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

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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

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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

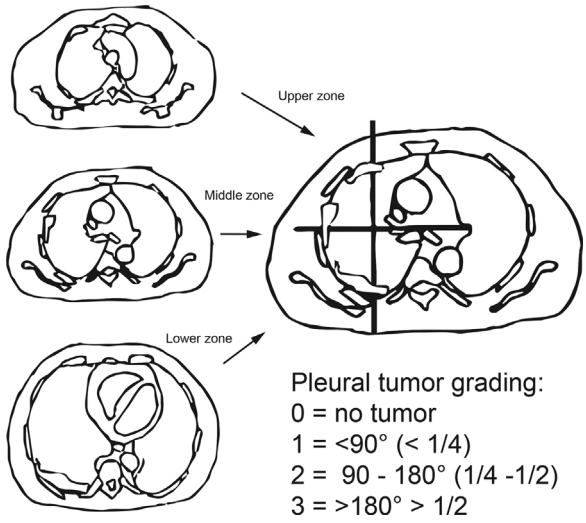

Fig. 1. The extension of the tumor in the pleural cavity. The pleural cavity is divided into three zones: the upper zone (arch of the aorta to lung apex), the middle zone (from the arch of the aorta down to the inferior pulmonary vein), and the lower zone (from the inferior pulmonary vein to the diaphragm). The tumor extension is evaluated separately for each of the three zones, and the final extension is summed and graded at the level of carina. Modified from Kusaka Y et al. with permission [17].

tumor extent grade.

Pleural plaques and calcifications were recorded from both pleural sides separately (yes = 1, no = 0), and then combined into one metric (bilateral existence/absence). The maximal axial thickness of pleural effusion was measured. The fibrosis and emphysema scores were evaluated on a previously published scale, where 0 represents no pathology and 5 extreme changes [18,19] (Table 2).

Table 2
Overview of the CT findings.

CT Finding	Value
Pleural effusion (mm); median (range)	50.0 (0–165)
Tumor thickness (mm); median (range)	18.0 (0–102)
Tumor size; median (range)[a]	36.0 (0–306)
Tumor extent; n (%)	
Grade 0	12 (7%)
Grade 1	53 (33%)
Grade 2	32 (20%)
Grade 3	64 (40%)
Bilateral pleural plaques; n (%)	99 (62%)
Bilateral pleural calcification; n (%)	74 (46%)
Fibrosis, 0–5; n (%)	
Scale 0	120 (74%)
Scale 1	30 (19%)
Scale 2	10 (6%)
Scale 3	1 (1%)
Emphysema, 0–5; n (%)	
Scale 0	111 (69%)
Scale 1	42 (26%)
Scale 2	7 (4%)
Scale 4	1 (1%)
Radiological stage; n (%)	
Stage 0	12 (7%)
Stage IA	14 (9%)
Stage IB	32 (20%)
Stage II	5 (3%)
Stage IIIA	14 (9%)
Stage IIIB	60 (37%)
Stage IV	24 (15%)

[a] Tumor size estimated by multiplying the measured maximal tumor thickness with the 4-point tumor extent grade of the pleural circumference at the carina level.

2.3. Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS institute, Inc. Cary, NC) and figures were drawn with SPSS version 24.0 (IBM SPSS Statistics, Chicago, IL). A p-value < 0.05 was considered significant. Intra-observer agreement was defined using weighted kappa ($w\kappa$) for categorical variables and intra-class correlation coefficient (ICC) for continuous variables [20,21]. The Spearman rank correlation coefficient was calculated to assess the pairwise relationship of tumor size with age, pleural effusion and TNM stage. The associations between radiological findings and histological subgroups, TS and stage were evaluated by the Kruskal-Wallis analysis of variance.

The proportional odds model for logistic regression was used for analyzing the independent variables' associations with the TNM stage. The potential predictors considered for the TNM stage were pleural effusion, pleural plaques and calcification, age, sex, histology, compensated asbestos exposure-related occupational disease, fibrosis and emphysema. The survival analysis was carried from the date of the diagnosis to the end of the follow-up or until death. Both all-cause and disease-specific mortalities were recorded, and since only two (1%) patients died of other causes than MPM, the latter was used in the analyses. The survival curves were computed using the Kaplan-Meier method, and the log rank test was used to determine statistical significance between the TS, tumor extent grade and stage groups. We stratified TS into quartiles (low 0–11, middle 12–79 and high 80–306) for the Kaplan-Meier analysis. The Cox regression was used for the univariate and multivariate survival analyses. The coefficient of determination for the final multivariate model was calculated [22]. The predictors identified by the univariate model (TS, laterality, pleural effusion, stage, histology, age and pleural calcification) as well as gender were included in the final multivariate model. Because of the small number of patients in different stage groups, we combined stages IA, IB with II and IIIA with IIIB in the survival models. We added a variable that considers the signs of thoracentesis or pneumothorax to adjust for pleural effusion in multivariate models.

3. Results

3.1. Radiological characteristics at diagnosis

There were 161 MPM patients diagnosed between 2007 and 2012 at HUS district with CT-images available. The most common CT findings were pleural thickening and pleural effusion, which were found on 149 (93%) and 144 (89%) cases, respectively. Most of the patients had stage IB (20%) or IIIB (37%) disease, while 12 (7%) patients had no recognizable tumor in the CT scan (Table 2). Univariate analysis between TNM stage and clinicopathological factors gave no statistically significant results, therefore a multivariate model was not applied. The right sided tumors tended to be more advanced (p = 0.090). The intra-observer agreements are summarized in Table 3. They were mostly good to excellent, except for metastasis and emphysema scale where they were fair to moderate.

3.2. Tumor size and itś relationship to other radiological parameters

The distribution of TS estimation was rightward skewed with the median value of 36 (0–306). There were differences with TS according to different histological subgroups (p = 0.003, Kruskal-Wallis analysis of variance): The median size of the sarcomatoid type was 66 (12–306), epithelioid 33 (0–213), and biphasic 16 (0–156). There was also an association between tumor thickness and histological subtypes (p = 0.003, Kruskal-Wallis analysis of variance), while other CT-findings failed to show such relations. The TS increased along with an advancing tumor stage (p < 0.0001), except for the stage 2 disease where patients are classified with T1-T2N1 disease (Fig. 2). The TS correlated with TNM T-class (r = 0.70, p < 0.0001), N-class (0.41, p < 0.0001),

Table 3
Intra-rater agreement for CT-findings.

Variable	Wκ	ICC	95% Cl
T	0.74		0.57–0.90
N	0.69		0.44–0.94
M	0.29		−0.16–0.75
Stage	0.85		0.75–0.96
Bilateral plaques	0.86		0.66–1.00
Bilateral calcification	1.00		1.00–1.00
Fibrosis scale	0.75		0.55–0.95
Emphysema scale	0.41		0.08–0.73
Tumor extent	0.84		0.70–0.98
Tumor thickness		0.92	0.84–0.96
Tumor size		0.93	0.85–0.96
Pleural effusion		0.97	0.94–0.99

Wκ, weighted kappa; ICC, Intraclass correlation coefficient; Cl, confidence interval.

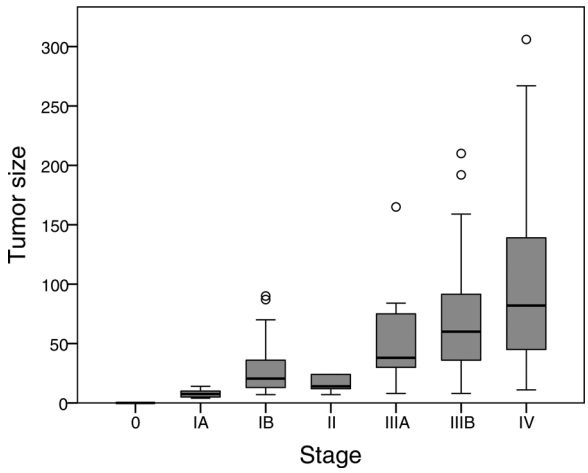

Fig. 2. The boxplot demonstrates tumor size distribution between different radiological stages.

and stage (r = 0.69, p < 0.0001), while no significant correlation was found between TS and age or pleural effusion. TS differed between the M0 status (median 29) and M1 status (median 84) (p = 0.003, Mann-Whitney *U* test).

3.3. Prognostic implications of radiological assessment and tumor size measurement

The median length of follow-up was 9.7 (range 0–104) months and a total of 214.0 person years were included in the follow-up. The median survival of this cohort was 9.1 (range 0–104) months. Six (4%) patients were still alive at the end of the study period. The Cox regression analyses for survival are summarized in Table 4. The univariate analysis showed that TS, age, laterality, pleural effusion, pleural calcification, histology and radiological stage were associated with mortality. Lung parenchymal fibrosis (p = 0.690) or emphysema (p = 0.596) had no association with survival. In multivariate analyses TS, pleural effusion along with non-epithelioid histological subtype were individual predictors of poor survival. When both tumor thickness and extent grade were added to the final model instead of TS, only tumor extent proved to be an independent predictor of mortality (p = 0.001). The TNM stage was suggestively associated with mortality in univariate analysis (p = 0.075) but not after multivariate adjustment (p = 0.225). The coefficient of determination for the final multivariate model was 0.361, while the individual values for histology, TS and TNM stage were, 0.190, 0.107 and 0.051, respectively. It is related to the proportion of variance in the model explained by the independent variables, thus implicating that TS was a better predictor for survival than the TNM stage.

In Kaplan-Meier analysis the median survival was lowest in TNM stage IV (median 6.3, range 0.4–50.6 months) and highest in stage 0 (median 24.1, range 2.1–87.5 months), while there was no difference between stage groups I–III (p = 0.776) (Fig. 3A). When the tumor size variant was classified into three groups, survival of the lowest quartile was significantly higher than in the remaining groups (p = 0.016). The median survival in the lowest quartile was 14.0 (range 0.5–103.6) months compared to 11.1 (range 0–79.7) months in the middle and 5.4 (range 0–68.7) months in the highest quartile (Fig. 3B). Furthermore, the extent grade alone proved to be a significant prognostic factor (p < 0.001) (Fig. 3C).

4. Discussion

This is one of the first studies to use the 8th revised TNM classification for CT-based MPM evaluation. We found that in our well-defined cohort of MPM patients, a simple tumor size estimation was a stronger

Table 4
Factors associated with survival.

	Unadjusted		Adjusted[a]	
Variable	HR (95% Cl)	p-value	HR (95% Cl)	p-value
Age (continuous)	1.02 (0.99–1.04)	0.061	1.02 (1.00–1.04)	0.144
Sex, male	1.05 (0.66–1.67)	0.828	1.13 (0.68–1.88)	0.640
Side, right	1.36 (0.98–1.88)	0.067	0.99 (0.70–1.42)	0.966
Effusion (continuous)	1.01 (1.00–1.01)	0.038	1.01 (1.00–1.01)	< 0.001
TS (continuous)	1.01 (1.00–1.01)	< 0.001	1.01 (1.01–1.02)	< 0.001
Pleural calcification, yes	1.39 (1.01–1.91)	0.046	1.22 (0.84–1.78)	0.298
Histology				
Epithelioid	1.00		1.00	
Sarcomatoid	4.46 (2.83–7.04)	< 0.001	4.71 (2.88–7.69)	< 0.001
Biphasic	1.61 (1.02–2.54)	0.043	2.07 (1.27–3.38)	0.003
Radiological stage				
Stage 0	1.00		1.00	
Stage I + II	2.10 (1.06–4.16)	0.034	1.60 (0.78–3.28)	0.197
Stage III	2.22 (1.14–4.33)	0.019	1.06 (0.50–2.24)	0.879
Stage IV	2.66 (1.26–5.60)	0.010	1.20 (0.49–2.94)	0.690
Occupational disease, yes	0.95 (0.67–1.33)	0.744		
Pleural plaques, yes	1.17 (0.84–1.63)	0.340		

HR, hazard ratio; Cl, confidence interval; TS, tumor size.
[a] Cox regression model adjusted with age, sex, side, pleural effusion, TS, bilateral pleural calcification, histology, stage and signs of thoracentesis.

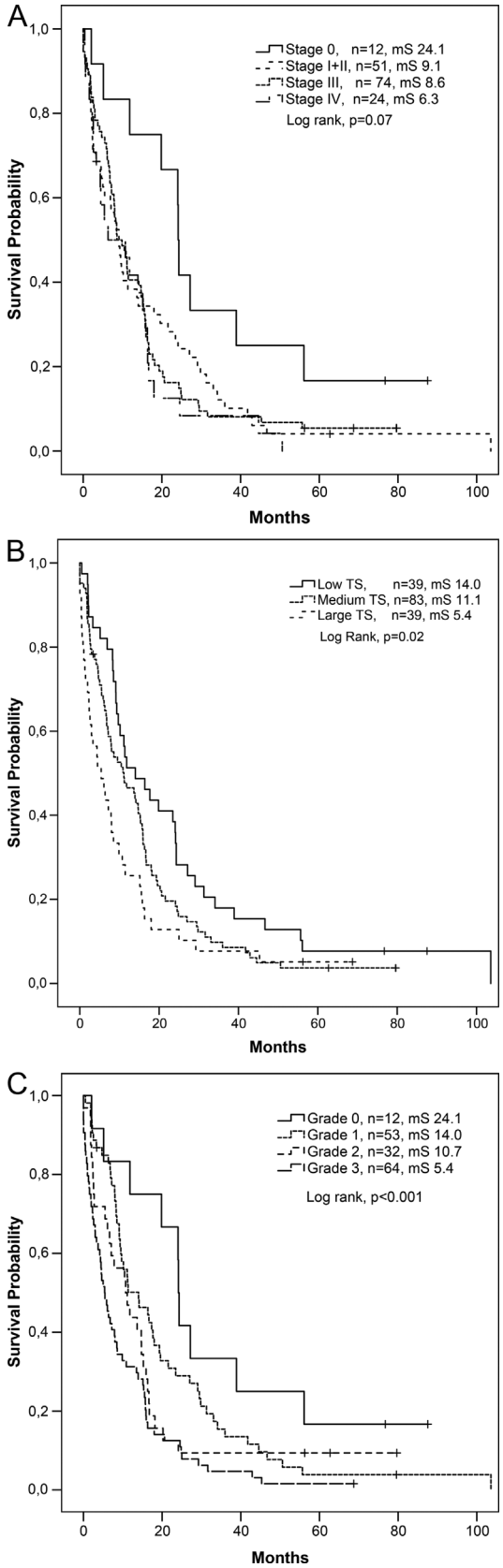

Fig. 3. Kaplan-Meier curve for survival according to A) radiological stage, B) tumor size, C) tumor extent grade. mS, median survival.

predictor for mortality than the traditional TNM stage. Also, we observed that non-epithelioid histology and the amount of pleural effusion are markers for worse prognosis in mesothelioma patients.

Clinical staging of MPM patients is critical for appropriate treatment decisions and for evaluating the effectiveness of given treatment [23]. Although CT remains the primary modality for MPM evaluation due to its accessibility, there are some well-known limitations regarding tumor assessment and staging [24]. The current TNM T classification is based only on invasion to adjacent structures and it does not take into account the actual size of the tumor. CT tends to underestimate the tumor extent and most patients are upstaged during surgery [9]. Furthermore, CT based nodal evaluation has been reported to be poor when comparing to nodal sampling, thus some centers recommend pre- or perioperative lymph node sampling to rule out N2 disease [25]. Limitations in CT based staging may explain that in this present study the TNM staging failed to be an independent factor for survival. Most MPM patients are diagnosed at locally advanced disease [26], which was the case also in this study. In turn, MPM can exist even in a CT scan that appears normal. In our series, there were 12 (7%) patients with no distinct tumor findings in CT, but who were diagnosed from a surgical pleural biopsy. Similar reports have been previously published [27].

Some studies have suggested that assessing tumor thickness or volume could replace or supplement the TNM T category [7,28]. Tumor volume is a more comprehensive and better studied measure than its thickness, but assessing the exact tumor volume from CT images can be complex, time-consuming and prone to errors. No single volumetric application has still not been introduced for universal clinical use. Either single unidimensional maximal tumor thickness or the sum of three separated pleural thicknesses measured at the upper, mid, and lower regions were correlated with survival and nodal metastases [9]. Manual measurements have been criticized for their inter-observer variability and semi-automated thickness measurements has been suggested [23,29]. In this study, we used tumor thickness as part of tumor size evaluation and have demonstrated a strong relationship between TS and mortality, TNM classification and sarcomatoid histology. In addition, we found that tumor extent grade was a more powerful predictor for survival than tumor thickness.

In our study, the thickness of pleural effusion was another independent factor for poor prognosis. Pleural effusion can be the first presentation of MPM, but there are only few studies with contradicting results regarding its prognostic value. Tanrikulu et al. showed that the presence of pleural effusion was associated with a poor prognosis [30]. In a recent study, malignant pleural effusion in mesothelioma demonstrated active biological properties [31]. Thus, the presence of effusion might reflect the activity of the disease. However, this measurement can be biased by previous thoracentesis, even though we tried to adjust for that. Tumor laterality has previously been reported as a prognostic factor, but the reason for that remains unknown [32]. Here, we also found that right-sided tumors had a worse prognosis and they were found to be more advanced at the time of diagnosis.

Apart from mesothelioma, asbestos exposure is known to be associated with asbestosis, pleural plaques and calcification. In previous publications, the association between benign pleural disease and mesothelioma has been controversial [33]. Pleural plaques are reported to be the most common marker of a previous asbestos exposure and a large screening study for patients with a history of occupational exposure to asbestos showed that the presence of pleural plaques was an independent risk indicator for MPM [34]. The prevalence of pleural plaques and calcification in this study is higher than previously published in MPM patients, but similar to other Finnish asbestos-exposure studies [35]. Calcification of the pleura was also associated with a poor survival in univariate analyses, which hasn't been reported before in MPM patients. However, pleural plaques were associated with all-cause mortality and both pleural plaques and calcification were predictors for thoracic cancer mortality in a follow-up study of asbestos-exposure patients without MPM [36]. Even though both asbestos-induced

pulmonary fibrosis and MPM are linked to asbestos exposure in a dose-dependent manner, there is a lack of publications about their relationship with each other [37]. In the present study, the lung parenchymal fibrosis and emphysema were mainly absent or minor. In this respect, the power of our analysis was limited to show their association with the outcome.

4.1. Limitations of the study

The main limitation of our study is its retrospective design. The variability of CT imaging can affect the imaging measurements, but that is unavoidable in a retrospective study like this. Our study population is relatively large considering the rarity of this disease. Still, stratifying patients in many TNM groups leads to poor power. A clear advantage of the new TNM system is that no attention is paid to the fact whether the tumor involves the visceral or parietal pleura, because they can seldom be separated in CT images.

Only a single experienced radiologist was available for this project, thus the inter-reader agreement was not measured. The intra-rater reproducibility for CT findings was good to excellent, except for the emphysema scale and metastasis. The reason for the first was especially the difficulty to separate between minimal emphysema and a normal finding. This may become easier as more modern CT equipment is implemented to hospitals. It is also almost impossible to know whether an incidental mass distant from the tumor is a sign of metastasis or not. Such sign may be divergently classified. The divergent technology of multicenter CT imaging may also have introduced some inconsistency in image reading.

4.2. Conclusions

In conclusion, we launched a novel MPM size evaluation that has a strong relationship with mortality, sarcomatoid histology and the TNM stage groups. Our results suggest that TS could be used for refining the prognostic evaluation of MPM patients with the new TNM classification. Further studies are needed to evaluate whether TS could be a useful tool in assessing treatment responses. In addition, both non-epithelioid histology and the amount of pleural effusion were independent markers for a worse prognosis.

Disclosure

The authors declare no conflict of interest.

Acknowledgements

Grant support was received from a special governmental subsidy for health and sciences research from the Helsinki University Hospital, The Finnish Work Environment Fund, The Sigrid Juselius Foundation, the Cancer Society of Finland. The authors are grateful for the Finnish Cancer Registry for providing data on Finnish mesothelioma patients. The authors wish to thank study coordinator Eva Sutinen for enabling patient data collection.

References

[1] M. Ray, H.L. Kindler, Malignant pleural mesothelioma: an update on biomarkers and treatment, Chest 136 (2009) 888–896.
[2] B.P. Lanphear, C.R. Buncher, Latent period for malignant mesothelioma of occupational origin, J. Occup. Med. 34 (1992) 718–721.
[3] A.C. Bibby, S. Tsim, N. Kanellakis, H. Ball, D.C. Talbot, K.G. Blyth, N.A. Maskell, I. Psallidas, Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment, Eur. Respir. Rev. 25 (2016) 472–486.
[4] H.I. Pass, D. Giroux, C. Kennedy, E. Ruffini, A.K. Cangir, D. Rice, H. Asamura, D. Waller, J. Edwards, W. Weder, H. Hoffmann, J.P. van Meerbeeck, V.W. Rusch, Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC staging committee, J. Thorac. Oncol. 9 (2014) 856–864.
[5] J.M. Seely, E.T. Nguyen, Andrew M. Churg, et al., Malignant pleural mesothelioma: computed tomography and correlation with histology, Eur. J. Radiol. 70 (2009) 485–491.
[6] Z.J. Wang, G.P. Reddy, M.B. Gotway, C.B. Higgins, D.M. Jablons, M. Ramaswamy, R.A. Hawkins, Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET, Radiographics 24 (1216) (2004) 105–119.
[7] M.B. Amin, S.B. Edge, F.L. Greene, D.R. Byrd, R.K. Brookland, M.K. Washington, J.E. Gershenwald, C.C. Compton, K.R. Hess, D.C. Sullivan, J.M. Jessup, J.D. Brierley, L.E. Gaspar, R.L. Schilsky, C.M. Balch, D.P. Winchester, E.A. Asare, M. Madera, D.M. Gress, L.R. Meyer, AJCC Cancer Staging Manual, 8th ed., Springer International Publishing, Cham, 2017.
[8] D. Rice, K. Chansky, A. Nowak, H. Pass, H. Kindler, L. Shemanski, I. Opitz, S. Call, S. Hasegawa, K. Kernstine, C. Atinkaya, F. Rea, P. Nafteux, V.W. Rusch, The IASLC mesothelioma staging project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma, J. Thorac. Oncol. 11 (2016) 2100–2111.
[9] A.K. Nowak, K. Chansky, D.C. Rice, H.I. Pass, H.L. Kindler, L. Shemanski, A. Billé, R.C. Rintoul, H.F. Batirel, C.F. Thomas, J. Friedberg, S. Cedres, M. de Perrot, V.W. Rusch, The IASLC mesothelioma staging project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma, J. Thorac. Oncol. 11 (2016) 2089–2099.
[10] P.E. Van Schil, I. Opitz, W. Weder, C. De Laet, A. Domen, P. Lauwers, J.M. Hendriks, J.P. Van Meerbeeck, Multimodal management of malignant pleural mesothelioma: where are we today? Eur. Respir. J. 44 (2014) 754–764.
[11] F. Liu, B. Zhao, L.M. Krug, N.M. Ishill, R.C. Lim, P. Guo, M. Gorski, R. Flores, C.S. Moskowitz, V.W. Rusch, L.H. Schwartz, Assessment of therapy responses and prediction of survival in malignant pleural mesothelioma through computer-aided volumetric measurement on computed tomography scans, J. Thorac. Oncol. 5 (2010) 879–884.
[12] H.I. Pass, B.K. Temeck, K. Kranda, et al., Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma, J. Thorac. Cardiovasc. Surg. 115 (1998) 310–318.
[13] M.J. Byrne, A.K. Nowak, Modified RECIST criteria for assessment of response in malignant pleural mesothelioma, Ann. Oncol. 15 (2004) 257–260.
[14] M. de Perrot, Z. Dong, P. Bradbury, D. Patsios, S. Keshavjee, N.B. Leighl, A. Hope, R. Feld, J. Cho, Impact of tumour thickness on survival after radical radiation and surgery in malignant pleural mesothelioma, Eur. Respir. J. 49 (2017) 1601428.
[15] M.K. Leinonen, J. Miettinen, S. Heikkinen, et al., Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours, Eur. J. Cancer 77 (2017) 31–39.
[16] N. Suganuma, Y. Kusaka, K.G. Hering, T. Vehmas, T. Kraus, H. Arakawa, J.E. Parker, L. Kivisaari, M. Letourneux, P.A. Gevenois, S. Tuengerthal, M.D. Crane, H. Shida, M. Akira, D.A. Henry, Y. Nakajima, Y. Hiraga, H. Itoh, Y. Hosoda, Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases, J. Occup. Health. 51 (2009) 210–222.
[17] Y. Kusaka, K.G. Hering, J.E. Parker, International Classification of HRCT for Occupational and Environmental Respiratory Diseases, Springer-Verlag, Tokyo, 2005.
[18] O. Huuskonen, L. Kivisaari, A. Zitting, et al., Emphysema findings associated with heavy asbestos-exposure in high resolution computed tomography of Finnish construction workers, J. Occup. Health 46 (2004) 266–271.
[19] O. Huuskonen, L. Kivisaari, A. Zitting, et al., High-resolution computed tomography classification of lung fibrosis for patients with asbestos-related disease, Scand. J. Work. Environ. Heal. 27 (2001) 106–112.
[20] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, Biometrics 33 (1977) 159–174.
[21] V. Rousson, T. Gasser, B. Seifert, Assessing intrarater, interrater and test-retest reliability of continuous measurements, Stat. Med. 21 (2002) 3431–3446.
[22] D.R. Cox, E.J. Snell, Analysis of Binary Data, 2nd ed., Chapman & Hall, London, 1989.
[23] V.W. Rusch, R. Gill, A. Mitchell, D. Naidich, D.C. Rice, H.I. Pass, H.L. Kindler, M. De Perrot, J. Friedberg, V.W. Rusch, M. Ginsberg, R. Gill, D.C. Rice, J. Erasmus, H.I. Pass, D. Naidich, H.L. Kindler, S. Armato, C. Strauss, W. Vigneshwaran, J. Friedberg, S. Katz, M. de Perrot, D. Patios, D. Giroux, L. Shemanski, A. Mitchell, A multicenter study of volumetric computed tomography for staging malignant pleural mesothelioma, Ann. Thorac. Surg. 102 (2016) 1059–1066.
[24] M.T. Truong, C. Viswanathan, M. Godoy, Malignant pleural mesothelioma: role of CT, MRI, and PET/CT in staging evaluation and treatment considerations, Semin. Roentgenol. 48 (2013) 323–334.
[25] J.H. Schouwink, L. Schultze Kool, E.J. Rutgers, F.A. Zoetmulder, N. van Zandwijk, M.J. v.d. Vijver, P. Baas, The value of chest computer tomography and cervical mediastinoscopy in the preoperative assessment of patients with malignant pleural mesothelioma, Ann. Thorac. Surg. 75 (2003) 1715–1718.
[26] British Thoracic Society Standards of Care Committee, BTS statement on malignant mesothelioma in the UK, 2007, Thorax 62 (Suppl. 2) (2007) ii1–ii19.
[27] A. Şenyiğit, H. Bayram, C. Babayiğit, F. Topçu, H. Nazaroğlu, A. Bilici, I.H. Leblebici, Malignant pleural mesothelioma caused by environmental exposure to asbestos in the southeast of Turkey: CT findings in 117 patients, Respiration 67 (2000) 615–622.
[28] S.G. Armato, K.G. Blyth, J.J. Keating, S. Katz, S. Tsim, J. Coolen, E. Gudmundsson, I. Opitz, A.K. Nowak, Imaging in pleural mesothelioma: a review of the 13th international conference of the international mesothelioma interest group, Lung Cancer 101 (2016) 48–58.
[29] S.G. Armato, G.R. Oxnard, M. Kocherginsky, N.J. Vogelzang, H.L. Kindler, H. Macmahon, Evaluation of semiautomated measurements of mesothelioma tumor thickness on CT scans, Acad. Radiol. (2005) 1301–1309.

[30] A.C. Tanrikulu, A. Abakay, M.A. Kaplan, M. Küçüköner, Y. Palanci, O. Evliyaoglu, C. Sezgi, H. Sen, A.I. Carkanat, G. Kirbas, A Clinical, radiographic and laboratory evaluation of prognostic factors in 363 patients with malignant pleural mesothelioma, Respiration 80 (2010) 480–487.
[31] H.M. Cheah, S.M. Lansley, J.F. Varano della Vergiliana, A.L. Tan, R. Thomas, S.L. Leong, J. Creaney, Y.C.G. Lee, Malignant pleural fluid from mesothelioma has potent biological activities, Respirology 22 (2017) 192–199.
[32] R.M. Flores, M. Zakowski, E. Venkatraman, L. Krug, K. Rosenzweig, J. Dycoco, C. Lee, C. Yeoh, M. Bains, V. Rusch, Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center, J. Thorac. Oncol. 2 (2007) 957–965.
[33] A. Reid, The additional risk of malignant mesothelioma in former workers and residents of Wittenoom with benign pleural disease or asbestosis, Occup. Environ. Med. 62 (2005) 665–669.
[34] J.C. Pairon, F. Laurent, M. Rinaldo, B. Clin, P. Andujar, J. Ameille, P. Brochard, S. Chammings, G. Ferretti, F. Galateau-Sallé, A. Gislard, M. Letourneux, A. Luc, E. Schorlé, C. Paris, Pleural plaques and the risk of pleural mesothelioma, J. Natl. Cancer Inst. 105 (2013) 293–301.
[35] M. Tiitola, L. Kivisaari, A. Zitting, M. Huuskonen, S. Kaleva, A. Tossavainen, T. Vehmas, Computed tomography of asbestos-related pleural abnormalities, Int. Arch. Occup. Environ. Health 75 (2002) 224–228.
[36] T. Vehmas, P. Oksa, L. Kivisaari, Lung and pleural CT signs predict deaths: 10-year follow-up after lung cancer screening of asbestos-exposed workers, Int. Arch. Occup. Environ. Health 85 (2012) 207–213.
[37] E. Jamrozik, N. de Klerk, A.W. Musk, Asbestos-related disease, Intern. Med. J. 41 (2011) 372–380.