Lung Cancer 116 (2018) 73–79

Contents lists available at ScienceDirect

Lung Cancer

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

Computed tomography in the evaluation of malignant pleural mesothelioma—Association of tumor size to a sarcomatoid histology, a more advanced TNM stage and poor survival

Juuso Paajanen[a,*], Sanna Laaksonen[b], Ilkka Ilonen[a], Henrik Wolff[c], Kirsti Husgafvel-Pursiainen[c], Eeva Kuosma[d], Hely Ollila[d], Marjukka Myllärniemi[a], Tapio Vehmas[c,d]

[a] Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Faculty of Medicine, Helsinki, Finland
[b] Department of Pathology, University of Helsinki, and HUSLAB, Helsinki University Hospital, Helsinki, Finland
[c] Finnish Institute of Occupational Health, Helsinki, Finland
[d] University of Helsinki, Faculty of Medicine, Helsinki, Finland

ARTICLE INFO

Keywords:
Mesothelioma
Computed tomography
Tumor size
Staging

ABSTRACT

Objectives: Appropriate clinical staging of malignant pleural mesothelioma (MPM) is critical for correct treatment decisions. Newly revised TNM staging protocol has been released for MPM. We investigated baseline computed tomography (CT) characteristics of MPM patients, the new staging system and a simple tumor size (TS) assessment in terms of survival.

Materials and methods: As part of our study that included all MPM patients diagnosed in Finland 2000–2012, we retrospectively reviewed 161 CT scans of MPM patients diagnosed between 2007 and 2012 in the Hospital District of Helsinki and Uusimaa. TS was estimated by using the maximal tumor thickness and grading tumor extension along the chest wall. Cox Regression models were used to identify relationships between survival, clinicopathological factors and CT-findings.

Results: The median length of follow-up was 9.7 months and the median survival 9.1 months. The right sided tumors tended to be more advanced at baseline and had worse prognosis in the univariate analyses. In the multivariate survival model, TS, pleural effusion along with non-epithelioid histology were predictors of poor survival. Tumor size correlated significantly with a sarcomatoid histopathological finding and several parameters linked to a more advanced TNM stage. Most patients were diagnosed with locally advanced stage, while 12 (7%) had no sign of the tumor in CT.

Conclusion: In this study, we demonstrate a novel approach for MPM tumor size evaluation that has a strong relationship with mortality, sarcomatoid histology and TNM stage groups. TS could be used for prognostic purposes and it may be a useful method for assessing therapy responses.

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer that arises from the surface of pleural mesothelial cells [1]. The main etiological factor is asbestos exposure with a latency period of 15 years or more [2]. The prognosis of MPM remains poor and the median survival ranges from 8 to 14 months [3]. Several prognostic factors have been proposed, with histopathological subtype, age, sex, performance status, treatment, blood cell count and stage identified as the most important ones [4].

Computed tomography (CT) imaging is the primary diagnostic modality for pleural diseases. The most common CT findings in MPM are pleural effusion and nodular pleural thickening. Pleural plaques with or without calcification are found in approximately 20% of MPM patients [5]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) may give additional information on tumor assessment or staging [6].

A new tumor, node, metastases (TNM 8th edition) classification has been proposed by the International Association for the Study of Lung Cancer (IASLC) and it has been integrated into the 8th edition of the

Abbreviations: AJCC, American joint committee on cancer; CI, confidence interval; CT, computed tomography; FCR, Finnish cancer registry; HUS, hospital district of Helsinki and Uusimaa; IASLC, international association for the study of lung cancer; ICC, intra-class correlation coefficient; MPM, malignant pleural mesothelioma; MRI, magnetic resonance imaging; PET, positron emission tomography; TNM, tumor, node, metastasis; TS, tumor size; UICC, union for international cancer control

* Corresponding author at: Department of Pulmonary Medicine, Heart and Lung Center, Helsinki University Hospital, Haartmaninkatu 4, 00029 Helsinki, Finland.
E-mail address: juuso.paajanen@hus.fi (J. Paajanen).

https://doi.org/10.1016/j.lungcan.2018.01.001
Received 9 September 2017; Received in revised form 5 December 2017; Accepted 1 January 2018

American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging [7]. The major changes in clinical and pathological classifications are that the new T1 group combines the previous T1a with T1b groups, and the previous N1 and N2 groups merge into a new N1 group. There are no changes in the M groups [8,9].

Mesothelioma grows typically in an irregular, rind-like extension along the pleural surface with invasion into the lung parenchyma, mediastinum, chest wall, and diaphragm [10]. Because of the unusual growth pattern, there have been several different attempts for the quantification of MPM besides the TNM classification. Tumor volume quantified either manually or semi-automatically has been found to associate with survival and therapeutic responses [11,12]. Additionally, the sum of several multilevel measurements of tumor thickness has been the standard assessment for treatment response and identified as an independent predictive factor for patients after radical therapy [13,14].

In this retrospective study, we investigated the CT characteristics of MPM at the time of diagnosis in a representative study population. We defined a novel and simple approach for CT-based tumor size evaluation using the maximal tumor thickness and the tumor extension along the chest wall. The purpose was to create an easy and reproducible estimation that would reflect the tumor burden. Secondly, we assessed the usefulness of the novel TNM classification for the evaluation of patient survival and factors that contribute to the baseline clinical stage.

2. Material and methods

2.1. Patients

This retrospective cohort study was a part of an epidemiological research project that explores MPM in Finland between 2000 and 2012 with 1010 patients identified from the Finnish Cancer Registry (FCR), a nationally comprehensive cancer registry (Laaksonen, in press). We have retrospectively reviewed a subcohort of that study, namely 161 patients who had CT studies available at the time of the diagnosis (years 2007–2012) from the Hospital District of Helsinki and Uusimaa (HUS). Survival follow-up closed on February 17, 2017, or at the time of the patient's death. The patient characteristics are summarized in Table 1.

The Finnish Cancer Registry is known to be of high quality and accuracy, with a recent quality assessment showing 96% completeness for solid tumors [15]. The data from FCR used in this study included date of birth, gender, and histologic type. The underlying causes and the dates of death were complemented from the National Registry of Causes of Death at Statistics Finland. Since there is a delay in entering the mortality rate to the death registry, a few patients' data was authenticated from the clinical records. The exact date of the diagnosis and missing clinical data were supplemented and verified from clinical patient records. The information on an occupational disease due to exposure to asbestos at work was collected from the Finnish Workers' Compensation Center. Five (3%) patients with a suspicion of occupational disease were considered having received compensation. The study was approved by the ethics committee of the Helsinki University Hospital (418/13/03/02/2015).

The histopathological diagnosis of MPM was obtained by thick needle biopsies from 71 patients (44%) and surgical biopsies from 89 patients (55%). In addition, one (1%) patient was diagnosed post mortem. The histological diagnosis was made at the Helsinki University Hospital according to morphological and immunohistochemical criteria evaluated by an experienced pathologist. All of the cases were reviewed in an oncological multiprofessional team. The mesothelioma subtype was not specified in 16 cases (10%) in the original dataset. One of the authors (H.W.) with experience in mesothelioma diagnostics evaluated the written pathology reports of these 16 cases and assigned the subtype based on the reports.

Table 1
Overview of patient characteristics (n = 161).

Characteristics	Value
Age (years); median (range)	68.7 (43–89)
Sex; n (%)	
Male	138 (86%)
Female	23 (14%)
Tumor side; n (%)	
Right	85 (53%)
Left	74 (46%)
Bilateral	2 (1%)
Histology; n (%)	
Epithelioid	111 (69%)
Sarcomatoid	27 (17%)
Biphasic	23 (14%)
Compensated occupational disease; n (%)[a]	
Yes	109 (68%)
No	52 (32%)
Cause of death; n (%)	
MPM	153 (95%)
Other cause	2 (1%)
Alive[b]	6 (4%)

[a] Information from the Finnish Workers' Compensation Center.
[b] Alive at the end of the study period (17.2.2017); MPM, malignant pleural mesothelioma.

2.2. Imaging

The pretreatment CT scans taken closest to the date of the diagnosis, either prior to or after it, were analyzed. The mean interval between the diagnosis and the CT scan was 2.0 months (SD 3.0). The spiral CT images were performed using different scanners and imaging protocols as in use in various hospitals. At the beginning of the study period CT imaging was mainly axial with slice thickness about 5 mm. Due to the natural evolution of CT technology, thinner images with a typical slice thickness of 2,5–3 mm and multiplanar reconstruction were used later on. One hundred and eighteen patients (73%) had coronal and/or sagittal images in addition to axial images, while 43 (27%) patients had axial images only. In 17 (11%) cases only chest images were available; in the rest 144 (89%) cases the imaged area also covered abdomen. No brain scans were available. Intravenous contrast medium was used if not contraindicated. A contrast-enhanced CT was available on 152 (94%) patients. CT scans were evaluated in a blinded fashion by a senior radiologist specialized in occupational diseases (T.V.). A set of 30 (19%) images were re-evaluated one month later by the same radiologist to determine the intra-rater agreement. The images were inspected and measurements performed by using the Impax CS5000 work station (Agfa Health Care Finland) supplied with Barco NIO 2MP greyscale monitors.

Mesotheliomas were radiologically staged by using the proposed 8th edition of the AJCC/UICC staging system [7]. Tumor thickness was evaluated in axial planes perpendicular to the chest wall or mediastinum, and the apparently maximal value was measured. To approximate the extension of the tumor in the pleural cavity, we used a previously published method for evaluating pleural abnormalities [16]. First, the pleural cavity was divided into three zones: the upper zone (arch of the aorta to lung apex), the middle zone (from the arch of the aorta down to the inferior pulmonary vein) and the lower zone (from the inferior pulmonary vein to the diaphragm). The slice with the greatest extension of the tumor was evaluated separately for each of the three zones, and the final extension was virtually summated at the level of carina. The final extension was graded at a 4-point scale (0 = no tumor, 1 ≤ 90°, 2 = 90–180°, 3 ≥ 180° of the pleural circumference at the carina level) [17] (Fig. 1). Tumor size (TS) was then estimated by multiplying the measured maximal tumor thickness with the above