; score 3+, moderate staining of the entire cytoplasm in >10% of tumor cells; and score 4+, strong staining of the entire cytoplasm in >10% of tumor cells. Expression scores which were equal to or less than median values were classified as negative while those which were higher were classified as positive.

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

## RESULTS AND DISCUSSION

ERCC1: Correlation coefficient between the biopsy and surgical specimens was r=0.512 (p=0.003), and median H score was 0.67 and 0.53, respectively. Fifteen of 32 biopsy specimens

and 16 of 32 surgical specimens were positive. Concordance rate was 78.1%.

RRM1: Correlation coefficient between biopsy and surgical specimens was r=0.411 (p=0.020), and median H score was 0.88 and 1.43, respectively. Sixteen out of 32 biopsy specimens and 14 out of 32 surgical specimens were positive. Concordance rate was 75%.

TS: Correlation coefficient between biopsy and surgical specimens was r=0.475 (p=0.006), and median H score was 1.00 and 2.00, respectively. Fifteen out of 32 biopsy specimens and 15 of 32 surgical specimens were positive. Concordance rate was 62.5%.

BT: Correlation coefficient between biopsy and surgical specimens was r=0.404 (p=0.027), and median H score was 1.00 and 2.00, respectively. Ten of 30 biopsy specimens and 14 of 30 surgical specimens were positive. Concordance rate was 53.3%.

We also compared TBLB to CT-guided lung biopsies. Larger samples can be obtained with CT-guided core biopsy over TBLB. Concordance rates in the two groups were not significantly different. Because all eligible samples were from operable cases, most tumors were so small (median: 3 cm) that any heterogeneity in the tumor was likely also small. We also compared concordance rates between T1 and T2 or more advanced stage disease. Differences were again not statistically significant. Thus, assessment of biomarker expression with biopsy samples appears to be reliable regardless of tumor size and biopsy method.

We demonstrated the feasibility of simultaneous assessment of the expression of four key predictive biomarkers in the treatment of NSCLC in samples of small size and we also confirmed a moderate correlation among them. This is the first study to identify these correlations. These findings suggest that expression of these biomarkers in biopsy samples can be reliably used in the development of individualized therapies.

## CONCLUSION

We showed that a correlation exists in the expression of ERCC1, RRM1, TS, and BT in biopsy and surgical specimens in patients who had undergone surgery for NSCLC. IHC assessment can be performed in small tumor samples and provides promising data for designing individualized therapy. Introduction into clinical practice awaits retrospective confirmation of the usefulness of this analysis and the establishment of appropriate cut-off values.