10-year PCA-specific mortality (PCSM) of the 290 men with high-risk PCA was only 10.3% at a median follow-up of 8.18 years. It may be difficult to compare these reports directly because many patients in the cohort of Boorjar et al. (15) had received any adjuvant treatments after RP. Moreover, the definition of high-risk PCA also differed between these two reports (10,15). Considering these three reports, including our study, however, the 10-year CSS rate of high-risk PCA treated with RP is ~90%.

Some investigators have demonstrated the various advantages of RP for high-risk PCA (9,15,16). They insist that RP for high-risk PCA is acceptable local cancer control and that it enables the gathering of specific anatomopathological information that is likely to help accurately predict the outcome and thus pinpoint patients who are likely to benefit from adjuvant treatments (16,17). Yossepowitch et al. (18) investigated the pathological characteristics and the outcome of patients with high-risk factors based on eight previously described definitions. They concluded that because it was difficult to correctly predict the outcome of patients who were not good candidates for RP using some definitions of high-risk PCA, urologists should not uniformly disqualify patients from undergoing curative surgery.

Second, the oncological outcome of RP for patients with one, two and all three high-risk factors was various, namely, patients with high-risk PCA did not have a uniformly poor prognosis after RP. In our study, the 10-year PSA failure-free survival rate of high-risk PCA patients with one, two and all three high-risk factors was 58.5, 39.9 and 22.7%, respectively, ($P = 0.0001$) and PCA patients with two or all three high-risk factors had HRs of 1.89 (95% CI: 1.20–2.98, $P = 0.006$) and 2.99 (95% CI: 1.64–5.21, $P = 0.0006$) when compared with PCA patients with only one high-risk factor. This finding can be interpreted as indicating that although patients with only one high-risk factor who underwent RP may be cured by RP without any adjuvant treatments, it is difficult for patients with all three high-risk factors to be cured by RP monotherapy and, therefore, RP for them may be considered as a first step of multimodal treatment with adjuvant radiation therapy and/or ADT. Lodde et al. (10) reported that in the 1109 RP series, the 10-year biochemical recurrence-free survival and PCSM rates of PCA patients with no, one and two high-risk factors were 75.5, 49.4 and 35.2%, and 1.4, 7.9 and 16.1%, respectively. Therefore, they concluded that a more detailed substratification in the high-risk PCA group is needed to predict the correct oncological outcome of patients in the group. Spahn et al. investigated the oncological outcome of 712 patients with PSA >20 ng/ml who underwent RP. They reported that the rates of patients with favorable pathology for patients with PSA >20 ng/ml, PSA >20 ng/ml and clinical T3 stage, PSA >20 ng/ml and bGS of ≥8 and all three risk factors were 27, 11.1, 1.9 and 0%, respectively (19) They concluded that PCA patients with PSA >20 ng/ml have varying risk levels of disease progression and PCSM. Considering additional risk factors further stratifies this group into subgroups that can guide the clinician in preoperative patient counseling.

In our study, of the 105 patients with only one high-risk factor, the high GS group had the best 10-year PSA failure-free survival rate (74.6%). In particular, that of patients without GG 5 was 100% ($P = 0.032$). Therefore, we believe that patients with high GS alone, especially those without GG 5 are the most suitable RP candidates in the high-risk PCA group. Nanda et al. (20) performed EBRT or RP for 312 PCA patients with clinical T1c-3N0M0 and bGS of 7 with tertiary GG 5 or bGS 8–10. They reported that the PSA failure rate of patients with bGS of 8 was significantly lower than that of patients with bGS of 9, and that of patients with bGS 7 with tertiary GG 5 was almost the same as of patients with bGS of 9–10. They concluded that patients with high GS should be subclassified into bGS of 8, 9–10 and 7 with tertiary GG 5. Wambi et al. (21) also emphasized the oncological differences between bGS of 8 and 9 tumors. They analyzed the oncological outcome of 368 patients with bGS of 8–9 who underwent robotic RP and reported that their PSM rates were 40 and 64%, respectively. Furthermore, the 5-year biochemical recurrence-free survival rates of patients with bGS of 8 and 9 were 47 and 21%, respectively ($P < 0.001$). We agree with the conclusions of these two investigative teams regarding the significance of the existence of GG 5 in relation to the prognosis of patients with high-risk PCA.

Our study has several limitations. First, the patient number in our cohort was relatively small and some of the final pathological findings were unclear because approximately half of the patients received NADT before RP. Second, we could not analyze the subclassification of high-risk PCA with regard to mortality related to PCA and all events because the number of events was too small.

In conclusion, RP can be considered as a valuable therapeutic option for patients with one high-risk factor, especially for those without GG 5 in the high GS group.

In contrast, RP monotherapy has apparent limitations for patients with all three high-risk factors. In these patients, RP can be performed as the initial treatment strategy, but should be considered as a part of multimodal treatment. Thus, because patients with high-risk PCA do not have a uniform prognosis after RP, a more detailed subclassification of the high-risk patients according to the number of high-risk factors can offer further prognostic information.

Conflict of interest statement

None declared.

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BJUI BJU INTERNATIONAL

Extended biopsy based criteria incorporating cumulative cancer length for predicting clinically insignificant prostate cancer

Yoshinobu Komai, Satoru Kawakami, Noboru Numao, Yasuhisa Fujii, Kazutaka Saito, Yuichi Kubo†, Fumitaka Koga, Jiro Kumagai*, Shinya Yamamoto†, Junji Yonese†, Yuichi Ishikawa‡, Iwao Fukui† and Kazunori Kihara

*Departments of Urology and *Pathology, Tokyo Medical and Dental University Graduate School; and Departments of †Urology and ‡Pathology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan*

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Study Type – Prognosis (inception cohort)
Level of Evidence 2

What's known on the subject? and What does the study add?
The criteria used for selecting patients with prostate cancer for active surveillance (AS) are still not satisfactory due to the difficulty in predicting the significance of the prostate cancer.

Urologists could predict insignificant prostate cancer by incorporating cumulative cancer length and biopsy Gleason score, derived from extended biopsy. The present study has added new criteria for predicting insignificant prostate cancer, which would lead to a better selection of candidates for AS.

OBJECTIVE

- To develop extended biopsy based criteria for predicting insignificant cancer (IC) using extended biopsy findings.

PATIENTS AND METHODS

- From 2000 to 2009, 1575 patients with prostate cancer were primarily treated by radical prostatectomy in two referral hospitals.
- Of these, the study cohort comprised 499 patients with extended biopsy confirmed, clinically organ-confined (cT1–2N0M0) prostate cancer with PSA levels of <20 ng/mL.
- Cancer information obtained through extended biopsy included cumulative cancer length (CCL) divided by the number of biopsy cores (CCL/core).

RESULTS

- Pathological examination revealed 39 ICs (7.8%). All these ICs fell in a category of prostate cancer with clinical stage ≤T2a and 2005 International Society of Urological Pathology Consensus Conference (ISUP) modified biopsy Gleason score ≤7.
- Accordingly, we analysed predictors of IC in a subset cohort of 370 patients in this category. A multivariate logistic regression analysis revealed that 2005 ISUP modified biopsy Gleason score and CCL/core were independently significant predictors of IC.
- We determined a threshold value of CCL/core of 0.20 mm for predicting IC using receiver operating characteristic analysis.
- Based on these findings, we developed simple extended biopsy based criteria for predicting IC as follows: (i) PSA level of <20 ng/mL; (ii) Clinical stage ≤T2a; (iii) 2005 ISUP modified biopsy Gleason score ≤6; (iv) CCL/core of <0.20 mm.
- The specificity of the criteria was 91%, which was significantly higher than the value from a subset of criteria without item iv ($P < 0.001$).

CONCLUSION

- We have developed extended biopsy based criteria for predicting IC incorporating the 2005 ISUP modified biopsy Gleason score and CCL/core.

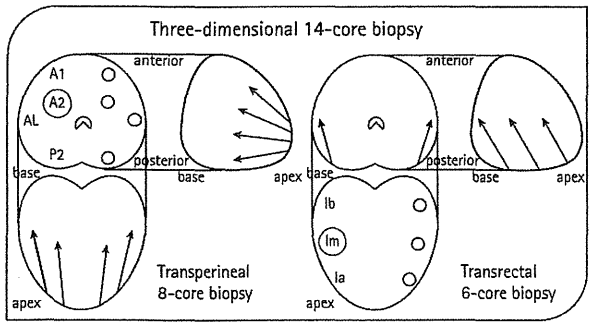
KEYWORDS

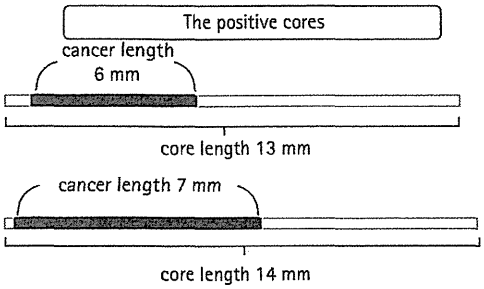
biopsy, extended, insignificant cancer, prostate

INTRODUCTION

Although PSA screening has been proven to reduce the mortality from prostate cancer, it may be associated with an increased number of insignificant cancers (ICs) detected by prostate biopsy [1]. Thus, the significance of active surveillance (AS) has progressively emerged in the past two decades and currently, ≈10% of patients with low-risk prostate cancer choose AS for the initial management of their disease [2]. As the feasibility of AS totally depends on the accurate assumption of clinical insignificance of the cancer, a panel of models for predicting IC by integrating multiple clinicopathological parameters have been proposed to date [3–7].

FIG. 1. A panel of quantitative pathological parameters calculated in a biopsy session.





Maximum cancer length (=the longest cancer lesion in a biopsy session)	7 mm
%positive cores (=the ratio of positive to total biopsy cores)	2/14 = 14%
Cumulative cancer length/ core (=(total cancer length)/ (number of biopsy cores))	(6+7)/14 =0.93 mm

Reported AS series recruiting patients according to these non-extended biopsy based inclusion criteria, however, have resulted in up to 30% incidence of PSA rapid risers [8]. Recently, Lee *et al.* [9] also reported the difficulty in predicting the significance of prostate cancer even after obtaining prostate biopsy information. They investigated the rate of significant cancer using radical prostatectomy (RP) specimens and only 37% of IC could be predicted using the Epstein's criteria [10]. These results warrant that AS indicated by non-extended biopsy based criteria might result in increased risk of disease progression during AS.

Diagnostic superiority of extended biopsy protocols with ≥10 cores over non-extended biopsy has been shown repeatedly [11–14] and extended biopsy is now considered as a standard practice for diagnosing prostate cancer [15]. However, to date, no extended biopsy based model for predicting IC except for one has been developed for selecting patients suitable for AS. Although Nakanishi *et al.* [16] reported an extended biopsy based (11–13 cores) nomogram for predicting the probability of low-volume/ low-grade cancer, it can be applied only to patients with one positive core, which alone cannot be a prerequisite for determining IC [17].

Gleason score, serum PSA level and clinical stage have been considered as the most important factors to predict disease outcomes [18]. Nevertheless, in the era of extended biopsy and PSA screening, the detailed histological features of positive biopsy have gained importance as a predictive factor for prostate cancer [19]. We have reported the importance of maximum cancer length, one of such features, to select patients suitable for nerve-sparing RP [20]. We herein developed criteria for predicting IC by incorporating one of the detailed histological features, cumulative cancer length (CCL) divided by the number of biopsy cores (CCL/core). We paid special attention to a high specificity of the new criteria to avoid misapplying AS to patients with clinically significant cancer.

PATIENTS AND METHODS

Between 2000 and 2009, 1575 patients with prostate cancer were primarily treated by RP at Tokyo Medical and Dental University Hospital or at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Of those, 499 patients with extended biopsy confirmed, clinically organ-confined (cT1–2N0M0) prostate cancer with PSA levels of <20 ng/mL constituted the study cohort. No patient underwent neoadjuvant treatment. The total PSA and free PSA levels were determined in all patients before RP. Clinical T stage was determined based on DRE findings. In 274 patients (55%), findings on multi-parametric MRI with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced T1-weighted images were also considered in T staging [21]. Prostate volume was determined based on TRUS measurements.

PROSTATE BIOPSY

In the present study, extended biopsy was defined as one in which ≥12 cores were taken. Of the 499 patients, 440 (88%) underwent in-house extended biopsy according to the procedures reported elsewhere [14,22,23]. In the remaining 59 patients (12%), pathological slides of the biopsies performed at hospitals other than ours were reviewed by the pathologists at our institutions (J.K. and Y.I.). All biopsy specimens were evaluated according to the 2005 International Society of Urological Pathology (ISUP) Consensus Conference [24]. Each biopsy core was separately labelled to analyse the location and site of cancer positive cores and all biopsy specimens. Cancer information obtained through extended biopsy was represented as biopsy Gleason score and quantitative pathological parameters including maximum cancer length in a core, percentage of positive cores and CCL/core. Maximum cancer length in a core was defined as the longest length of continuous cancer lesion without gap of benign tissue in a given biopsy session. CCL/ core was the ratio of the sum of the length of all cancerous lesions in mm to the total number of biopsy cores (Fig. 1).

RP SPECIMENS

The RP specimens were processed as previously reported [25]. In summary, all RP specimens were submitted in their entirety. After fixation, the apical and the bladder neck portions of the prostate were separated from the rest of the gland, and serially sectioned sagittally. The remaining prostate was submitted for whole-mount processing with transverse 3–5 mm slices cut perpendicular to the rectal surface. Each cancerous lesion was evaluated separately and the volume of each lesion was calculated using the formula 0.4 × length × width × cross-section thickness [16]. IC was

defined according to the Epstein criteria; tumour volume of ≤0.5 mL, confined to the prostate and RP Gleason score of ≤6 [10]. All RP specimens were evaluated according to the 2005 ISUP Consensus Conference [24].

DATA ANALYSIS

Using univariate and multivariate logistic regression analyses, we identified variables for predicting IC from preoperative variables including patient age, PSA and free PSA levels, clinical T stage, prostate volume, biopsy scheme, number of biopsy cores, biopsy Gleason score, percentage of positive cores, maximum cancer length in a core and CCL/core.

Incorporating all significant and independent predictors thereof, we constructed a logistic regression-based predictive model for IC. Predictive accuracy of the model was assessed in terms of an area under the receiver operating characteristic curve (AUC) value. For comparison, AUC values were also obtained by applying previously established Epstein biopsy criteria [10], which included: (i) PSA density, (ii) biopsy Gleason score, (iii) the presence of tumour in two or fewer cores and (iv) no more than 50% involvement by tumour in any single core, and the Nakanishi *et al.* [16] nomogram which included age, PSA density and tumour length in only one positive core, to the study cohort. All analyses were performed using JMP version 7.0 (SAS Institute, Cary, NC, USA). All calculated *P* values were two-sided and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

As shown in Table 1, pathological examination of the 499 RP specimens revealed 39 (7.8%) ICs. All 39 ICs were clinical stage ≤T2a with 2005 ISUP modified biopsy Gleason scores of ≤7. Accordingly, we analysed predictors of IC in the 370 patients with prostate cancer in this category. Baseline characteristics of the patients are shown in Table 1.

Over 90% of the 370 patients underwent prostate biopsy using a perineal approach. A multivariate logistic regression analysis showed that 2005 ISUP modified biopsy Gleason score and CCL/core were independently significant predictors of IC (Table 2). The AUC value of a multivariate logistic regression model incorporating 2005 ISUP modified biopsy Gleason score and CCL/core was 0.91 (Fig. 2). When the Epstein *et al.* [10] biopsy criteria and the Nakanishi *et al.* [16] nomogram were applied to the study cohort, AUC values of 0.81 and 0.70 were obtained, respectively. Based on the receiver operating characteristic analysis, we determined a threshold value of CCL/core of 0.20 mm for predicting IC with 91% specificity and 72% sensitivity (Table 3). Based on these findings, we developed simple extended biopsy-based criteria for predicting IC in patients diagnosed by extended biopsy as follows:

(i) PSA level of <20 ng/mL
(ii) Clinical stage of ≤T2a
(iii) 2005 ISUP modified biopsy Gleason score ≤6
(iv) CCL/core of <0.20 mm

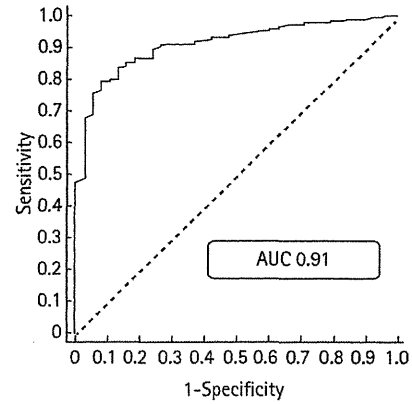
The specificity of the criteria was 91%, which was significantly higher than the value from a subset of criteria without item iv) (71%, $P < 0.001$). The criteria could predict significance of cancers accurately in 301 of the 331 cases.

DISCUSSION

We have developed novel criteria for predicting IC in patients with prostate cancer diagnosed by extended biopsy. These criteria yielded as high a specificity as 91% and could be used to predict 'IC of Epstein Criteria'. Recently, Klotz *et al.* [26] reported a low rate of cancer-specific mortality in patients initially managed with AS whose indication was determined by the information obtained through 8- to 14-core biopsy. During the study period, 30% of the patients were re-classified as harbouring higher risk cancer and offered definitive therapy. By taking such an informative parameter as CCL into the consideration at the initial decision-making, the incidence of conversion from AS to active treatment might be saved.

Several models for predicting IC have been reported to date. A model reported by Goto *et al.* [27] claimed a higher specificity (98%) than that of our present new criteria.

FIG. 2. Receiver operating characteristic curve of the current criteria for predicting IC.



Considering that their study cohort included patients with advanced disease but ours strictly excluded those patients, it might be difficult to compare these two models directly. Nakanishi *et al.* [16] reported an extended biopsy-based nomogram for predicting low-volume/low-grade prostate cancer. However, that study enrolled only patients with a single positive core in a biopsy session. A single positive core is one of the numerous indicators of low-volume cancer but not necessarily a 'must-have' feature. A low-volume cancer can be presented in two or more positive cores when a more meticulous biopsy method is applied. Therefore, the fact that they limited their study cohort to patients with single positive cores also limited the applicability of their results to general population. Lee *et al.* [9] evaluated the diagnostic power of the Epstein Criteria for predicting IC and concluded it would predict organ-confined disease but not IC.

In clear contrast to these previous studies, which emphasised the predictive ability of PSA and/or PSA-related parameters, the present study showed that only biopsy Gleason score and CCL/core were significant predictors. In the presence of overwhelming predictive impact of CCL/core, PSA could serve only as an indicator of patients in whom the possibility of IC could be considered. It might be reasonable that biopsy based pathological quantitative parameters would gain more importance in the current extended biopsy era than in previous non-extended biopsy era. To estimate cancer volume quantitatively,

TABLE 1 Baseline characteristics of the study cohort

Variable	Patients with clinical stage T1–T2 and PSA level of <20 ng/mL	Patients with IC	Patients with biopsy 2005 ISUP modified Gleason score ≤7 and clinical stage ≤T2a
N	499	39	370
Median (IQR):			
Age, years	66 (61–70)	64 (58–67)	65 (61–70)
PSA level, ng/mL	7.1 (5.3–9.8)	6.9 (5.3–9.7)	6.9 (5.2–9.6)
Prostate volume, mL	28.0 (21.4–35.4)	31.9 (26.7–44.4)	28.2 (21.5–35.3)
N (%):			
Approach of prostate biopsy:			
Transrectal	42 (8.4)	3 (7.6)	26 (7.0)
Transperineal	65 (13)	4 (10.2)	49 (13)
3D	392 (78)	32 (82)	295 (75)
Clinical stage*:			
T1c	226 (45.2)	25 (64.1)	198 (53.5)
T2a	199 (39.8)	14 (35.8)	172 (46.4)
T2b	27 (5.4)	0	0
T2c	47 (9.4)	0	0
Biopsy 2005 ISUP modified Gleason score:			
≤6	149 (29.8)	35 (89.7)	132 (35.6)
7	285 (57.1)	4 (10.3)	238 (64.3)
≥8	65 (13.0)	0	0
Pathological T stage:			
T2a	94 (18.8)	19 (48.7)	74 (20.0)
T2b	23 (4.6)	1 (2.7)	18 (4.9)
T2c	260 (52.1)	19 (48.7)	195 (52.7)
T3a	97 (19.4)	0	72 (19.4)
T3b	24 (4.8)	0	11 (3.0)
T4	1 (0.2)		0
RP 2005 ISUP modified Gleason score:			
5	20 (4.0)	7 (17.9)	17 (4.6)
6	97 (19.4)	32 (82.1)	83 (22.4)
3 + 4	214 (42.9)	0	169 (45.7)
4 + 3	114 (22.8)	0	85 (22.9)
≥8	54 (10.8)	0	16 (4.3)
Median (IQR):			
Maximum cancer length, mm	5 (3–7)	1.75 (1–3.25)	4 (2–7)
% positive core	23 (7.69–33.3)	7.1 (5.26–11.5)	15.3 (7.69–28.5)
CCL/core, mm	0.781 (0.19–1.08)	0.11 (0.05–0.19)	0.46 (0.17–0.92)

**Determined by DRE and/or MRI; IQR, interquartile range.*

several biopsy based pathological parameters have been developed. One of the most meticulous parameters is percentage of biopsy cores involved with cancer (cumulative cancer length divided by the total length of obtained core; %CCL). However, it is too cumbersome to obtain the %CCL value, because not only must the cancer length in positive cores be measured but also the total length of all biopsy cores [28]. Therefore, we used CCL/core instead of %CCL in the present study. To obtain CCL/core value, we only know the length of cancer in positive cores and the number of biopsy cores. We believe that the stringent threshold value of CCL/core of 0.2 mm is acceptable to avoid overlooking significant cancers.

Are there any other diagnostic tools that might result in a positive effect on selection for AS? First, the use of MRI is promising, as recently it has been reported that MRI, particularly diffused-weighted images before biopsy, could reveal not only the presence of cancer but also the size and localisation of disease [21]. In AS candidates, the cancer foci would be small and MRI could serve as a triage test, for example, by indicating 'T1c' disease. As second test for predicting IC, new markers such as prostate cancer antigen 3 [29] and human kallikrein 2 [30] may be useful because these markers appear to be capable of increasing predictive accuracy of multivariate biopsy models. Of course, a careful evaluation is needed

regarding cost-effectiveness. While, both 2005 ISUP modified biopsy Gleason score and CCL/core were parameters available in every set of prostate biopsy without additional expense.

There are several limitations to the present study. First is a lack of external validation. Predictive ability of our criteria should be validated using an independent patient cohort examined by extended biopsy in the near future. The concept of CCL/core is totally dependent on a systematic biopsy sampling. Therefore, it is currently unknown whether our criteria can be applied to patients examined by targeted biopsy method. If targeted samplings were focused on a presumed cancerous lesion suggested by pre-biopsy imaging studies, e.g. MRI, CCL/core can be overestimated. The second limitation of the present study is that the current criteria were developed using the data of a cohort in which >90% of the subjects underwent transperineal biopsy. A further study including men examined by extended transrectal biopsy would be needed. The third, perhaps foremost limitation is that, given the fact Gleason score 6 disease almost never kills the patients [31,32], the current criteria might be of merely academic interest for predicting 'IC of the Epstein Criteria'. It is impossible for us to respond to the limitation clearly because we have not prospectively compared the outcomes of AS between patients who meet the criteria and those who did not. However, 48% of ICs (28/58) could be predicted using the current criteria, in contrast, only 27% (36/132) of ICs could be predicted by biopsy Gleason score 6 alone ($P < 0.001$) in patients with PSA levels of <20 ng/mL and clinical stage ≤IT2a. And furthermore, CCL/core was still one of the independent predictors for both RP Gleason score 6 and organ-confined disease together with PSA level, free PSA level and patient age (data not shown). Thus, CCL/core has the ability to predict not only 'IC of the Epstein Criteria' but also 'clinically IC'.

In conclusion, we have developed a set of extended biopsy based criteria for IC incorporating 2005 ISUP modified biopsy Gleason score and CCL/core. Considering the high specificity of these criteria and that they require no additional expense, it is strongly recommended that urologists and patients become acquainted with these two parameters for determining the suitability for AS.

TABLE 2 Univariate and multivariate logistic regression analyses for prediction of IC in patients with PSA levels of <20 ng/mL, biopsy Gleason scores of ≤7 and clinical stages of ≤T2a

	Univariate	Multivariate		
		Full model	Final model	
Variable	*P*	*P*	Odds ratio (95% CI)	*P*
Patient age, years	0.10	0.50	–	
PSA level, ng/mL	0.50	0.93	–	
free PSA level, ng/ml	0.19	0.78	–	
Clinical T stage, T1c vs T2a	0.16	0.24	–	
Prostate volume, mL	0.10	0.64	–	
Approach, 2D* vs 3D†	0.082	0.09	–	
Biopsy Gleason score, ≤6 vs 7	<0.001	<0.001	16.4 (5.52–70.1)	<0.001
Number of biopsy cores	0.22	0.29	–	
Maximum cancer length, mm	<0.001	0.82	–	
% positive cores	<0.001	0.18	–	
CCL/core, mm	<0.001	0.24	71.6 (9.97–991)	<0.001

**The 2D approach biopsy represents one in which either transrectal or transperineal approach was used; †The 3D approach biopsy represents one in which both transrectal and transperineal approaches were used.*

TABLE 3 Optimising threshold CCL/core value in IC prediction

Threshold value of CCL/core, mm	Specificity	Sensitivity	Accuracy
0.05	0.97	0.23	0.67
0.075	0.96	0.39	0.71
0.10	0.94	0.47	0.77
0.15	0.93	0.63	0.83
0.20	0.91	0.72	0.91
0.25	0.87	0.78	0.89
0.30	0.86	0.80	0.86
0.35	0.84	0.81	0.85

CONFLICT OF INTEREST

None declared.

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Correspondence: Satoru Kawakami, Department of Urology, Tokyo Medical and Dental University, Graduate School, 1-5-45, Yushima, Bunkyo-ku, 113-8519, Tokyo, Japan.
e-mail: kawakami@saitama-med.ac.jp

Abbreviations: **AS**, active surveillance; **AUC**, area under the receiver operating characteristic curve; **IC**, insignificant cancer; **ISUP**, International Society of Urological Pathology; **RP**, radical prostatectomy.

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

Huashi Zhou[a,1], Taro Tamura[a,2], Yukinori Kusaka[a,*], Narufumi Suganuma[b,3], Ponglada Subhannachart[c,4], Chomphunut Vijitsanguan[c,4], Weeraya Noisiri[c,4], Kurt G. Hering[d,5], Masanori Akira[e,6], Harumi Itoh[a,f,7], Hiroaki Arakawa[g,8], Yuichi Ishikawa[h,9], Shinji Kumagai[i,10], Norio Kurumatani[j,11]

[a] Department of Environmental Health, School of Medicine, University of Fukui, 23-3 Shimoaitsuki, Matsuoka, Eihezi-cho, Fukui Prefecture 910-1193, Japan
[b] Department of Environmental Medicine, Kochi University School of Medicine, Japan
[c] Central Chest Disease Institute of Thailand, 39 Moo 9, Tiwanon Road, Muang Nonthaburi 11000, Thailand
[d] Department of Diagnostic Radiology, Radiooncology and Nuclear Medicine, Radiological Clinic, Miner's Hospital, Radiologische Klinik, Lansppaschaftskranhaus Dortmund, Wieckesweg 27 44309, Dortmund, Germany
[e] Department of Radiology, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-cho, Kita-ku, Sakai, Osaka 591-8555, Japan
[f] Department of Radiology, School of Medicine, University of Fukui, 23-3 Shimoaitsuki Matsuoka, Eiheizi-cho, Fukui Prefecture 910-1193, Japan
[g] Department of Radiology, Dokkyo University School of Medicine, 880 Oaza-Kitakobayashi, Mibu-cho, Shimotsuga-gun, Tochigi 321-0207, Japan
[h] Department of Pathology, Cancer Institute, 1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo 170-8455, Japan
[i] Department of Environmental Management, School of Health Sciences, University of Occupational and Environmental Health, 1-1, Iseigaoka, Yahata-nishi-ku, Fukuoka, Kitakyushu 807-8555, Japan
[j] Department of Community Health and Epidemiology, Nara Medical University School of Medicine, 840 Shijo-cho Kashihara, Nara 634-8521, Japan

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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

* Corresponding author. Tel.: +81 776 61 8335; fax: +81 776 61 8107.
E-mail addresses: zhouhua@u-fukui.ac.jp (H. Zhou), tarou@u-fukui.ac.jp (T. Tamura), kusakayk@gmail.com (Y. Kusaka), nsuganuma@kochi-u.ac.jp (N. Suganuma), pongladas@gmail.com (P. Subhannachart), Chompoo_vj@yahoo.com (C. Vijitsanguan), weeraya_tat@yahoo.com (W. Noisiri), k.g.hering@t-online.de (K.G. Hering), akira@kch.hosp.go.jp (M. Akira), hitoh@fmsrsa.fukui-med.ac.jp (H. Itoh), arakawa@dokkyomed.ac.jp (H. Arakawa), ishikawa@jfcr.or.jp (Y. Ishikawa), shkumagai@health.uoeh-u.ac.jp (S. Kumagai), knorio@naramed-u.ac.jp (N. Kurumatani).
[1] Tel.: +81 776 61 8338; fax: +81 776 61 8107.
[2] Tel.: +81 776 61 8335; fax: +81 776 61 8107.
[3] Tel.: +81 88 880 2407; fax: +81 88 880 2407.
[4] Tel.: +66 2 5803423x7505; fax: +66 2 5806992.
[5] Tel.: +49 0231 9221280; fax: +49 0231 9221648.
[6] Tel.: +81 722 52 3021; fax: +81 722 51 1372.
[7] Tel.: +81 776 61 8368; fax: +81 776 61 8137.
[8] Tel.: +81 282 87 2171; fax: +81 282 86 4940.
[9] Tel.: +81 3 3570 0448; fax: +81 3 3570 0558.
[10] Tel.: +81 93 691 7282; fax: +81 93 691 2694.
[11] Tel.: +81 744 298841; fax: +81 744 290673.

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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	+	+	–	+	+	+	+	+	+	+

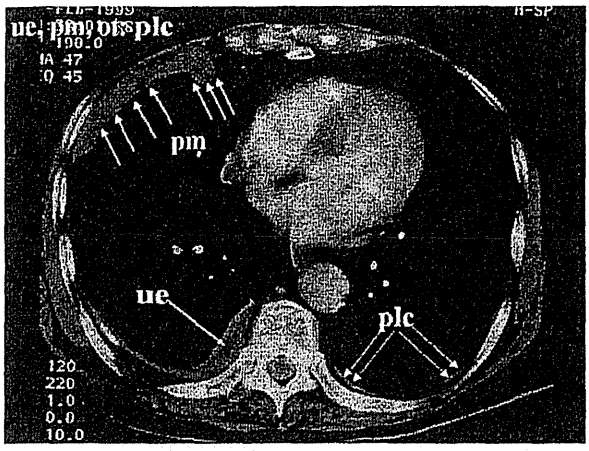

Fig. 1. The MPM features of unilateral pleural effusion ("ue"), pleural mass ("pm") and plaque calcification ("plc").

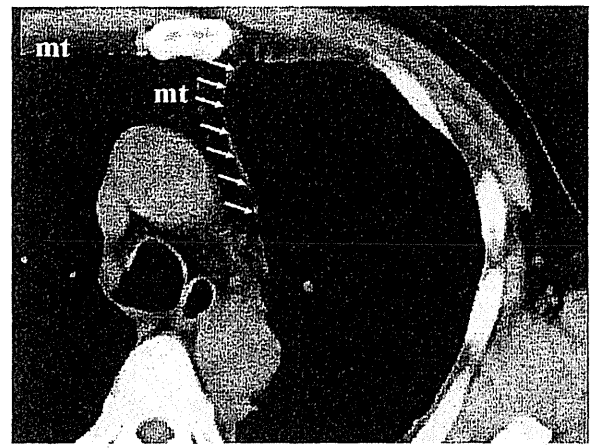

Fig. 4. Mediastinal pleural thickening ("mt").

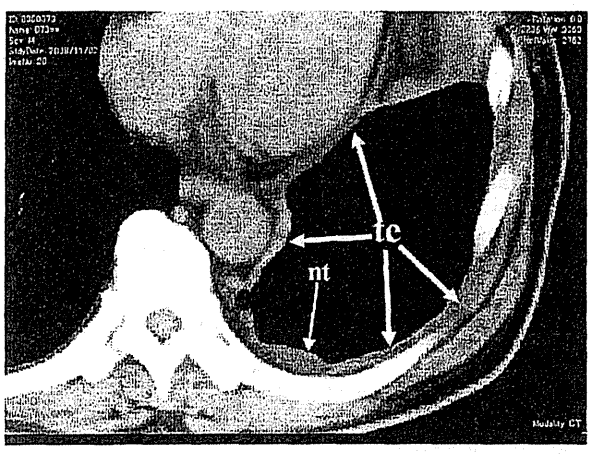

Fig. 2. Tumoral encasement of lung ("te") and nodular pleural thickening ("nt").

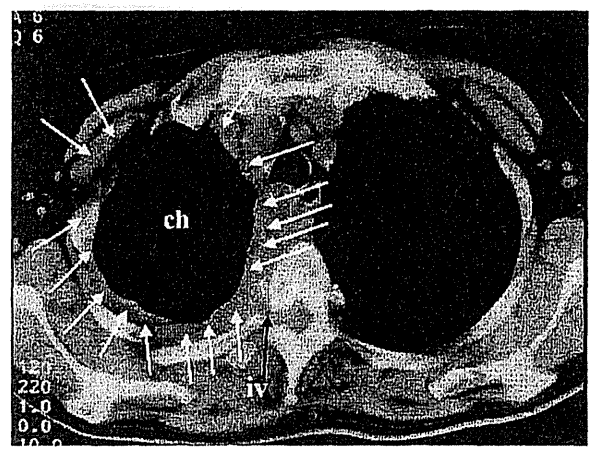

Fig. 5. Invasion "iv" of MPM into the site adjacent to vertebral column (indicated by black arrow); contract hemithorax ("ch") (indicated by white arrow).

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.

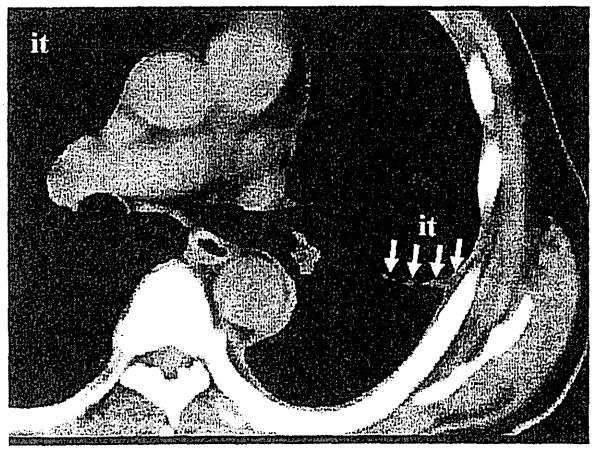

Fig. 3. Interlobar fissure pleural thickening ("it").

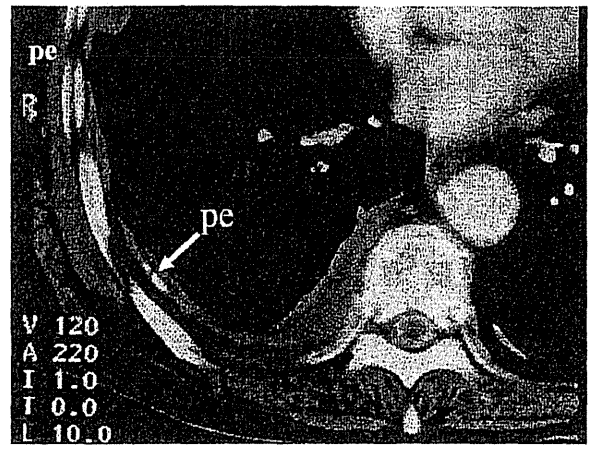

Fig. 6. Calcified plaque engulfment ("pe").

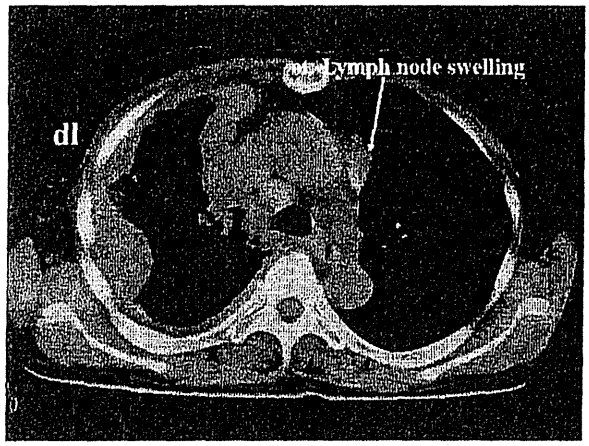

Fig. 7. Diminished lung ("dl") and lymph node swelling.

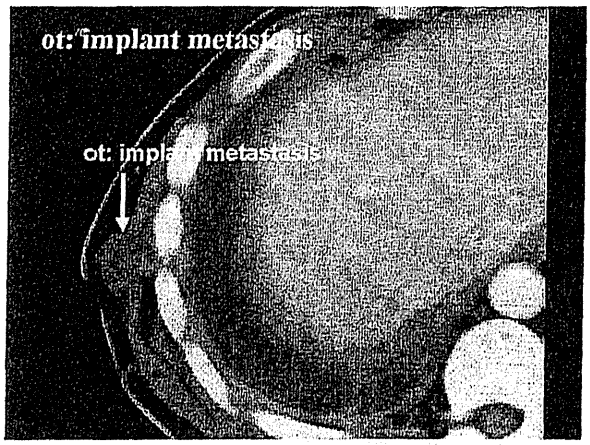

Fig. 8. Implant metastasis.

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.

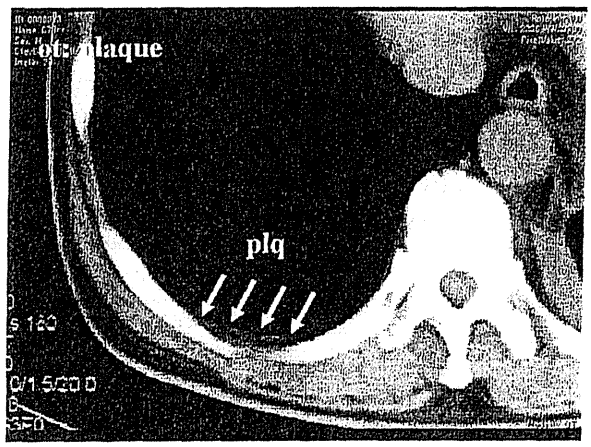

Fig. 9. Pleural plaque on the chest wall of right lung.

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

Takuya Nagashima, MD,[1] Yukinori Sakao, MD, PhD,[1] Mingyon Mun, MD, PhD,[1] Yuichi Ishikawa, MD, PhD,[2] Ken Nakagawa, MD,[1] Munetaka Masuda, MD, PhD,[3] and Sakae Okumura, MD[1]

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,

[1]*Department of Thoracic Surgical Oncology, Japanese Foundation for Cancer Research, Cancer Institute Hospital, Tokyo, Japan*
[2]*Department of Pathology, Japanese Foundation for Cancer Research, Cancer Institute Hospital, Tokyo, Japan*
[3]*Department of Surgery, Yokohama City University School of Medicine, Yokohama, Japan*

Received: November 11, 2011; Accepted: May 23, 2012
Corresponding author: Yukinori Sakao, MD, PhD. Department of Thoracic Surgical Oncology, Japanese Foundation for Cancer Research, Cancer Institute Hospital, 3-10-6, Ariake, Koto-ku, Tokyo 135-8550, Japan
Email: ysakao@aichi-cc.jp

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

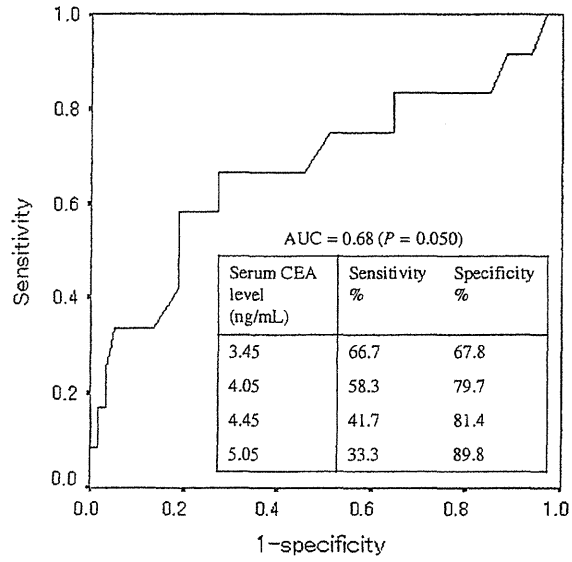

Fig. 1 Receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity and specificity of preoperative serum carcinoembryonic antigen (CEA) levels for tumor recurrence. The Youden index was used to identify the optimal cutoff point of 4.05 ng/mL for predicting recurrence.

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