Study Protocol

Prospective registry database of patients with malignant mesothelioma: directions for a future Japanese registry-based lung cancer study

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Background: The International Association for the Study of Lung Cancer, in collaboration with members of the International Mesothelioma Interest Group (IMIG), developed a large international database and TNM-based system to study malignant pleural mesothelioma (MPM). However, this database has some limitations since it was a retrospective study and it was based predominantly on surgical cases. The Japanese Joint Committee of Lung Cancer Registry (JJCLCR) employs a project of prospective registry database of patients in Japan with MPM in order to clarify MPM's epidemiology, current management practices, and prognosis and also to investigate the potential capabilities to target the best patients for therapy.

Methods: Tumor stage is described using the 7th and 8th versions of IMIG staging system. This prospective cohort study has been conducted from April 1, 2017 to March 31, 2019.

Discussion: We will analyze the data in this registry to determine the most recent outcomes and trends related to MPM treatment in Japan. The present prospective study is expected to validate the 8th version of IMIG staging system, and to investigate whether tumor thickness is a reliable T-descriptor.

Trial registration: ClinicalTrials.gov Identifier: UMIN 000024664

Keywords: Malignant pleural mesothelioma (MPM); prospective registry database

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Introduction

Malignant pleural mesothelioma (MPM) is a rare but aggressive neoplasm and deadly disease throughout the world. The number of MPM cases in Japan is expected to rise (1,2). Although there is a clear association between occupational and environmental asbestos and mineral fiber exposure and the development of MPM (3), its epidemiology, adequate management protocols, and prognosis are less studied. Surgery, chemotherapy, and radiation are the 3 standard therapies used to treat mesothelioma, but these are palliative treatments and demonstrate poor median overall survival (4,5). The International Association for the Study of Lung Cancer (IASLC), in collaboration with members of the International Mesothelioma Interest Group (IMIG), developed a large international database and TNM-based system to study MPM (6-8). It must be pointed out that the IASLC clinical database has limitations. The most obvious problems of the MPM database are the predominance of surgical cases and lack of data on nonsurgical staging tools such as positron emission tomography (PET) (9). The database also has been used in retrospective analyses. Thus, we will obtain new prospective data from Japanese teaching hospitals to overcome the limitations of this retrospective database.

The Japan Lung Cancer Society, the Japanese Association for Chest Surgery, the Japanese Respiratory Society, the Japan Society for Respiratory Endoscopy jointly established the Japanese Joint Committee of Lung Cancer Registry (JJCLCR), which regularly constructs nationwide registrations of lung cancer cases. JJCLCR collects the characteristics of lung cancer patients and aims to develop treatments and provide data that support the TNM classification organized by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (10,11). JJCLCR currently maintains a prospective registry database of patients in Japan with MPM to better understand MPM's epidemiology, current management protocols, and prognosis and clarify potential capabilities to target the best patients for each therapy.

Accurate diagnosis of MPM can be challenging because it is often difficult to distinguish from benign conditions. Furthermore, MPM staging is difficult (12). A new TNM classification for MPM was integrated into the 8th TNM classification of the AJCC/UICC staging system (9). To validate these staging systems, tumor stage is described using the 7th and 8th TNM classifications in the JJCLCR registry. Furthermore, evaluating tumor volume using three measurements of pleural thickness seems to have a high prognostic value (13). As tumor thickness measurements are found to be practical and reproducible, theses clinical MPM classifications will further improve for inclusion in the 9th edition of the TNM staging system, and we will include these registration contents in our registry.

Purpose

The aim of this study is to assess the clinicopathologic features of new MPM cases diagnosed in Japan.

Study setting

This is a non-interventional, prospective, observational cohort study of patients with MPM diagnosed from April 1, 2017 to March 31, 2019 in Japan. This study will review the medical records of each patient.

Methods of analysis

Registry methods

JJCLCR maintains a prospective observational registry of patients with MPM. The JJCLCR committee asked teaching hospitals certified by the Japan Lung Cancer Society, the Japanese Association for Chest Surgery, or the Japanese Respiratory Society to join the study, and JJCLCR committee also asked the hospitals affiliated with the Japan Mesothelioma Interest Group and Japan Organization of Occupational Health and Safety to participate.

This study was approved by the institutional review board (IRB) of Osaka University Medical Hospital, where the registry office is located, on October 11, 2016 (approval no. 16038). This study is registered at the UMIN Clinical Trials Registry as UMIN 000024664 (http://www.umin.ac.jp/ctr/index.htm).

Institutions participate in this registry by accessing a website established by JJCLCR. Each participating institution is sent a USB flash drive that contains software for accessing the registry after IRB approval by each institution. Each institution is authorized to use the registration form on the JJCLCR server after entering their credentials (this form is also mailed to each institution). For these procedures, JJCLCR uses SSL certification, which is considered reliable and more secure than postal mail. The data sheet containing the patient's identification and registration number (used for anonymity purposes) is kept on the USB flash drive and placed in a location that can be

locked by each participating institution. In addition, each USB flash drive is coded with an individual serial key sent from JJCLCR and known only by the institution.

This registry follows the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare on June 17, 2002 and revised on February 28, 2017.

The following data will be collected and analyzed: (I) demographic characteristics including date of registration, sex, birth month and year, and asbestos exposure; (II) preoperative status including Eastern Cooperative Oncology Group performance status, preoperative comorbidity, smoking status, pretreatment laboratory values [hemoglobin (Hb), white blood cells (WBC), platelets (PLT), total protein (TP), albumin (Alb), creatinine (Cr), C-reactive protein (CRP), fibronectin, ferritin, hyaluronic acid, and soluble mesothelin-related peptides] and tumor markers [carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), and cytokeratin fragment 21-1 (Cyfra)], maximum standardized uptake value (SUV) of the pleura on PET, and respiratory function [forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), % predicted FVC, and % predicted FEV_1]; (III) disease description at diagnosis including date of diagnosis, diagnostic method (cytology or histology), immunohistochemical evaluation results [CEA, thyroid transcription factor 1 (TTF-1), cytokeratin (CK) 5/6, calretinin, D2-40, Wilms tumor 1 protein (WT-1), desmin, and p16], histologic type, clinical T factor status (i.e., tumor involvement), pleural thickness, presence of effusion, clinical N factor status (lymph nodes), and clinical M factor status (metastasized organs); (IV) surgical characteristics including induction therapy, operations, combined resection, status of residual rumor, and postoperative morbidity; (V) postoperative diagnosis including tumor histology and pathologic T, N, and M factors; (VI) chemotherapy regimen; (VII) radiotherapy characteristics including irradiated sites and type of radiation therapy; and (VIII) follow-up characteristics including date of last follow-up, vital status at last follow-up, date of initial relapse, and location of initial relapse. A case report form is described online: http://jtd.amegroups.com/public/addition/jtd/supp-jtd.2018.03.53-1.pdf.

Endpoints

Primary endpoints

We will analyze the data obtained from this registry to reveal the most recent outcomes (overall and disease-specific survival) and trends related to MPM treatment in Japan.

Secondary endpoints

Secondary endpoints include patient background, surgical results, stage-specific prognosis, and correlations with the primary endpoints.

Eligibility criteria

All new cases of MPM diagnosed in Japan from April 1, 2017 to March 31, 2019 will be included. MPM diagnosis has to be confirmed by the industrial accident compensation insurance or approved by the Environmental Restoration and Conservation Agency of Japan.

Exclusion criteria

Patients who refuse to participate in this study will be excluded.

Enrollment and study periods

Enrollment period

Patients can enroll from April 1, 2017 to March 31, 2019.

Study period

The study will be conducted from April 1, 2017 to March 31, 2026.

Statistical considerations

The association between patient background and survival (overall and disease-specific survival) will be analyzed using pertinent statistical methods, including the Kaplan-Meier method and Cox proportional hazard modeling, by a statistical collaborator.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board (IRB) of Osaka University Medical Hospital, where the registry office is located, on October 11, 2016 (approval no. 16038).

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