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Development of a guideline on reading CT images of malignant pleural mesothelioma and selection of the reference CT films

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ABSTRACT

Purpose: International experts developed a guideline on reading CT images of malignant pleural mesothelioma for radiologists and physicians. It is intended that it act as a supplement to the current *International Classification of HRCT for Occupational and Environmental Respiratory Diseases.*
Methods: The research literatures on mesothelioma CT features were systematically reviewed. Ten mesothelioma CT features were adopted into the guideline prepared according to experts' opinion. The terminology of mesothelioma CT features and mesothelioma probability were agreed by consensus of experts. The CT reference films for each mesothelioma feature were selected based on agreement by experts from 22 definite mesothelioma cases confirmed pathologically and immunohistochemically. To support the validity of the mesothelioma probability, 4 experts' readings of CT films from 57 cases with or without mesothelioma were analyzed by kappa statistics between the experts; sensitivity and specificity for mesothelioma were also assessed.
Results: The mesothelioma CT Guideline was developed, providing the terminology of CT features and the mesothelioma probability, the judgement of severity, the distribution of mesothelioma, and the revised CT reading sheet including mesothelioma items. The CT reference films with ten mesothelioma typical

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features were selected. The average linearly and quadratically weighted kappa of the agreement on the 4-point scale mesothelioma probability were 0.58 and 0.71, respectively. The average sensitivity and specificity for mesothelioma were 93.2% and 65.6%, respectively.
Conclusion: The evidence-based mesothelioma CT Guideline developed may serve as a good educational tool to facilitate physicians in recognising mesothelioma and improve their proficiency in diagnosis of mesothelioma.

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor that develops from the mesothelial cells of the pleura. Although all types of asbestos e.g., white, blue and brown asbestos were widely abandoned in many industrialized countries in the 1980s, the incidence of MPM is still growing in most of these countries [1]. The patients suffering from MPM often present symptoms such as dyspnea, chest pain, cough, and weight loss. The prognosis of MPM is so poor that half of the patients can survive less than one year following the confirmed diagnosis.

MPM is likely to be misdiagnosed as tuberculous pleurisy, and metastatic pleural tumors of lung cancer. Early diagnosis of the mesothelioma is often difficult, and it has usually reached an advanced stage by the time it is accurately diagnosed. Conventional CT is more sensitive and specific than plain chest radiography in the diagnosis of both parenchymal and pleural diseases related to asbestos exposure. CT remains the main imaging modality used in the initial evaluation of patients with suspected MPM. Improvement in the proficiency of reading MPM CT and the early diagnosis for MPM poses challenges to occupational physicians in health surveillance and screening for patients.

The International Classification of HRCT for Occupational and Environmental Respiratory diseases (ICOERD) has been developed for screening, epidemiological and clinical study of respiratory diseases caused by occupational and environmental factors [2]. This classification was partly validated because it could describe and assess the parenchymal and pleural abnormalities of pneumoconiosis on CT images [3,4]. Since asbestos exposure associated MPM has aroused an extensive social concern issue in many countries, experts considered the possibility of developing a guideline for radiologists, chest physicians, general physicians and occupational physicians regarding the reading of MPM CT images that act as a supplement part to the ICOERD.

The current study describes the process of the development of the guideline on reading CT films of MPM (MPM-CT Guideline) and selection of the reference MPM CT films by experts. In order to support the validity of MPM probability, the experts' CT readings were statistically analyzed to assess the agreement in the diagnosis of MPM between experts and also calculated the sensitivity and specificity for MPM over the experts' CT readings.

2. Materials and methods

2.1. Development of the MPM-CT guideline

2.1.1. Literature review for MPM typical CT features

The MPM-CT Guideline was developed based on the systematic search and review of the literatures on MPM CT findings published since 1980 from PubMed database. The MPM CT features were described in different studies [5,6]. Kawashima and Libshitz [7] reported CT findings from MPM in 50 patients included pleural thickening in 46 (92%), interlobar fissure pleural thickening in 43 (86%), and pleural effusions in 37 (74%), contractions of the involved hemithorax in 21 (42%), and focal pleural masses were seen in 4 (8%). Half of these cases demonstrated chest wall invasion.

Okten et al. [8] retrospectively reviewed CT scans of 66 patients, which were performed before any invasive procedure was done. The most common CT findings of these MPM cases were pleural effusion (80.3%), pleural thickening (77.2%), volume contraction (37.9%), involvement of mediastinal pleura (31.8%) and interlobar fissure (28.8%).

From the CT scans of 99 MPM cases, Metintas et al. [9] found that the most common MPM CT features were circumferential lung encasement by multiple nodules (28%); pleural thickening with irregular pleuropulmonary margins (26%); and pleural thickening with superimposed nodules (20%).

Wang et al. [10] reported that the key CT findings suggesting MPM include "unilateral pleural effusion", "nodular pleural thickening", and "interlobar fissure thickening".

Ten features frequently observed in MPM cases were therefore adopted into the current guideline according to experts' expertise: unilateral pleural effusion ("ue"), nodular pleural thickening ("nt"), interlobar fissure thickening ("it"), mediastinal pleural thickening ("mt"), tumoral encasement of lung ("te"), calcified plaque engulfment ("pe"), invasion (iv"), diminished lung ("dl"), contracted hemithorax ("ch") and pleural mass ("pm").

2.1.2. Workshops on defining the terminology

There were two workshops at which the experts discussed the development of the guideline. In the 1st workshop, experts participated in the discussion for developing guideline, and proposed some important MPM CT features to be adopted into the guideline. At the 2nd workshop, the MPM CT features "ch", "dl" "pm" and "others" were added into the guideline according to experts' proposal. The contents of the guideline were reviewed and modified according to experts' suggestion, including the terminology of CT features, MPM probability, judgement, and so on. On the text of the guideline, the "localized" or "diffuse" type were provided for the reader to make a judgement of the MPM type according to its distribution. The MPM severity is to be assessed according to the overall impression of the CT findings as: "mild", "moderate" or "advanced".

The MPM probability was defined as follows: Grade 1: negative; no abnormal findings on CT, or abnormal findings of other diseases; Grade 2: low probability of MPM; Grade 3: moderate probability of MPM; Grade 4: high probability of MPM.

2.2. Selection of MPM CT reference films

2.2.1. Subjects for CT readings

In June 2005, a newspaper article reported that five students suffered from MPM, who had live near the Kubota Plant, a currently closed large asbestos cement pipe factory in Amagasaki City, Hyogo Prefecture, Japan. The factory used crocidolite and chrysotile to produce cement pipes between 1957 and 1975 with an annual average usage of 4670 tons of crocidolite and an annual average of 4600 tons of chrysotile [11]. Many residents supposed that their diseases such as MPM and lung cancer that they experienced might be due to environmental asbestos exposure from the plant. As of April 2007, two of the authors (N.K. and S.K.) investigated medical records including the pathological reports when available,

Table 1
Confirmed examination performed on the 57 cases.

Clinical diagnosis	No.	Pathological examination	Note
MPM	22	Both histopathological and immunohistochemical staining	Considered as "Gold standard" for selection of reference CT features
	16	Histopathology alone	
	6	Cytology alone	
Lung cancer	5	–	Clinically diagnosed at local hospitals
Pleural plaque	2	–	Clinical diagnosis
	1	–	Possible benign mesothelioma
Other cases	5	Indefinite	No records available, clinically possible carcinoma, metastasis of malignancy or MPM

occupational history and residence of the patients, and successfully obtained CT films of 57 cases. Of the 57 cases, 44 were MPM cases, out of which 22 MPM cases ("Gold standard" cases) were confirmed both by histopathological examination and immunohistochemical staining, 16 MPM cases were confirmed by histopathology alone, and 6 MPM cases were confirmed by cytology. There were 5 cases clinically diagnosed as lung cancer, 3 pleural plaque cases, and 5 indefinite cases because that the detailed information on clinical diagnosis or histopathological examinations were not obtained, as shown in Table 1.

2.2.2. MPM diagnosis by means of immunohistochemical staining

When biopsy tissue of MPM cases were provided, immunohistochemical staining in addition to clinical and histopathological diagnosis were performed and judged by experienced pathologists. The positive staining markers applied to determine the epithelial type of MPM included calretinin, WT1, mesothelin, thrombomodulin, D2-40, HBME-1, cytokeratin 5/6. In order to exclude the lung adenocarcinoma in the epithelial type of MPM, the negative staining of markers included CEA, TTF-1, Napsin A, Ber-EP4, MOC31 were used. The positive markers applied to determine the sarcomatoid type of MPM included CAM5.2 and AE1/AE3, and negative markers to the sarcomatoid type of MPM in order to exclude the sarcoma included desmin [12,13]. A combination of results from positive and negative markers staining was taken into consideration.

2.2.3. CT reading trial by experts

Four experts participated in independent reading of CT films of the 57 cases. They were blinded to the histopathological results on reading CT films. The CT reading sheet for ICOERD was modified with the special section for recording MPM CT features. Parenchymal and pleural abnormalities with occupational and environmental disorders were recorded according to the ICOERD guideline. The compatible MPM features and the MPM probability were recorded. The reading results were input to a database and summarized by statistical analysis.

2.2.4. Reference CT images chosen

The MPM CT features were determined by statistical analysis based on MPM feature distribution from experts' reading after the 1st workshop, and agreed by consensus by the experts at the 2nd workshop. Experts read the CT films of the 22 "Gold standard" cases out of 57 cases again at the 2nd workshop. Then at the 2nd workshop, considering that many typical MPM CT features were present on the CT films of the two "Gold standard" MPM cases out of 22 cases, experts decided these two cases as CT reference images. As a result, the CT slices from these two cases with typical features including "ue", "nt", "mt", "it", "te", "pe", "iv", "ch", "pm" with good agreement were obtained. The features such as "dl" and others, i.e., lymph node swelling, implant metastasis were chosen from other "Gold standard" cases.

2.3. Statistical analysis

The Cohen's linearly weighted kappa and Fleiss–Cohen's quadratically weighted kappa for the agreement on the 4-point scale MPM probability between experts were calculated using R software version 2.14.1(http://www.r-project.org/). The quadratically weighted kappa can be interpreted as an intraclass correlation coefficient (ICC) of reliability [14]. A kappa value < 0.20 = poor agreement, 0.21–0.40 = fair agreement, 0.41–0.60 = moderate agreement, 0.61–0.80 = good agreement and 0.81–1.00 = excellent agreement [3]. The kappa for multiple readers' agreement on MPM probability (Km) was calculated. According to the definition for MPM probability in the MPM-CT Guideline, the sensitivity for MPM is the proportion of cases for which MPM probability was recorded as Grade ≥ 2 by expert among the MPM cases, and the specificity for MPM is the proportion of cases for which probability = 1 was recorded by expert among the non-MPM cases. The sensitivity and specificity for MPM in terms of MPM probability with a cut-off point between 1 (−) and 2 (+) were calculated by SPSS 16.0 (SPSS Inc., USA). Five indefinite cases were excluded for calculation for MPM sensitivity and specificity.

3. Results

3.1. MPM-CT guideline

The MPM-CT Guideline was developed, as shown in the Supplementary Appendix A. The guideline provides the terminology of MPM features and MPM probability, the MPM judgement in terms of distribution and severity, as well as the recording the MPM CT findings on the revised ICOERD reading sheet.

3.2. The reference CT images of MPM

The MPM reference CT images are shown as in Figs. 1 through to 9. Each MPM feature was indicated by an arrow on the reference CT digital images and the reference CT hard-copied films so that physicians can easily interpret the MPM CT features.

The typical MPM CT features of the two cases for reference films are summarized in Table 2.

Table 2
Summary of the MPM CT features in the two MPM cases for MPM reference CT films.

MPM case	MPM probability	MPM CT features									
		ue	nt	it	mt	te	pe	iv	dl	ch	pm
Case 1	Grade = 4	+	+	+	+	–	–	–	+	–	–
Case 2	Grade = 4	+	+	–	+	+	+	+	+	+	+

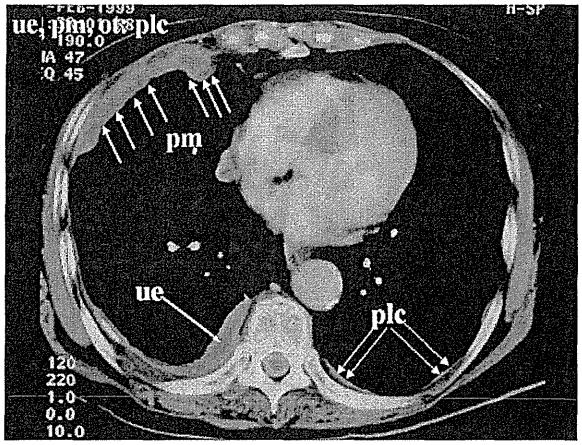

Fig. 1. The MPM features of unilateral pleural effusion ("ue"), pleural mass ("pm") and plaque calcification ("plc").

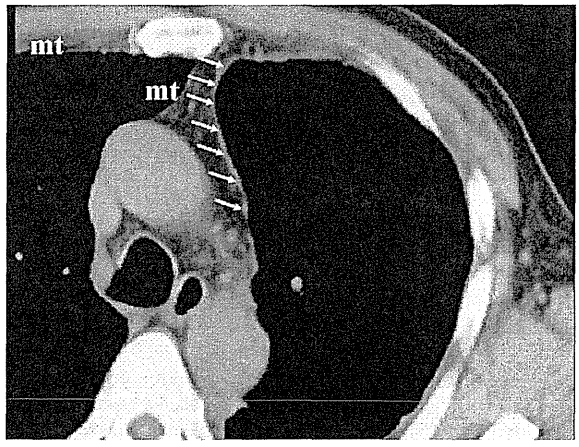

Fig. 4. Mediastinal pleural thickening ("mt").

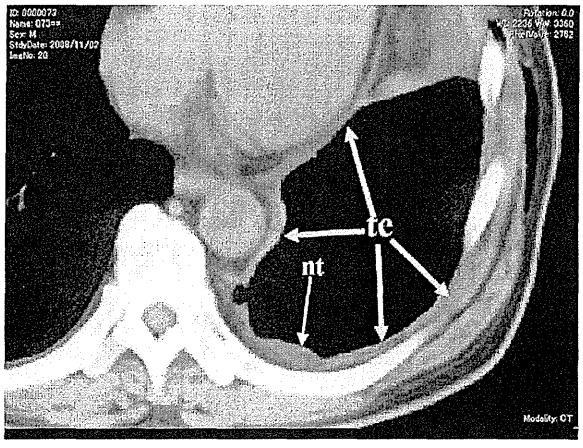

Fig. 2. Tumoral encasement of lung ("te") and nodular pleural thickening ("nt").

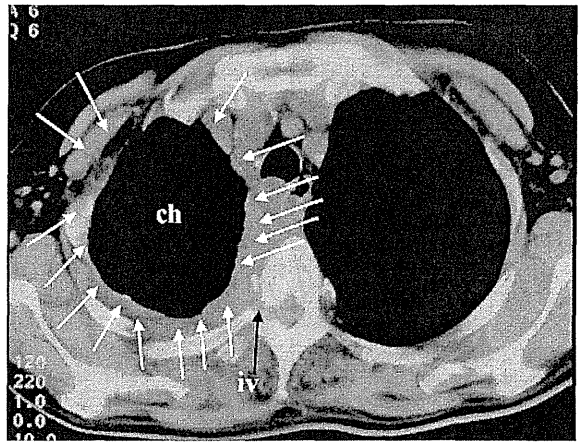

Fig. 5. Invasion "iv" of MPM into the site adjacent to vertebral column (indicated by black arrow); contract hemithorax ("ch") (indicated by white arrow).

3.3. *Development of the special section for recording features and MPM probability on the current ICOERD reading sheet*

The special section for recording MPM features and MPM probability was developed at the bottom part of the current ICOERD-classification CT reading sheet, shown as a supplement in Appendix B. This part includes the MPM type: (1) Localized type and (2) Diffuse type. The ten MPM CT features are shown on the check list. The assessment for the severity of MPM: mild, moderate and severe. The MPM probability at Grade 1 through to Grade 4 was provided at the bottom of the reading sheet for reader to finally check.

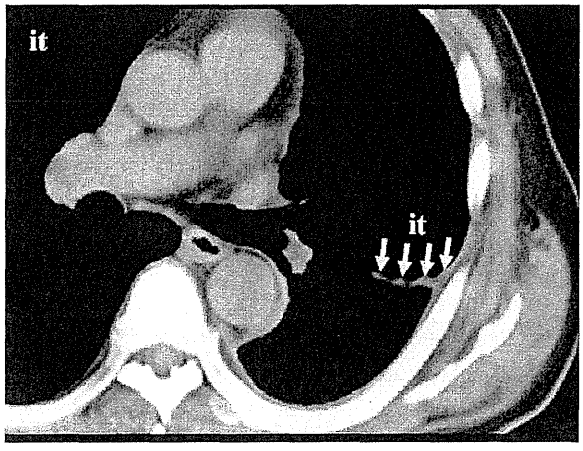

Fig. 3. Interlobar fissure pleural thickening ("it").

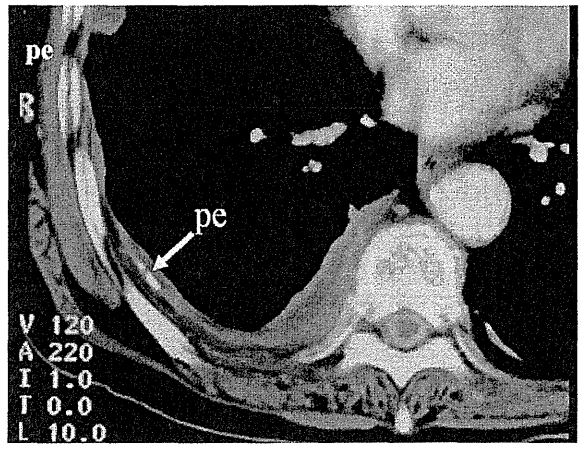

Fig. 6. Calcified plaque engulfment ("pe").

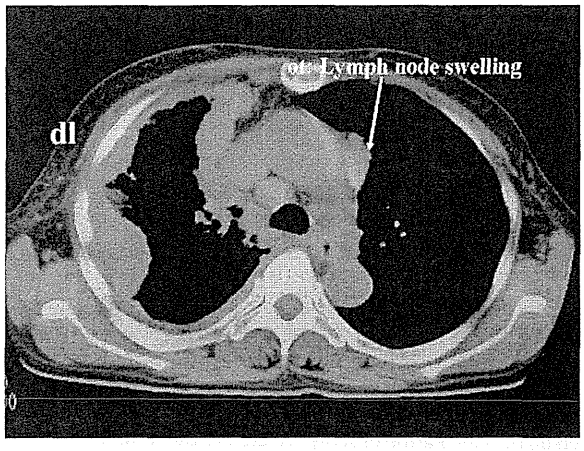

Fig. 7. Diminished lung ("dl") and lymph node swelling.

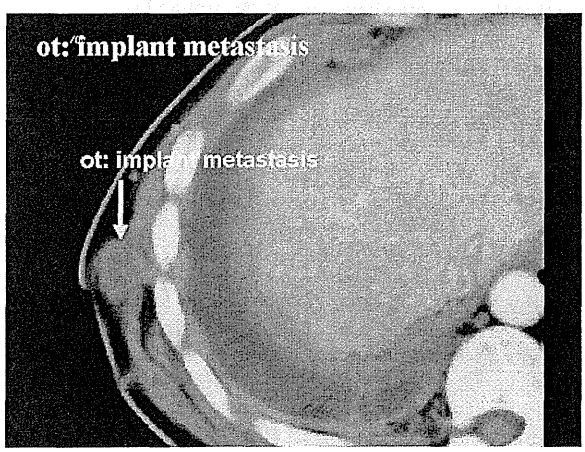

Fig. 8. Implant metastasis.

3.4. Development of the score system for recording the grade of the severity of feature

The table on the score system for recording the features and the grade of the severity of feature was developed, as shown in Appendix C. For instance, if the severity grade of one feature is 1, the score for that feature is to be given score 1. The total accumulated score of each feature is to be calculated by the summation of the score of the severity of all ten features listed in the guideline. The total accumulated score reflects the information of the CT images and contributes to the judgement of the MPM probability.

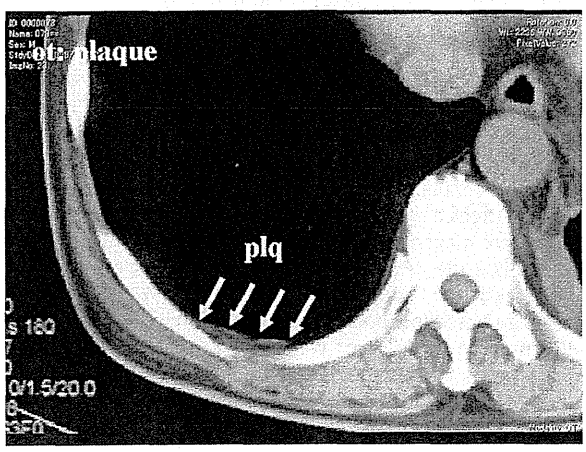

Fig. 9. Pleural plaque on the chest wall of right lung.

Table 3
The inter-reader agreement on the MPM CT features of the 57 cases by kappa statistics.

Reader	ue	nt	it	mt	te	iv	dl[a]
Reader 1 vs Reader 2	0.79	−0.25	0.42	0.65	0.54	0.28	–
Reader 1 vs Reader 3	0.47	0.34	0.30	0.54	0.64	0.28	–
Reader 1 vs Reader 4	0.51	0.51	0.62	0.64	0.35	0.28	–
Reader 2 vs Reader 3	0.43	−0.08	0.47	0.67	0.44	0.41	0.07
Reader 2 vs Reader 4	0.47	−0.11	0.48	0.70	0.47	0.51	−0.05
Reader 3 vs Reader 4	0.63	0.44	0.31	0.73	0.40	0.55	0.17
Average	0.55	0.14	0.43	0.65	0.47	0.38	0.06

[a] Reader 1 had not recorded the MPM CT feature "dl" at the CT trial because the MPM CT feature "dl" was not provided in his reading sheet.

3.5. Development of the recording flow from addition symbol to probability

When a patient is suspected to have MPM, the "ME" (mesothelioma) in the section of "Symbol" on CT reading sheet should be checked (shown as on the Supplementary Appendix B), and physicians should then go to the additional special section for MPM. Firstly they should check the MPM type by ticking "Diffuse" or "Localized" according to the distribution of the MPM; secondly they should check the features of MPM; thirdly check the assessment of severity of "ME", and finally check the MPM probability in the range of 1–4.

3.6. Supporting evidences from statistics for MPM CT references and MPM probability

3.6.1. The inter-reader agreement on MPM CT features of the 57 cases

The results of kappa statistics for the inter-reader agreement on the MPM CT features among experts of the 57 cases are shown in Table 3.

For the CT feature "ue", the agreement on this feature between the Reader 1 and Reader 2, and between Reader 3 and Reader 4 was good (kappa = 0.79 and 0.63, respectively). The agreement on "ue" among experts was moderate with average kappa 0.55. Except for the agreement between Reader 1 and Reader 3 (kappa = 0.54), the agreement on MPM CT feature "mt" between each other was good (kappa > 0.6).

For the three MPM CT features "it", "te" and "iv", the inter-reader agreement between each other was moderate or fair (average kappa = 0.43, 0.47 and 0.38, respectively). Their agreement on MPM CT feature "dl" was poor. Reader 2 had poor agreement with other three experts on MPM CT feature "nt", while other three experts had fair or moderate agreement on "nt" (kappa = 0.34, 0.44 and 0.51, respectively).

3.6.2. MPM probability agreement

The agreement on the 4-point scale MPM probability between experts is shown as in Table 4.

Good agreement on the MPM probability were observed between Reader 1 and 2, Reader 2 and 3, and Reader 2 and 4 (Cohen's linearly weighted kappa > 0.6). Agreement on the MPM probability between Reader 1 and 3 was approximate to good (Cohen's linearly weighted kappa = 0.59). The overall inter-reader agreement by experts for the MPM probability was approximate to good with an average linearly weighted kappa 0.58 ± 0.06. If the Fleiss–Cohen's quadratically weighted kappa was applied, the

Table 4
Inter-reader overall agreement on the 4-point scale MPM probability for 57 cases recorded by experts.

Inter-reader	Observed agreement	Linearly weighted kappa (95% CI)	Quadratically weighted kappa (95% CI)
Reader 1 vs Reader 2	56.14%	0.61 (0.48, 0.73)	0.76 (0.65, 0.87)
Reader 1 vs Reader 3	63.16%	0.59 (0.44, 0.75)	0.69 (0.54, 0.85)
Reader 1 vs Reader 4	47.37%	0.51 (0.37, 0.64)	0.68 (0.55, 0.82)
Reader 2 vs Reader 3	68.42%	0.65 (0.49, 0.80)	0.74 (0.58, 0.90)
Reader 2 vs Reader 4	61.40%	0.60 (0.46, 0.75)	0.71 (0.57, 0.85)
Reader 3 vs Reader 4	50.88%	0.51 (0.36, 0.66)	0.65 (0.48, 0.81)
Average	57.90%	0.58 ± 0.06	0.71 ± 0.04

Table 5
The multiple readers' agreement on the MPM probability grade by kappa statistics.

MPM probability	Km	Z	Prob > Z
Grade 1	0.60	11.15	0.0000
Grade 2	0.15	2.79	0.0026
Grade 3	0.23	4.33	0.0000
Grade 4	0.53	9.89	0.0000
Combined	0.40	12.47	0.0000

Km, kappa value of multiple readers' agreement.

agreement on MPM probability among experts can be considered as good since all quadratically weighted kappa values were over 0.60 with average 0.71.

The kappas for multiple readers' agreement on classified MPM probability Grade are shown as in Table 5.

For the MPM probability Grade 1, the Km of the agreements among four experts was 0.60. For the agreement on MPM probability Grade 4, the Km was 0.53. For the agreement on MPM probability Grade 2 and Grade 3, the Km values were 0.15 and 0.23, respectively. These results showed that the agreement on MPM probability Grade 1 and Grade 4 among the experts was better than that on MPM probability Grade 2 and Grade 3, indicated that there were great variances even among the experts for the agreement on MPM probability Grade 2 and Grade 3.

3.6.3. Sensitivity and specificity for MPM on the basis of MPM probability

The results of sensitivity and specificity for MPM by experts are shown as in Table 6.

The MPM sensitivity by experts in terms of MPM probability was quite high (average value 93.2%, $n = 44$) and the MPM specificity was satisfactory (average value 65.6%, $n = 8$).

4. Discussion

The MPM-CT Guideline was developed by the efforts of experts with the objective of providing a standardized way for recording the MPM CT features with the assistance of the MPM CT reference films for diagnosis of MPM. In the current study, the MPM probability, ranging from Grade 1 through to Grade 4 was independently determined by experts firstly by the impressions gained from CT findings among 57 cases. Additionally weight was placed on the basis of comprehensive evaluations of the CT findings, either being consistent with typical findings or being consistent with untypical findings of MPM, the severity/extent of the disease, and the location of the lung structure involvement. The number of the MPM CT features recorded by readers and the severity of each feature contribute to the judgment of the MPM probability. The score system is based on the calculation of scores related to the number of features and the severity grade of each feature, which could be considered as one kind of quantitative method. The high total accumulated score imply that the case may have high MPM probability.

Table 6
Sensitivity and specificity for MPM recorded by the experienced experts (excluded 5 indefinite cases).

Reader	Sensitivity	Specificity
Reader 1	39/44 (88.64%)	6/8 (75%)
Reader 2	41/44 (93.18%)	6/8 (75%)
Reader 3	41/44 (93.18%)	5/8 (62.5%)
Reader 4	43/44 (97.73%)	4/8 (50%)
Average	93.2%	65.6%

One limitation of this study was that very few non-mesothelioma cases in the 57 cases, i.e., either lung cancer, other malignancies or benign diseases had only clinical diagnoses, with no pathological examination record being available, because neither histopathological nor cytological examinations took place in these patients. This might affect judgement of the specificity for MPM in terms of MPM probability. The MPM cases included in the study were, however, confirmed by histopathological or cytological examination, therefore the results of the calculation of the sensitivity for MPM by experts was reliable and credible.

For the MPM CT features, although low kappa for "nt" was observed between Reader 2 and other three readers, he had good agreement on MPM probability with other readers (quadratically weighted kappa = 0.71, 0.74 and 0.76, respectively). In the case that the majority of the CT features had been identified, even one of the CT features was missed, it may not affect the final correct recording the MPM probability too much, because the interpretation of CT images depends on the overall evaluation of the majority of CT features. For the CT feature "dl", it was new proposed MPM CT feature in this guideline, expert may had missed this feature at the reading trial, resulted in low kappa value for it among three readers.

In the current study, the statistical analysis of experts' CT reading results showed good agreement (average linearly and quadratically weighted kappa were 0.58 and 0.71, respectively) on the 4-scale MPM probability by experts and high MPM sensitivity (93.2%). This suggests that the currently developed MPM-CT Guideline using the recording system may be reliable in clinical practice. Furthermore, the MPM reference CT images could help physicians identify the MPM features.

All these MPM cases included in the current study were confirmed certainly ascribed to the cause of the environmental asbestos pollution, mainly by exposure to crocidolite fiber from the Kubota asbestos factory and not due to other factors. Therefore, the causality between the onset of the MPM and the carcinogenicity of asbestos was explicit.

The methods of immunohistochemical staining are valuable for the accurate diagnosis of MPM and considered as the gold standard in this study [12]. At the present study, there were 22 definite MPM cases as the "Gold standard", and out of which 2 cases were selected and used for choosing reference films. Therefore, the MPM CT features on these cases were reliable, useful and applicable. Most of the features selected are suggestive of MPM and frequently observed on the CT images of MPM. The two definite MPM cases did contain the most typical MPM features, and they can systematically and comprehensively provide the physicians with much

information of the typical MPM CT features, and therefore contribute to the diagnosis of MPM.

The TNM (tumor-node-metastasis) staging system for MPM proposed by International Mesothelioma Interest Group (IMIG) was released in the year 1995 [15], wherein MPM is to be classified into a stage I through to IV by examination by CT, MRI and thoracoscopy. This staging system describes the anatomical extent of disease, and can facilitate the selection of patients for surgical resection. It also permits accurate assessment of new treatment regimens. This staging system was designed to provide the framework for proper analysis of the results of prospective clinical trials aimed at improving the prognosis of MPM.

The Guideline of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma was published in the year 2010 [16], and recommendations were made for performing thoracoscopy to obtain an earlier and reliable diagnosis of MPM, classifying MPM stage using the IMIG TNM stage system, and a three step pre-treatment assessment before combination treatments for MPM including surgery, radiotherapy and chemotherapy. It was recommended that a diagnosis of MPM should always be based on immunohistochemical examination using specific markers. This guideline mainly serves for chest physicians and surgeons in the management of the MPM.

On the other hand, the aim of our MPM-CT Guideline was to improve the radiologists and physicians reading proficiency of MPM CT by identifying of the MPM CT features. Although the CT findings are not pathognomonic, they can provide a valuable clue in supporting the diagnosis of MPM for patients with a history of asbestos-exposure. In particular, for those patients who do not want invasive biopsy, CT is the preferred non-invasive diagnostic method.

There may be little difference between the terminology of some features listed in the current MPM-CT Guideline and those reported in the literature [17,18]. "Circumferential pleural thickening" in the literature [17] may emphasize the widely spread pleural thickening involved in MPM, while the "ch" focus the hemithorax being contracted due to the MPM [18]. Similarly, the feature "te" used in the current MPM-CT Guideline focuses on the meaning of tumoral encasement to the lung by MPM. The features "te", "ch" and "dl" imply that MPM advances and the severity of MPM becomes increased to high. In these cases MPM occupies the thorax, involves the hemithorax leading to contraction and the lung volume gets reduced.

Calcified pleural plaques of MPM patients may become engulfed by the primary tumor, causing the tumor to mimic calcified MPM [10], described as "calcified plaque engulfment" ("pe") in the current guideline. For the patient with a history of asbestos exposure, calcified pleural plaques with a large pleural effusion without mediastinal shift or volume loss of the ipsilateral chest are highly suggestive of MPM [19]. MPM has a propensity for spread along the fissures; hence the feature of inter-lobar fissure pleural thickening ("it") was incorporated in the current study.

The current authors' CT features as well as the published ones are useful to distinguish MPM from benign pleural disease. Lee et al. [20] reviewed the CT features of nine proven cases of benign fibrous MPM: while they found that neither invasion into the lung parenchyma nor invasion into chest wall was noted; there was no pleural effusion. These revealed that invasion and effusion may rarely be seen in benign pleural mesothelioma.

It is important to differentiate between benign asbestosis pleurisy and an effusion associated with MPM. Garg and Lynch [19] stated that the MPM shows "freezing the hemithorax" as it grows. This mechanically prevents the contralateral mediastinal shift associated with a large effusion. On the other hand, benign asbestos pleurisy is usually recurrent and bilateral, usually does not affect the mediastinal pleura.

The current MPM-CT Guideline allows the physicians to make appropriate judgement for the probability of diagnosing a case as MPM. For instance, physicians can make practical comparison of the patients' CT images with those on the reference CT images, and check on the features mostly similar to either of the reference CT images, and then record the probability of MPM. We are planning to evaluate these useful functions of the current MPM-CT Guideline among inexperienced radiologists.

5. Conclusion

The developed MPM-CT Guideline and the reference CT films of MPM may serve as good tools in education, clinical practice, and secondary prevention to improve the radiologists or physicians' proficiency in diagnosis of MPM. The guideline should facilitate recognition of MPM CT features that contribute to early diagnosis for MPM in radiologists, occupational physicians and chest physicians in health surveillance, screening in asbestos-exposed workers and residents.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2012.08.008.

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Original Article

A Clinicopathological Study of Resected Small-Sized Squamous Cell Carcinomas of the Peripheral Lung: Prognostic Significance of Serum Carcinoembryonic Antigen Levels

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Purpose: The purpose of this retrospective study was to evaluate common clinicopathological factors and clarify the prognostic factors of small-sized peripheral-lung squamous cell carcinomas.

Methods: We retrospectively reviewed 71 patients with peripheral squamous cell carcinoma ≤3 cm in diameter, who were surgically treated between January 1989 and December 2010. Patients undergoing partial lung resection without lymph node dissection were excluded. The median follow-up for living patients was 63 months.

Results: The overall 3- and 5-year survival rates were 83.9% and 74.7%, respectively. Although the ROC curve of serum carcinoembryonic antigen (CEA) levels showed marginally significance ($P = 0.050$), multivariate analyses revealed that age ($P = 0.043$), lymph node metastasis ($P = 0.004$), and preoperative serum carcinoembryonic antigen (CEA) level ($P = 0.037$) were independent prognostic factors. For pathologic N0 patients, there was a significant difference for recurrence-free survival based on CEA levels: patients with normal CEA levels ($n = 40$), 5-year-recurrence-free rate = 93.5%; elevated CEA ($n = 14$), 5-year-recurrence-free rate = 72.7% ($P = 0.0160$). The distribution of tumor cells immunoreactive for CEA was significantly associated with serum CEA levels ($P = 0.033$).

Conclusion: Age, lymph node metastasis, and serum CEA level are independent prognostic factors for small-sized peripheral-lung squamous cell carcinoma.

Keywords: squamous cell cancer, lung cancer, carcinoembryonic antigen

Introduction

Among small-sized peripheral-lung carcinomas, adenocarcinoma is the most common histological type. The incidence of squamous cell carcinomas arising from peripheral lung has been increasing, although in the past, most squamous cell lung carcinomas were reported to develop in the central region of the lung.[1–3] While the characteristics of small-sized peripheral adenocarcinomas have been thoroughly investigated, there have only been a few reports published on the prognostic factors of small-sized peripheral-lung squamous cell carcinomas.[3–6]

In a 2006 study of patients with small (≤30 mm in diameter) peripheral squamous cell tumors,

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Maeshima et al. proposed that the size of the minimal tumor nest (defined as the smallest group of tumor cells observed in the primary tumor), a background of typical interstitial pneumonia, and lymph node metastasis were significant clinicopathological prognostic factors.[5] In 2003, Funai et al. proposed a classification of 3 subgroups, which was based on histological growth patterns and the conditions of the elastic framework of the alveolar septa; these investigators found that alveolar space-filling tumors were noninvasive cancers, irrespective of tumor size.[3]

Although the factors described in these studies may be useful prognostic factors for small-sized peripheral-lung squamous cell carcinoma, this has not yet been confirmed. In this retrospective study, we evaluated common clinicopathological variables of patients with small-sized peripheral-lung squamous cell tumors in an attempt to identify prognostic factors.

Materials and Methods

Patients

During a 20-year period from January 1989 through December 2010, 2681 patients underwent surgical resection for primary lung carcinoma at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research in Tokyo. Patients with synchronous double cancers and patients who underwent partial lung resection without lymph node dissection because of conditions such as cardiac or pulmonary disorders were excluded. A total of 71 patients with peripheral squamous cell carcinoma ≤3 cm in diameter were included in this analysis. None of these patients had received preoperative treatments. All surgical specimens were pathologically demonstrated to be free of tumor cells at the surgical margins.

Peripheral-lung squamous cell carcinoma was defined as a tumor located in or more peripheral to the fourth branching bronchus. Tumor histology was determined using the World Health Organization classification. Pathological stage was determined according to the seventh edition of the TNM classification for lung cancer.

A total of 64 patients underwent lobectomy (one or more lobes) with lymph node dissection, and 7 patients underwent segmentectomy with lymph node sampling. The outcomes for all 71 patients were determined over a median follow-up time for surviving patients of 63 months (range: 0 to 186 months).

The following data were extracted and analyzed from patient files: age, sex, smoking index (<1000 vs. ≥1000), pathologic stage (IA vs. IB-IIIB), tumor size (10–20 mm vs. 21–30 mm), nodal status, vessel invasion, pleural invasion, differentiation (well- or moderately-differentiated vs. poorly-differentiated), preoperative serum carcinoembryonic antigen (CEA) levels, and preoperative serum squamous cell carcinoma antigen (SCC) levels.

Serum CEA levels and CEA immunostaining

Serum CEA levels were determined as part of the routine preoperative evaluation using a microparticle enzyme immunoassay (MEIA) and Abbot AxSYM instrumentation. To elucidate why serum CEA levels were elevated in patients with small-sized peripheral-lung squamous cell carcinoma, tumor specimens were immunostained for CEA expression. After pathologic assessment of hematoxylin-and-eosin stained slides of sections of surgical specimens, slides with the largest tumor diameters were selected for CEA immunostaining. Staining of slides from all 65 patients was carried out using EnVision+ kits (Dako, Glostrup, Demark) and an anti-CEA mouse monoclonal antibody (Code 422771; Nichirei, Tokyo, Japan). The percentage of CEA-immunoreactive tumor cells was assessed by a pathologist (Y.I) who was blinded to clinical information. Cases that were examined were classified into 4 groups for analysis, according to percentage of CEA-positive cells (0%, 1–5%, 6–50%, >50%).

Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity of preoperative serum CEA levels for tumor recurrence. The Youden index was used to identify the serum CEA level cut-off value. The duration of recurrence-free survival was determined from the date of surgery to the date of follow-up or recurrence. Five-year recurrence-free survival was determined using the Kaplan-Meier method. Univariate analyses were performed using the log-rank test, and the Cox proportional hazards model was used for multivariate analysis. Variables from univariate analysis with a significance level ≤0.10 were entered into the multivariate model, and backward elimination was used to select variables for the final model, which included variables with a

Table 1 Clinical characteristics of 71 patients with resected squamous cell carcinoma (≤3 cm in diameter)

Characteristics	Values
Age (years)	47–85, median 69
Gender	
Male/Female	62/9
Pathological stage	
IA/IB	44/6
IIA/IIB	8/4
IIIA/IIIB	7/2
pN factor	
N0/N1/N2/N3	54/8/8/1
Tumor size (mm)	
Range	10–30, median 23
Type of surgery	
Pneumonectomy/Bilobectomy/Lobectomy/Segmentectomy	2/3/59/7

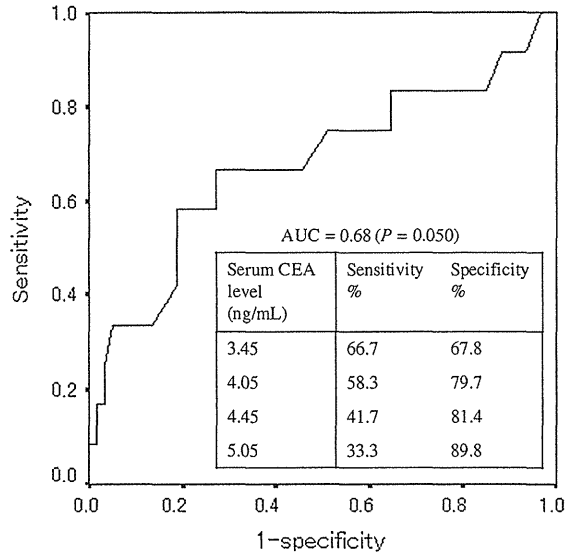


Fig. 1 Receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity and specificity of preoperative serum carcinoembryonic antigen (CEA) levels for tumor recurrence. The Youden index was used to identify the optimal cutoff point of 4.05 ng/mL for predicting recurrence.

significance value of ≤0.05. The chi-square test was used for comparison of proportions. All analyses were performed using SPSS software (SPSS Inc., Release 11.0.1J). Differences were considered significant for *P*-values <0.05.

Results

All patients were smokers. Their clinicopathological characteristics are summarized in **Table 1**. The overall 3- and 5-year survival rates of the 71 evaluated patients were 83.9% and 74.7%, respectively. A total of 27 patients died from the following: recurrence ($n = 10$), perioperative acute lung injury ($n = 1$), secondary lung cancer ($n = 5$), other cancers ($n = 4$), pneumonia ($n = 4$), and other diseases ($n = 3$). Because there were more non-disease-specific deaths than disease-specific deaths, recurrence-free survival rates were used to determine prognostic factors. Recurrence-free 3- and 5-year survival rates were 89.2% and 81.2%, respectively. Twelve patients developed recurrence (16.9%), including 6 locoregional and 6 distant recurrences.

The ROC curve of CEA levels had an area under the curve of 0.680 ($P = 0.050$, **Fig. 1**). The Youden index identified 4.05 ng/mL as the optimal cut-off CEA value for predicting recurrence. Moreover, to determine the best preoperative serum CEA level cut-off point for the probability of recurrence-free survival, 4 values were evaluated: 3.5, 4.0, 4.5, and 5.0 ng/mL, and 4.0 ng/mL provided the lowest log-rank *P*-value. For evaluation of preoperative serum SCC levels, a cut-off value of 1.5 ng/mL was used. This value was determined by the serum SCC assay manufacturer, and no other values provided a significant difference in our analysis (data not shown).

Univariate analyses of the clinicopathological factors listed in **Table 2** showed that pathologic stage, presence of lymph node metastasis, vessel invasion, and serum CEA level (≤4.0 vs. >4.0 ng/mL) were significant prognostic factors, while age was a marginally significant prognostic factor. In contrast, sex, smoking index, tumor size (≤20 vs. >20 mm), lymphatic invasion, pleural invasion, differentiation, and serum SCC level (≤1.5 vs. >1.5 ng/mL) were not significant prognostic factors.

Multivariate analysis showed that age ($P = 0.043$), lymph node metastasis ($P = 0.004$), and serum CEA level ($P = 0.037$) were independent prognostic factors; pathologic stage and vessel invasion were eliminated from the final model (**Table 3**).

Figure 2 shows the overall survival curves and recurrence-free survival curves grouped by CEA concentrations. There was a significant difference for recurrence-free survival ($P = 0.0097$), but not for overall survival ($P = 0.30$).

Figure 3 shows the recurrence-free survival curves for pathologic N0 patients with small-sized peripheral squamous cell lung carcinoma grouped by CEA

Table 2 Clinico-pathological variables as possible prognostic factors (univariate analysis)

Clinico-pathological variables	Number	5-year disease-free survival	Univariate analysis (p-value)
Age	71		0.0540
Sex			
Male	62	80.7%	0.8208
Female	9	88.9%	
Smoking index			
100–1000	31	84.9%	0.6306
1000<	40	79.1%	
Pathologic stage			
IA	44	91.0%	0.0213
IB–IIIB	27	65.9%	
Tumor size (mm)			
10–20	24	90.3%	0.4232
21–30	47	76.4%	
Lymph node metastasis			
Negative	54	88.0%	0.0075
Positive	17	57.5%	
Lymphatic invasion			
Negative	58	85.6%	0.1109
Positive	13	62.5%	
Vessel invasion			
Negative	27	95.8%	0.0445
Positive	44	71.1%	
Pleural invasion			
Negative	62	84.3%	0.2523
Positive	9	64.8%	
Differentiation			
Well or moderate	40	82.3%	0.3188
Poor	31	79.6%	
Serum CEA (ng/ml)			
≦4.0	52	88.2%	0.0097
>4.0	19	63.5%	
Serum SCC (ng/ml)			
≦1.5	40	83.9%	0.4267
>1.5	19	71.4%	
Unknown	12		
Total	71		

CEA: carcinoembryonic antigen; SCC: squamous cell carcinoma antigen

concentrations. There was a significant difference for recurrence-free survival based on CEA levels: patients with CEA ≤4.0 ng/mL ($n = 40$), 5-year recurrence-free rate = 93.5%; patients with CEA >4.0 ng/mL ($n = 14$), 5 year recurrence-free rate = 72.7% ($P = 0.0160$).

Among pathologic N-positive patients, there was no significant difference for recurrence-free survival based on CEA levels: patients with CEA ≤4.0 ng/mL ($n = 12$), 5-year-recurrence-free rate = 66.3%; patients with CEA >4.0 ng/mL ($n = 5$); 5-year-recurrence-free rate = 21.9% ($P = 0.3057$).

Table 3 Multivariate analysis of clinicopathological variables as prognostic factors of recurrence-free survival

Prognostic factors	Hazard ratio	95% CI	P
Age	1.118	1.015–1.232	0.024
Lymph node metastasis	5.281	1.648–16.922	0.005
Serum CEA	4.228	1.304–13.701	0.016

CI: confidence interval; CEA: preoperative serum carcinoembryonic antigen

Sixty-eight percent of the 65 tumors analyzed were positive for CEA staining. The distribution of tumor cells immunoreactive for CEA was significantly associated with serum CEA levels ($P = 0.033$, **Table 4**).

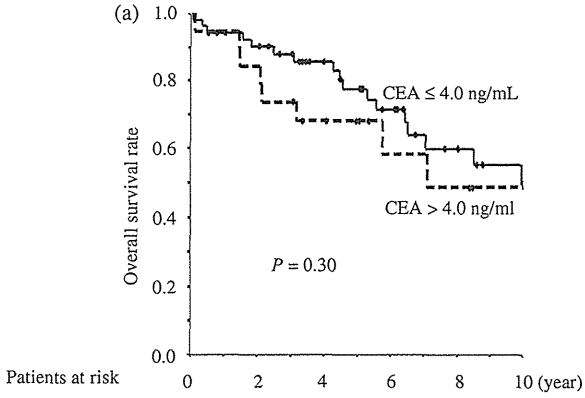
Discussion

In this study, multivariate analysis identified age, lymph node metastasis, and preoperative serum CEA concentration as prognostic indicators for small-sized (≤3 cm) squamous cell carcinoma of the peripheral lung. Age and lymph node metastasis had also been previously reported to be prognostic factors for squamous cell carcinoma of the peripheral lung.[5]

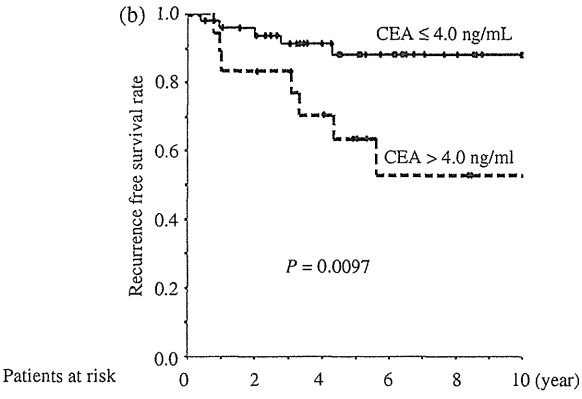
There have been several studies reporting that age was an independent prognostic factor for non-small cell lung cancer.[5,7–9] Some of these studies also showed that age was an independent prognostic factor for pathologic stage I non-small cell lung cancer.[7,8] Another study showed that younger patients with non-small cell lung cancer had significantly better recurrence-free survival than older patients. The investigators of that study suggested that the reasons that age was an independent prognostic factor might involve the differences between activated oncogenic pathways and the types of tumor microenvironment in young and old patients.[9]

Our study found that the serum CEA level was an independent prognostic factor for patients with small-sized peripheral-lung squamous cell carcinoma. Not only is this the first study to evaluate serum CEA levels in patients with peripheral-lung squamous cell carcinoma, it is also the first to show a significant association between CEA levels and prognosis.

Serum CEA levels have been shown to be elevated in patients with squamous cell carcinoma of the esophagus and the uterine cervix.[10–12] Moreover, one report



≤4.0 ng/mL	52	44	32	22	14	8
>4.0 ng/mL	19	16	11	6	5	3

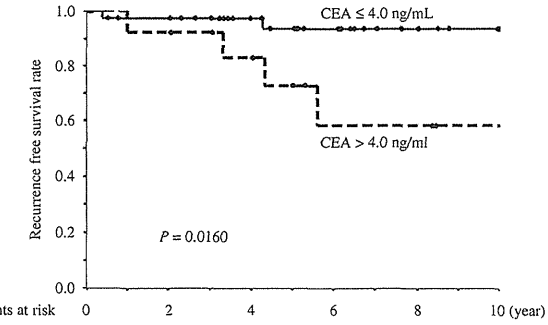


≤4.0 ng/mL	52	43	31	22	14	8
>4.0 ng/mL	19	15	11	5	5	3

Fig. 2 Overall survival curves (**a**) and recurrence-free survival curves (**b**) grouped by carcinoembryonic antigen (CEA) concentrations.

showed that serum CEA was associated with clinical stage and distant metastasis in esophageal cancer,[11] and another report showed that the pretreatment serum CEA level was a prognostic factor in cancer of the uterine cervix.[12] Although no patient in our study had a past history of other carcinomas, because it is sometimes difficult to differentiate histologically between primary squamous cell carcinoma of the lung and metastatic squamous cell carcinoma from other organs, the possibility of metastatic disease should be considered when diagnosing lung nodules associated with high serum CEA levels.

Most studies of head and neck squamous cell carcinomas have shown that the serum CEA level was not a prognostic factor,[13,14] and some reports demonstrated that the CEA level was more reflective of the alcohol



≤4.0 ng/mL	40	36	26	19	12	7
>4.0 ng/mL	14	12	9	4	4	2

Fig. 3 Recurrence-free survival curves of pathologic N0 patients with small-sized peripheral-lung squamous cell carcinoma based on preoperative serum carcinoembryonic antigen (CEA) levels.

consumption and smoking habits of their patients than disease status.[15,16] In our study, the serum CEA level was not related to the smoking index.

Elevated serum CEA levels have been observed in some studies of squamous cell lung carcinoma, regardless of tumor location.[17–20] Whether or not the serum CEA level is a prognostic factor for this tumor type remains controversial, and the preoperative serum CEA level cut-off value for squamous cell carcinoma of the peripheral lung has not been clarified.

In this study, the ROC curve of CEA levels for predicting recurrence showed marginally significance ($P = 0.050$, **Fig. 1**). Although this data did not show CEA levels was an absolutely significant indicator for prediction of recurrence, our results showed a significantly low recurrence-free survival rate for patients whose preoperative CEA concentration was >4.0 ng/mL. It was suggested that the serum CEA levels was one of the promising predictive factors for tumor recurrence in small peripheral squamous cell carcinomas. On the other hand, there was no significant difference for overall survival based on CEA levels. This may be explained the fact that there were more non-disease-specific deaths than disease-specific deaths.

Tomita et al. concluded that the serum CEA level was not a prognostic factor for squamous cell carcinoma of the lung.[19] In contrast, Tas et al. showed that the serum CEA level was significantly elevated in patients with stage IV squamous cell carcinoma;[17] Kulpa et al. showed that serum CEA levels were significantly different between operable and inoperable patients,[18] and Body et al. showed that an elevated

Table 4 Relationship of preoperative serum carcinoembryonic antigen (CEA) levels and tumors with specified percentages of CEA-positive cells

	Percentage of CEA immunoreactive tumor cells				
	0%	1–5%	6–50%	>50%	*P*
Serum CEA (ng/ml)					
≦4.0	17	20	9	0	0.033
>4.0	4	7	5	3	

CEA level was an adverse prognostic factor for squamous cell carcinoma of the lung.[20] However, these reports did not separately evaluate central-type versus peripheral-type tumors. In previous reports, the prevalence of peripheral-type lesions among all squamous cell carcinomas of the lung was reported to range from 15% to 30%[3,21]; thus, the varied results were likely influenced by the predominance of central-type lesions. Compared with the conflicting data from the reports we have described, our study focused on peripheral-type tumors only and found that an elevated CEA level was a prognostic factor.

Some reports have evaluated serum CEA levels in small-sized non-small cell lung carcinomas.[22–24] These studies indicated that the serum CEA level was a good predictor of a poor prognosis; however, the majority of these studies only examined adenocarcinomas. Matsuguma et al. found that the serum CEA level was a useful prognostic factor not only for adenocarcinoma, but also for nonadenocarcinomas, including squamous cell carcinoma and nonsquamous cell carcinoma, in patients with pathologic stage I non-small cell lung cancers.[22] These results plus our findings on small-sized peripheral-lung carcinomas that were not only adenocarcinomas but also squamous cell carcinomas, indicate that the serum CEA level may be a useful prognostic factor.

Our study found that a high serum CEA level was an adverse prognostic factor, particularly for pathologic N0 patients. Some previous studies reported that the serum CEA level was associated with advanced stages of lung squamous cell carcinoma,[17,18] but not with early stages. However, other studies found that the serum CEA level was a prognostic factor for early-stage non-small cell carcinoma or adenocarcinoma.[22–24]

There have been some studies of small-sized peripheral adenocarcinomas reporting that a high serum CEA level was a risk factor for lymph node metastases.[23,25] In our study, the serum CEA level was not associated with lymph node metastases. Furthermore, smoking index, differentiation, vascular invasion, lymphatic invasion, and tumor size were not associated with serum CEA levels.

Because of our findings, we examined tumor specimens for CEA staining. Limited data on CEA expression in lung cancer specimens are available. Some studies demonstrated tumor CEA positivity in a high proportion of squamous cell carcinomas of the lung.[26–28] Moreover, one study has reported that peripheral-type tumors more frequently expressed CEA than the central type (but the differences were not significant).[28] The results of these studies are similar to our results. In addition, one study found an association between prognosis and the immunostaining pattern of CEA in adenocarcinoma, but we were not able to find any differences in staining patterns in the squamous cell carcinomas of our patients.[26]

Giulia et al. found that CEA expression was significantly associated with serum CEA levels in patients with non-small cell lung carcinoma, but not in patients with squamous cell carcinoma.[26] In our study, however, the distribution of tumor cells immunoreactive for CEA was significantly associated with serum CEA levels ($P = 0.033$, **Table 4**). We think that the different finding in our study may reflect the fact that we only investigated peripheral-type squamous cell carcinomas.

In conclusion, age, lymph node metastasis, and preoperative serum CEA level are independent prognostic factors for small-sized peripheral-lung squamous cell carcinoma.

Disclosure Statement

The authors have no conflicts of interest.

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BJUI
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Characteristics and clinical significance of prostate cancers missed by initial transrectal 12-core biopsy

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Study Type – Diagnostic (exploratory cohort)
Level of Evidence 3a

What's known on the subject? and What does the study add?
Initial transrectal 12-core biopsy has a small but definite risk of missing anterior significant prostate cancers irrespective of age, PSA, prostate volume and DRE findings.

Our study yields valuable information for diagnosis and treatment decision of prostate cancer based on transrectal 12-core biopsy.

OBJECTIVE

- To characterize prostate cancers missed by initial transrectal 12-core biopsy.

PATIENTS AND METHODS

- Between 2002 and 2008, 715 men with prostate-specific antigen levels in the range 2.5–20 ng/mL or abnormal digital rectal examination underwent three-dimensional 26-core prostate biopsy (i.e. a combination of transrectal 12-core biopsy and transperineal 14-core biopsy) on initial examination.
- Of the 257 patients diagnosed with cancer, 120 patients subsequently underwent radical prostatectomy.
- Cancers were grouped into TR12-negative cancers (i.e. not detected through transrectal 12-core biopsy but detected through transperineal 14-core biopsy) and TR12-positive (i.e. detected through transrectal 12-core biopsy) cancers.
- Clinicopathological characteristics of the TR12-negative and TR12-positive cancers were evaluated.

RESULTS

- TR12-negative cancers comprised 21% of the three-dimensional 26-core biopsy-detected cancers.
- The frequency of cancers with a biopsy Gleason score ≤6 and that of cancers with a biopsy primary Gleason grade ≤3 was higher in TR12-negative cancers, at 58% and 83%, respectively, than in TR12-positive cancers, at 25% ($P < 0.001$) and 53% ($P < 0.001$), respectively.
- The median number of positive cores in TR12-negative cancers was two out of 26.
- TR12-negative cancers were more frequently located anteriorly than posteriorly.
- The incidence of the TR12-negative cancers was not associated significantly with any clinical variable.

CONCLUSION

- Many of the cancers missed by initial transrectal 12-core biopsy are probably low-grade and low-volume diseases, although initial transrectal 12-core biopsy has a small but definite risk of missing anterior significant cancers.

KEYWORDS

biopsy, prostatectomy, prostatic neoplasm

INTRODUCTION

In a pattern consistent with the worldwide trend toward choosing extended over non-extended prostate biopsy methods, transrectal 12-core prostate biopsy (TR12PBx) is currently one of the most preferred biopsy methods for detecting prostate cancers. A systematic review of prostate biopsy methods noted that TR12PBx strikes a satisfactory balance with sufficiently high rates of cancer detection and sufficiently low rates of biopsy-associated comorbidity, and that taking more than 12 cores adds no significant benefit [1]. TR12PBx also meets the criteria for initial biopsy provided by the representative clinical guidelines [2,3]. Yet several studies have reported that repeat biopsy after negative initial extended transrectal biopsy detects prostate cancer in 17–21% of men [4–6], suggesting that these initial extended transrectal biopsies may miss a substantial number of cancers.

To clarify the incidence and clinical importance of cancers missed by TR12PBx, it is necessary to analyze the results obtained using biopsy protocols that include not only all of the TR12PBx sampling sites, but also

additional sampling sites. To the best of our knowledge, there are currently three biopsy protocols that meet these requirements. The first is three-dimensional 26-core prostate biopsy (3D26PBx), a combination of transperineal 14-core prostate biopsy (TP14PBx) and TR12PBx (Fig. 1), introduced by our group [7–9]. In a previous analysis of 321 men examined through 3D26PBx, we reported that 3D26PBx increased cancer detection by 24% compared to TR12PBx [7]. The second is transrectal 21-core biopsy [10]. The transrectal 21-core biopsy can detect significantly more cancers (increased detection of 9.8%) than the TR12PBx. The third is transrectal 14-core biopsy (TR12PBx plus two extreme anterior apical biopsy sites) [11]. The addition of only two extreme anterior apical sampling sites to TR12PBx increased the cancer detection rate by 7.5%. Although these studies mainly focused on cancer detectability, characteristics of cancers missed by TR12PBx have not been fully assessed to date.

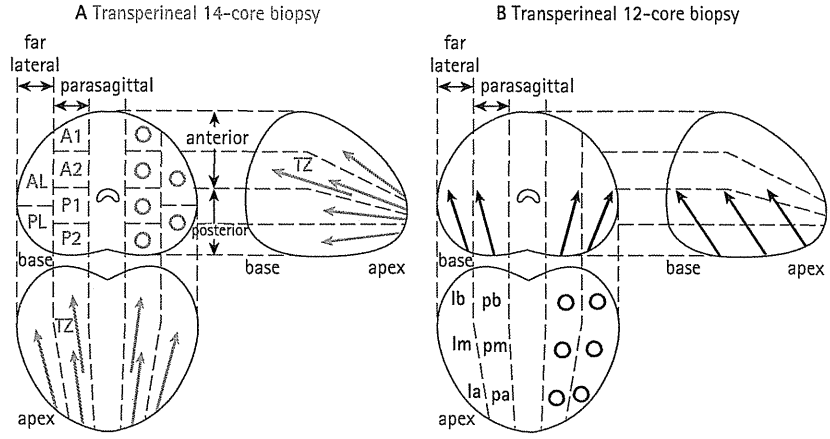
When a patient undergoes an initial TR12PBx and the result is negative for cancer, how much risk does he have for a clinically important cancer that is missed? What are characteristics of the cancers missed by TR12PBx? To address these questions, we evaluated the characteristics of cancers that were detected or missed by TR12PBx in a cohort of 715 men undergoing 3D26PBx.

PATIENTS AND METHODS

PATIENTS

Between June 2002 and June 2008, 757 men prospectively underwent 3D26PBx as an initial biopsy at our institutions because of higher PSA levels >2.5 ng/mL and/or abnormal DRE findings in a clinical setting. Patients were excluded if they had diabetes mellitus or any rectal disease (e.g. uncontrolled hemorrhoids) because of the high risk of infection or rectal bleeding. In principle, those with apparently palpable mass, age ≥75 years, PSA level ≥20 ng/mL or poor state of health were excluded from recommendation for 3D26PBx. Written informed consent was obtained from all patients and 3D26PBx was performed under spinal, general or, recently, local anaesthesia [12], as described previously [7–9]. Of these 757 patients, 42 were excluded from the current study because of palpable stage T3/4 tumours, PSA level ≥20 ng/mL or lack of baseline clinical data. A total of 715 patients were subjected for analyses.

FIG. 1. Transverse, sagittal and coronal projections of three-dimensional 26-core prostate biopsy (3D26PBx), a combination of transperineal 14-core prostate biopsy (TP14PBx) and transrectal 12-core prostate biopsy (TR12PBx). The sampling sites are named: anterior 1 (A1), anterior 2 (A2), posterior 1 (P1), posterior 2 (P2), anterolateral (AL), posterolateral (PL) and transition zone (TZ) in TP14PBx; parasagittal apex (pa), parasagittal midprostate (pm), parasagittal base (pb), lateral apex (la), lateral midprostate (lm) and lateral base (lb) in TR12PBx.



PATHOLOGICAL EVALUATION

All biopsy and radical prostatectomy (RP) specimens were re-evaluated by a single pathologist according to the 2005 International Society of Urologic Pathology Consensus Conference on Gleason Grading [3,13,14]. Each biopsy core was individually labelled so that the location of cancer-positive cores could be analyzed. All RP specimens were processed as described previously [9]. Tumour volume, Gleason score (GS), pathological stage and location of each isolated cancer focus in the RP specimens were recorded. Significant cancer was defined as a tumour volume ≥0.5 mL and/or Gleason pattern 4/5 and/or extraprostatic extension. A significant cancer focus was defined as one fulfilling the above-mentioned criteria for significant cancer, and was extensively evaluated. For analysis of cancer location, the prostate was divided into anterior, posterior and apical regions. The apical region was defined as the most inferior 10 mm of the gland. The remaining part of the gland was divided into anterior and posterior regions at the height of the urethra [15]. When a significant focus lay astride two regions, it was assigned to both regions.

DATA ANALYSIS

All cancers were grouped into two mutually exclusive groups: TR12-negative (i.e. not detected through transrectal 12-core biopsy but detected through transperineal 14-core biopsy) and TR12-positive (i.e. detected through transrectal 12-core biopsy) cancers. The former group did not have cancer-positive cores within the TR12PBx scheme but had cancer-positive cores within the TP14PBx scheme, and the latter had cancer-positive cores within the TR12PBx scheme. These two groups were compared with regard to patient age, PSA level, prostate volume, DRE findings, biopsy GS and the number of positive cores. In patients treated with RP, the two groups were also compared with regard to RP GS, pathological stage, tumour volume, frequency of significant cancer and cancer location. The study cohort was categorized by age, PSA level, prostate volume and DRE findings to identify any patient subgroups in which TR12PBx did not exhibit sufficient cancer detection rates.

STATISTICAL ANALYSIS

All analyses were performed using JMP, version 7 (SAS Institute Inc., Cary, NC, USA). Continuous variables were analyzed using Mann–Whitney's *U*-test. Categorical variables were analyzed using the chi-squared test or Fisher's exact test. The