Prognostic factors after complete resection of pN2 non–small cell lung cancer

Makoto Sonobe, MD, PhD,[a] Hiroshi Date, MD, PhD,[a] Hiromi Wada, MD, PhD,[a,b] Kenichi Okubo, MD, PhD,[a,c] Hiroshi Hamakawa, MD, PhD,[a,d] Satoshi Teramukai, PhD,[e] Akihide Matsumura, MD, PhD,[f] Tatuo Nakagawa, MD, PhD,[g] Shin-ichi Sumitomo, MD, PhD,[h] Yoshihiro Miyamoto, MD, PhD,[i] Norihito Okumura, MD, PhD,[j] Sadanori Takeo, MD, PhD,[k] Kenzo Kawakami, MD, PhD,[l] Minoru Aoki, MD, PhD,[m] and Shinji Kosaka, MD, PhD,[n] The Japan-Multinational Trial Organization

Objectives: This retrospective, multicenter study aimed to determine prognostic factors of completely resected pathologic N2 stage IIIA non–small cell cancer (NSCLC).

Methods: From 25 participating hospitals, 496 patients (325 men and 171 women; median age, 65 years) who underwent complete resection without preoperative treatment for pT1-3 N2 M0, stage IIIA NSCLC between 2000 and 2004 were enrolled. Lobectomy/bilobectomy was performed in 462 patients and pneumonectomy in 34. Some kind of adjuvant chemotherapy was administered to 296 patients. Survivals were calculated using the Kaplan-Meier method, and prognostic factors were determined using the Cox proportional hazards model.

Results: Five-year overall survival (OS) and disease-free survival (DFS) were 44.8% and 24.2%, respectively. pT classification (hazard ratio (HR), pT1/pT2/pT3 = 1/1.32/2.03), single or multiple N2 metastases (HR, single/multiple = 1/1.36), and skip or nonskip N2 metastasis (HR, skip/nonskip = 1/1.30) were found to be independent prognostic factors for DFS. Sex (HR, female/male = 1/1.36), performance status (HR, PS-0/PS-1 = 1/1.37), tumor diameter (HR, 1.12 per 1-cm increase), pT-factor (HR, pT1/pT2/pT3 = 1/1.37/2.22), and extent of N2 metastasis (HR, localized/extended = 1/1.39) were shown to be independent prognostic factors for OS.

Conclusions: We found that pT classification was a significant prognostic indicator for OS and DFS whereas tumor diameter, performance status, and sex were ones for OS. Single N2 metastasis and skip N2 metastasis were demonstrated as favorable prognostic factors for DFS, limited N2 metastasis was one for OS, and these should be considered as stratification factors for trial on adjuvant therapy. (J Thorac Cardiovasc Surg 2013;146:788-95)

The prognosis of completely resected pathologic (p) N2 stage IIIA non–small cell lung cancer (NSCLC) is still unsatisfactory owing to a high incidence of metastasis or tumor recurrence.[1] A meta-analysis on cisplatin-based adjuvant chemotherapy after initial resection has shown that it improves survival.[2] However, the efficacy of adjuvant chemotherapy in Japanese phase III trials has been controversial.[3,4] Therefore, several phase II and III trials on adjuvant chemotherapy have been planned in Japan.

It is widely known that the prognosis of pN2 stage IIIA NSCLC is heterogeneous, and T and clinical (c) N classifications have been identified as prognostic factors.[5] These factors are considered as stratification criteria in clinical trials. Although pattern of metastasis to N2 regions has also been reported as a prognostic factor.[5,6] Its influence on adjuvant chemotherapy has not yet been clarified; thus, it is not considered as stratification criteria in clinical trials of adjuvant chemotherapy for patients with pN2 stage IIIA NSCLC.

In this study, we retrospectively investigated the outcome of patients with completely resected pN2 stage IIIA NSCLC, who were treated at institutions participating in

From the Department of Thoracic Surgery,[a] Kyoto University Hospital, Kyoto; Karasuma Wada Clinic,[b] Kyoto; Department of Thoracic Surgery,[c] Tokyo Medical and Dental University Hospital, Tokyo; Department of Thoracic Surgery,[d] Kobe City Medical Center General Hospital, Kobe; Department of Clinical Trial Design and Management,[e] Translational Research Center, Kyoto University Hospital, Kyoto; Department of Thoracic Surgery,[f] National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai; Department of Thoracic Surgery,[g] Tenri Hospital, Tenri; Department of Thoracic Surgery,[h] Japanese Red Cross Society, Wakayama Medical Center, Wakayama; Department of Thoracic Surgery,[i] National Hospital Organization Himeji Medical Center, Himeji; Department of Thoracic Surgery,[j] Kurashiki Central Hospital, Kurashiki; Department of Thoracic Surgery,[k] National Hospital Organization Kyushu Medical Center, Fukuoka; Department of Thoracic Surgery,[l] Shiga Medical Center for Adults, Moriyama; Department of Thoracic Surgery,[m] Nishi-Kobe Medical Center, Kobe; and Department of Thoracic Surgery,[n] Shimane Prefectural Central Hospital, Izumo, Japan.

The study was supported by an incorporated nonprofit organization, The Japan-Multinational Trial Organization (Nagoya, Japan).

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Nov 19, 2012; revisions received April 17, 2013; accepted for publication April 25, 2013; available ahead of print July 1, 2013.

Address for reprints: Hiroshi Date, MD, PhD, Department of Thoracic Surgery, Kyoto University Hospital, Shogoin-Kawara-cho 54, Sakyo-ku, Kyoto 606-8507, Japan (E-mail: hdate@kuhp.kyoto-u.ac.jp).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.04.043

Abbreviations and Acronyms

c = clinical
DFS = disease-free survival
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
HR = hazard ratio
IV-CT = intravenous chemotherapy
JMTO = Japan-Multinational Trial Organization
NSCLC = non–small cell lung cancer
OS = operative survival
p = pathologic
PS = performance status
UFT = tegafur-uracil

the clinical trial group Japan-Multinational Trial Organization (JMTO) to determine prognostic factors, particularly prognostic value of pattern of metastasis to N2 regions and adjuvant chemotherapy.

PATIENTS AND METHODS

Study Design

In this retrospective study, 25 institutions affiliated with the JMTO (listed in the Acknowledgements section) recruited patients who met the eligibility criteria, which began in January 2008, and all data including follow-up information until either death or December 2010 were assessed in April 2011.

Eligibility Criteria

Patients with NSCLC who had undergone complete resection by lobectomy, bilobectomy, or pneumonectomy with at least standard ipsilateral hilar/mediastinal lymph node dissection (defined by the General Rule for Clinical and Pathological Record of Lung Cancer[7]) between January 2000 and December 2004, and whose tumors were pathologically proven T1-3 N2 M0, stage IIIA according to the sixth edition of the International System for Staging Lung Cancer,[8] were eligible. The eligibility criteria included the following: no chemotherapy or radiotherapy before surgery; older than 20 years of age; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and written informed consent for surgical resection. Patients were excluded if they had 1 or more of the following factors: active double cancer; serious infections; cardiac, hepatic, renal, or psychologic diseases at the time of lung resection; history of preoperative treatment with chemotherapy or radiotherapy; and intraoperative anticancer drug administration in the thorax or pericardium. Patients who underwent sublobar resection such as segmentectomy for their NSCLC were also excluded. The study protocol was approved by the ethics committee of JMTO (JMTO LC 05-01 study) and the institutional ethics committee of each participating institution. From 25 institutions, 512 patients were recruited. Of these, 12 patients received sublobar resection and 4 patients received insufficient lymph node dissection. Finally, 496 patients were eligible in the study (Figure 1). Their characteristics are shown in Table 1. Of these, 2 (0.4%) patients died of postoperative complication within 30 days after surgery.

Adjuvant Therapy and Follow-up

In the period between January 2000 and December 2004, the significance of induction treatment, adjuvant chemotherapy, or adjuvant radiotherapy was not established. Therefore, indications for resection for cN2 disease and postoperative chemotherapy and/or radiotherapy were dependent on each institution. As adjuvant chemotherapy, oral tegafur-uracil (UFT) or intravenous chemotherapy (IV-CT) was selected. IV-CT regimens that were used included carboplatin and paclitaxel, cisplatin and docetaxel, cisplatin or carboplatin and gemcitabine, cisplatin and 5-fluorouracil, and a combination of cisplatin, mitomycin C, and vindesine. As adjuvant radiotherapy, irradiation with 50 to 60 Gy to hilar and mediastinal areas was performed. Of 496 patients, 122 (24.6%) received IV-CT, 89 (17.9%) received IV-CT and radiotherapy, 60 (12.1%) received UFT, 25 (5.0%) received UFT and radiotherapy, 49 (9.9%) received radiotherapy, and 151 (30.4%) did not receive adjuvant therapy.

The follow-up examination schedule was arranged by each individual institution; most of the patients received medical check-ups and chest x-ray films at least twice per year.

Data Collection

The collected data included age, sex, ECOG PS, cT and cN classifications, affected lobe of lung, operation date, operation mode, pT classification, maximum tumor size (centimeters), tumor histology in accordance with the World Health Organization classification,[9] station of node(s) with metastasis, adjuvant chemotherapy, adjuvant radiation therapy, presence or absence of recurrent tumor, date of diagnosis of recurrent tumor, and follow-up information until either death or December 2010. These data were obtained from the inpatient and outpatient medical records and imaging tests. These data were accumulated through a web-based registration system established by JMTO.

Patterns of Metastasis to N2 Regions

Metastasis to the N2 regions was classified as follows: (1) single (metastasis to 1 N2 station) or multiple (metastases to 2 or more N2 stations) N2 metastases; (2) skip (no metastasis to the N1 region) or nonskip (metastasis to the N1 region) N2 metastases; and (3) extent of N2 stations with metastasis, defined as localized or extended N2 metastasis. ''Localized N2 metastasis'' was defined as metastatic spread of the tumor to right #1, right #2, #3, and/or right #4 N2 station(s) of the right upper lobe; left #1, left #2, #3, left #4, #5, and/or #6 N2 station(s) of the left upper lobe; right #1, right #2, #3, right #4, and/or #7 N2 station(s) of the right middle lobe; #7, right #8, and/or right #9 N2 station(s) of the right lower lobe, and #7, left #8, and/or left #9 N2 station(s) of the left lower lobe. ''Extended N2 metastasis'' was defined as metastasic spread of the tumor to #7, ipsilateral #8, and/or ipsilateral #9 N2 station(s) of the upper lobe; right #8 and/or right #9 N2 station(s) in the right middle lobe; ipsilateral #1, #2, #3, and/or #4 N2 station(s) in the right lower lobe; and ipsilateral #1, #2, #3, #4, #5, and/or #6 N2 station(s) in the left lower lobe. Under these classifications, 294 (59.3%) patients had single N2 metastasis and 202 (40.7%) had multiple N2 metastasis. An equal frequency of skip and nonskip N2 metastases was observed; both were found in 248 (50.0%) patients. The number of patients with skip N2 metastasis by primary tumor location was 89 (50.3%) of 177 in the right upper lobe, 10 (40.0%) of 25 in the right middle lobe, 57 (47.5%) of 120 in the right lower lobe, 63 (57.3%) of 110 in the left upper lobe, and 29 (45.3%) of 64 in the left lower lobe. Localized N2 metastases were observed in 369 (74.4%) patients, and extended N2 metastases were in 127 (25.6%) patients. The number of patients with extended N2 metastasis by primary tumor location was 34 (19.2%) of 177 in the right upper lobe, 0 (0%) of 25 in the right middle lobe, 50 (41.7%) of 120 in the right lower lobe, 14 (12.7%) of 110 in the left upper lobe, and 29 (45.3%) of 64 in left lower lobe.

Statistical Considerations

Categorical data were examined using the χ^2 test. Prognostic evaluation was performed by consideration of the disease-free survival (DFS) and overall survival (OS). DFS was defined as time to lung cancer recurrence or non–lung cancer death. The impact of the following clinical-pathologic