Lung Cancer 108 (2017) 103–108

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Prognostic impact of uncertain parietal pleural invasion at adhesion sites in non-small cell lung cancer patients

Masashi Mikubo[a,*], Hiroyasu Nakashima[a,b], Masahito Naito[a], Yoshio Matsui[a], Kazu Shiomi[a], Shi-Xu Jiang[c], Yukitoshi Satoh[a]

[a] Department of Thoracic Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
[b] Department of Pathology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
[c] Department of Pathology, Toshiba Rinkan Hospital, 7-9-1 Kami-tsuruma, Minami-ku, Sagamihara, Kanagawa 252-0385, Japan

ARTICLE INFO

Article history:
Received 3 January 2017
Received in revised form 25 February 2017
Accepted 4 March 2017

Keywords:
Non-small cell lung cancer
TNM classification
Staging
Pathology
Adhesions
Pleural invasion

ABSTRACT

Objectives: Pleural invasion has been recognized as an important negative prognostic factor in non-small cell lung cancer (NSCLC), and therefore, accurate evaluation is required. However, when the visceral pleura adheres to the parietal pleura around a tumor and parietal pleural structures are destroyed and unrecognizable as a result of inflammation, it is often difficult to accurately evaluate pleural invasion, and classification of the T stage is unclear. To aid in categorization, we defined this status as pl1-3 and investigated the prognostic impact of the pl1-3 status on NSCLC.
Materials and methods: We retrospectively examined the clinicopathological characteristics and prognoses of 929 NSCLC patients who underwent curative surgical resection. The pl1-3 status was defined as invasion beyond the elastic layer of the visceral pleura (pl1 or higher) but showing unclear parietal pleural invasion. We compared the prognoses of pl1-3 status NSCLC patients with that of patients with other pleural invasion statuses.
Results: Thirty-one patients (3%) had a pl1-3 status. The 5-year overall survival rate for pl1-3 patients was 58.9%, and the prognosis was significantly worse than pl1 ($p = 0.04$). In pN0 cohort, pl1-3 disease had a significantly worse prognosis than pl1 and pl2 diseases ($p = 0.01$ and 0.04, respectively) and a similar prognosis to pl3 disease. Furthermore, similar relationships were also observed after adjusting for other prognostic factors in multivariate analysis. Among the pl1-3 and pN0 patients, 11 (46%) developed recurrences (9 patients had distant metastasis, one had local recurrence, and one had both). Although the proportion of pl1-3 patients who underwent adjuvant therapy was similar to that of T3 patients, more individuals received oral tegafur-uracil treatment than intravenous chemotherapy.
Conclusion: These results indicate that pl1-3 patients can be managed in the same manner as patients with T3 and pl3 disease. These results may be informative for treatment decisions during postoperative chemotherapy.

1. Introduction

Pleural invasion is one of the most important prognostic factors in lung cancer [1–5]. Several studies have analyzed the impact of pleural invasion on survival in non-small cell lung cancer (NSCLC), and consequently, a method of incorporating this factor into the T status was included in the 7th edition of the Tumor, Node, Metastasis (TNM) classification [6]. Pathologic pleural invasion can be classified as pl0, pl1, pl2, and pl3 according to the degree of pleural invasion. Tumors that invade beyond the elastic layer of visceral pleura are defined as pl1; those that invade the surface of the visceral pleura are classified as pl2; and those that invade any component of the anatomic structures of the parietal pleura are classified as pl3. Tumors ≤3 cm (T1a or T1b) with pl1 or pl2 are upgraded to T2a and pl3 tumors are classified as T3. These definitions remain the same in the recently published 8th edition of the TNM classification [7]. As the presence and degree of pleural invasion are related to the determination of tumor staging and therapeutic strategy, these factors should be accurately evaluated. However, in cases where the visceral pleura firmly adheres to the

Abbreviations: CI, confidence interval; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer; OS, overall survival; TNM, the tumor, node, metastasis.

* Corresponding author.
E-mail address: m.mikubo1220@hotmail.com (M. Mikubo).

http://dx.doi.org/10.1016/j.lungcan.2017.03.002
0169-5002/

parietal pleura around a tumor, pleural invasion can be difficult to evaluate due to the destruction of parietal pleural structures as a result of inflammatory processes. When a tumor extends beyond the elastic layer of the visceral pleura but the visceral pleural surface and the parietal pleura are unrecognizable, the tumor can be categorized as pl1 or higher, i.e., pT2a or higher, but accurate determination concerning pleural invasion is difficult. It is unclear how the degree of pleural invasion should be evaluated, in particular, how to classify the tumor based on T stage and determine the appropriate management of patients. In the present study, we referred to this status as "pl1-3" and retrospectively analyzed the survival of NSCLC patients with pleural invasion, including individuals with pl1-3 status, to investigate the prognostic impact and appropriate management of pl1-3 invasion.

2. Materials and methods

2.1. Patient cohort

From January 2002 to December 2012, a total of 971 consecutive patients with NSCLC underwent curative surgical resection at Kitasato University Hospital. Clinical information was obtained from the medical, surgical, and pathologic records of these patients. The staging definitions for the T, N, and M components were adopted from the 7th edition of the TNM Classification for Lung and Pleural Tumours. We defined curative surgical resection as segmentectomy, lobectomy, or more extensive lung resection with systemic ipsilateral hilar and mediastinal lymph node dissection and no evidence of residual cancer, i.e., complete (R0) resection. Patient exclusion criteria included positive surgical margins, clinically or pathologically confirmed distant metastasis and pleural dissemination, small cell carcinoma, T4 or T0 tumors, prior induction chemotherapy, radiotherapy or both, and incomplete data on pleural invasion status. Furthermore, we excluded patients with pulmonary metastasis in the same lobe and the invasion of the mediastinal pleura, diaphragm or the pericardium, which were classified as T3 and crucial prognostic factors. Thus, we primarily only evaluated the impact of pleural invasion into the chest wall side. The remaining 929 patients were enrolled in the present study. This study was approved by the institutional review board, and each patient provided written informed consent prior to treatment.

2.2. Histopathologic evaluation

Histopathologic diagnoses were based on the 4th edition of the World Health Organization Classification of Tumours. Pleural invasion data were collected from pathology reports. All tumor sections were stained with hematoxylin and eosin, and elastica-van-Gieson stain was used to visualize elastic fibers and facilitate the evaluation of pleural invasion of lung cancer. The following classification of pleural invasion was adopted from the 7th edition of the TNM Classification for Lung and Pleural Tumours: pl0, tumor with no pleural involvement beyond the elastic layer; pl1, tumor with invasion beyond the elastic layer of the visceral pleura but not exposed on the pleural surface; pl2, tumor with exposure on the visceral pleural surface; and pl3, tumor with invasion of any component of the parietal pleura. T1a and T1b tumors pathologically classified as pl1 or pl2 were upgraded to T2a. The pl1-3 status was defined as invasion extending beyond the elastic layer of the visceral pleura but showing unclear parietal pleural invasion, reflecting the destruction of parietal pleural structures in cases with firm adhesion between the tumor and the parietal pleura (Fig. 1). Tumors that clearly invaded into chest wall components such as fat, muscle or rib, those tumors were classified into the pl3 category, even if the elastic layer of the visceral pleura was unclear.

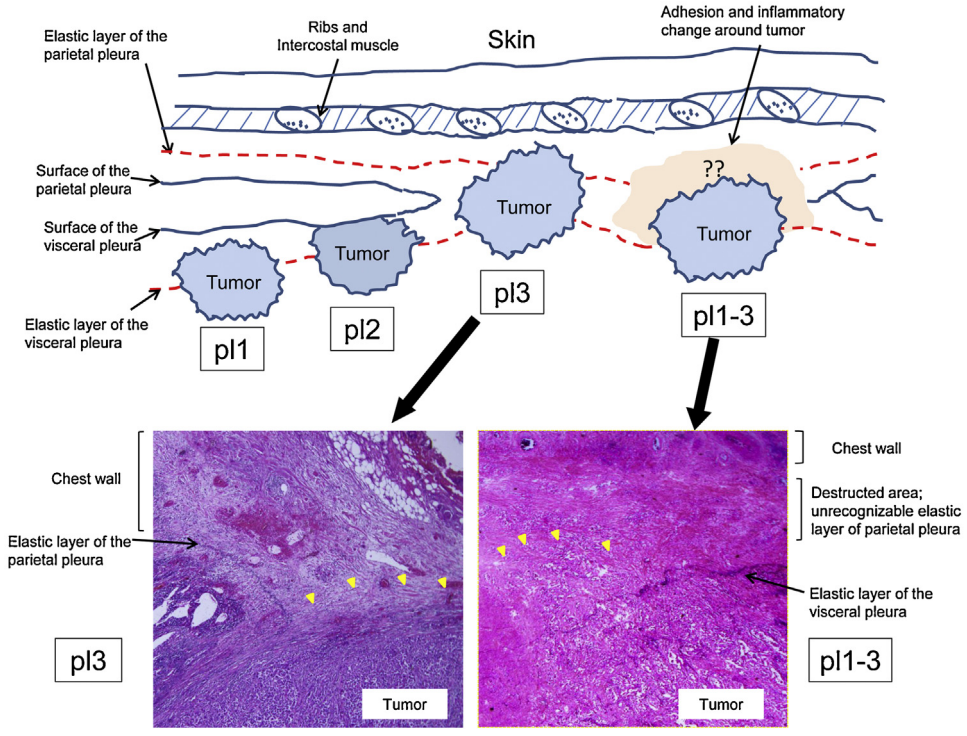

Fig. 1. Schematic illustration of pleural invasion statuses including pl1-3 and histopathologic findings of pl1-3 and pl3 tumors. A pl3 tumor invades (yellow arrow heads) beyond the elastic layer of the parietal pleura. A pl1-3 tumor extends (yellow arrow heads) beyond the elastic layer of the visceral pleura, but the elastic layer of the parietal pleura is disrupted and unclear at a tight adhesion site. Photomicrographs: double staining with hematoxylin and eosin and elastica-van-Gieson, 40×. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)