retrieved from the pathology files of our institution. This study was approved by the local Ethics Committees after confirmation of informed consent by the patients to a review of their records and images. The enrollment criteria consisted of (i) adult STS patients whose pathological specimens and medical charts were available for review; and (ii) patients who were not lost to follow-up. The exclusion criteria consisted of (i) subjects whose pathological specimens and medical charts were insufficient for review; and (ii) subjects whose pathological subtypes were considered to be rare in the clinical setting. Thus, 94 patients (19%) whose tumors comprised epithelioid sarcoma (n = 25), alveolar soft part sarcoma (n = 20), clear cell sarcoma (n = 16), extraskeletal myxoid chondrosarcoma (n = 20) or extraskeletal osteosarcoma (n = 13) were excluded from the analysis, and the 406 patients with common STSs were included in the analysis. The patients consisted of 223 men and 183 women, and they ranged in age from 16 to 87 years (median age: 53 years). During the period 1962–2003, the concept of MFH or myxofibrosarcoma changed. Twenty-three myxofibrosarcomas (34%) which were previously diagnosed as myxoid variant of MFH or solely fibrosarcoma were reclassified by the review of pathological examinations. Autopsy was performed in 16 cases (4%) and their pathological specimens were also available for review.

In the patients who developed multiple primary malignancies, we investigated: age at diagnosis, gender, family history, anatomic site, tumor size, depth, surgical margin, histological type, MIB-1 score, grade, whether chemotherapy has been performed, whether radiation therapy has been performed and the outcome. If the patient had died, the date and the cause of death were also noted.

Patients were followed-up with regard to survival until August 31, 2004, at which time 250 patients were alive with no evidence of disease, 26 patients were alive with disease and 130 patients had died of their disease. The malignancy-free survival period (MFSP) was measured from the date of diagnosis of STS to the date of the first observations of multiple malignancies. If the detection of malignancy other than STS preceded the date of diagnosis of the STS, the MFSP was recorded as 0. If a patient was alive without developing any multiple malignancies at the last visit, the data on MFSP were censored as of the date when the survival was confirmed. If a patient died without detection of other primary malignancies, the MFSP was censored at the date of death. If other primary malignancy was found at autopsy, the date of death was treated as an event.

Histological slides of the primary tumors of all patients were reviewed for diagnosis by two experts. Whenever necessary, immunohistochemistry was used to confirm the diagnosis or tumor type according to the WHO classification (12). MIB-1 immunostaining was performed to grade all tumors. An MIB-1 score of 1 was assigned to lesions with an MIB-1 labeling index (LI) of 0–9%, an MIB-1 score of 2 was given to lesions with an MIB-1 LI of 10–29%, and an MIB-1 score of 3 was given to lesions with an MIB-1 LI $\geq$ 30%. There were tumors with an MIB-1 score of 1 (n = 140; 35%), 2 (n = 62; 15%) and 3 (n = 204; 50%). The histological grade is a three-grade system obtained by adding the scores for tumor differentiation, tumor necrosis and MIB-1 score, each of which was given a score of 0–3 (13). By using the grading system, tumors corresponded to grade 1 (n = 128; 32%), grade 2 (n = 107; 26%) and grade 3 (n = 171; 42%), respectively. Tumor depth was measured relative to muscular fascia that had been invaded and was characterized as superficial or deep. The vast majority of lesions (n = 322; 79%) were deep seated, and 94 tumors were superficial.

Statistical Analysis

Univariate analysis of the cumulative incidence of multiple malignancies was performed by comparing Kaplan–Meier curves and log-rank tests from each histological type. The hazard ratio (HR) of each variable was estimated by using a Cox proportional hazards model in the univariate and multivariate analyses. The following factors are considered as potential confounding factors for the incidence of multiple malignancies: age at presentation, gender, family history of malignant neoplasm, anatomic site, tumor size, depth, surgical margin, histological type, MIB-1 score (1, 2 or 3) and grade (1, 2 or 3). Variable selection by the backward elimination (α = 0.2) procedure was performed in the multivariate analyses. All analyses were performed with SAS Software (version 6.12; SAS Institute, Cary, NC).

RESULTS

Tumors had a diameter >5 cm in 302 patients (74%). Most tumors were located in the extremities (n = 244; 60%) compared with the trunk (n = 96; 24%) and other sites (n = 66; 16%). The histological types consisted of liposarcoma (n = 159; 39%), myxofibrosarcoma (n = 67; 17%), pleomorphic MFH (n = 53; 13%), synovial sarcoma (n = 50; 12%), leiomyosarcoma (n = 32; 8%), malignant peripheral nerve sheath tumor (MPNST; n = 25; 6%) and fibrosarcoma (n = 20; 4%). Of these 406 tumors, 371 tumors (91%) did not develop multiple malignancies (Table 1).

A total of 35 patients (9%) with STS were documented in the study population, among whom the STS was preceded by (n = 15) and followed by (n = 20) malignancies other than STS. The median age at the time of diagnosis of the first tumors was 63 years (range 39–79 years). The SPTs were diagnosed a median of 64 months after the diagnosis of the first tumor. A third primary tumor (TPT) was found in eight patients, a median of 127 months after the first tumor. One patient was found to have a fourth primary tumor 331 months after the first tumor. The overall 5- and 10-year estimated cumulative incidence of multiple primary malignancy was 7.6% [95% confidence interval (CI) 4.7–10.4] and 12.3% (95% CI 7.4–18.0), respectively.

Information related to the patients is listed in Table 2. The most frequent histological types of STS were myxofibrosarcoma (n = 13; 19.4%) and pleomorphic MFH (n = 6; 11.3%).

Table 1. Demographics of patients without multiple malignancies

Variables	LS	MFS	PMFH	SS	LMS	MPNST	FS	Total
n	148	54	47	50	30	24	18	371
Mean age (years)	51.6	60.5	57.9	32.9	55.3	50.0	42.4	50.9
SD	12.8	13.1	14.3	15.4	13.8	15.5	21.5	16.3
Range	18–87	29–87	26–86	18–72	30–83	28–74	18–87	18–87
Gender								
Male	89	27	31	22	11	9	12	201
Female	59	27	16	28	19	15	6	170
Distribution								
Extremities	91 (62)	37 (69)	31 (66)	36 (72)	6 (20)	13 (54)	12 (67)	226 (60)
Trunk	21 (14)	16 (30)	15 (32)	11 (22)	9 (30)	10 (42)	5 (28)	87 (23)
Others	36 (24)	1 (2)	1 (2)	3 (6)	15 (50)	1 (4)	1 (6)	58 (15)
MIB-1 score								
1	99 (67)	10 (19)	2 (4)	5 (10)	2 (7)	5 (21)	7 (39)	130 (34)
2	17 (12)	14 (26)	3 (6)	12 (24)	3 (10)	1 (4)	6 (33)	56 (15)
3	32 (22)	30 (56)	42 (89)	33 (66)	25 (83)	18 (75)	5 (29)	185 (49)
Grade								
1	94 (64)	9 (17)	2 (4)	0	2 (7)	4 (17)	8 (44)	119 (31)
2	22 (15)	34 (63)	8 (17)	14 (28)	7 (23)	2 (8)	7 (39)	94 (25)
3	32 (22)	11 (20)	37 (79)	36 (72)	21 (70)	18 (75)	3 (17)	158 (42)
Depth								
Superficial	19 (13)	16 (30)	14 (30)	7 (14)	6 (20)	4 (17)	5 (28)	71 (19)
Deep	129 (87)	38 (70)	33 (70)	43 (86)	24 (80)	20 (83)	13 (72)	300 (79)
Size (cm)								
0–5	10 (7)	20 (37)	15 (32)	24 (48)	8 (27)	7 (29)	11 (61)	95 (26)
5–10	59 (40)	25 (46)	17 (36)	18 (36)	13 (43)	13 (54)	5 (28)	150 (40)
>10	79 (53)	9 (17)	15 (32)	8 (16)	9 (30)	4 (17)	2 (11)	126 (33)
Margin								
Adequate	105 (71)	46 (85)	44 (94)	45 (90)	26 (87)	17 (71)	15 (83)	298 (79)
Inadequate	43 (29)	8 (15)	3 (6)	5 (10)	4 (13)	7 (29)	3 (17)	73 (19)
Chemotherapy	28 (19)	13 (24)	24 (51)	31 (62)	12 (40)	13 (54)	6 (33)	127 (34)
Radiation therapy	36 (24)	19 (35)	14 (30)	11 (22)	10 (33)	10 (42)	4 (22)	104 (27)
Family history of cancer	21 (49)	4 (9)	6 (14)	2 (5)	2 (5)	6 (14)	2 (5)	43 (12)
Survival rate (%)								
5 year	86.7	89.3	51.6	61.8	27.5	45.2	66.2	71.7
10 year	78.5	69.6	41.4	48.4	27.5	24.1	48.4	57.7

The numbers in parentheses are percentages.
LS, liposarcoma; MFS, myxofibrosarcoma; PMFH, pleomorphic malignant histiocytoma; SS, synovial sarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; FS, fibrosarcoma.

Less common histological types consisted of fibrosarcoma ($n = 2$; 10%), liposarcoma ($n = 11$; 6.9%), leiomyosarcoma ($n = 2$; 6.3%) and MPNST ($n = 1$; 4%).

The risk of multiple malignancies differed significantly according to the histological type of the STS (log rank test: $P = 0.0055$). None of the patients with synovial sarcoma had multiple malignancies. The multivariate analysis adjusted for potential confounding variables showed a higher risk of multiple malignancy in patients with myxofibrosarcoma (Table 3). When patients with pleomorphic MFH and myxofibrosarcoma were combined into the same histological category, the risk of multiple malignancies was 2.13 (95% CI 1.00–4.55, $P = 0.0496$). However, no significant association was found between risk of multiple malignancies and survival rate, or familiar history of malignant neoplasm in pleomorphic MFH and myxofibrosarcoma.

Table 2. Demographics of patients with multiple malignancies

Variables	MFS	PMFH	Other tumors	Total
n	13 (37)	6 (17)	16 (46)	35
Mean age (years)	63.8	66.5	58.8	62.0
SD	11.4	13.1	10.9	11.5
Range	45–79	47–76	39–79	39–79
Gender				
Male	10	5	7	22
Female	3	1	9	13
Distribution				
Extremities	10 (77)	2 (33)	6 (38)	18 (51)
Trunk	3 (23)	4 (66)	2 (13)	9 (26)
Others	0	0	8 (50)	8 (23)
MIB-1 score				
1	3 (23)	0	7 (44)	10 (29)
2	3 (23)	0	3 (19)	6 (17)
3	7 (54)	6 (100)	6 (38)	19 (54)
Grade				
1	3 (23)	0	6 (38)	9 (26)
2	8 (62)	1 (17)	4 (26)	13 (37)
3	2 (15)	5 (83)	6 (38)	13 (37)
Depth				
Superficial	9 (69)	4 (66)	0	13 (37)
Deep	4 (30)	2 (33)	16 (100)	22 (63)
Size (cm)				
0–5	5 (38)	1 (17)	3 (19)	9 (26)
5–10	7 (54)	5 (83)	4 (26)	16 (46)
10+	1 (8)	0	9 (69)	10 (29)
Margin				
Adequate	11 (85)	6 (100)	11 (69)	28 (80)
Inadequate	2 (15)	0	5 (31)	7 (20)
Survival rate (%)				
5 year	84.6	50.0	66.1	70.0
10 year	70.5	16.7	27.3	43.1

The numbers in parentheses are percentages.
MFS, myxofibrosarcoma; PMFH, pleomorphic malignant fibrous histiocytoma.

Twelve patients (37.1%) had a family history of cancer. One patient had familial adenomatous polyposis (FAP) with a germline mutation in the APC gene. Two patients with a second or third primary STS had previously received systemic chemotherapy and radiation therapy. Patients with a second or third primary cancer whose STS preceded it had previously received chemotherapy ($n = 3$) and radiation therapy ($n = 4$). Only one patient had a third primary cancer within the radiation field.

Age at the time of diagnosis was associated with increased risk of multiple malignancies in the unadjusted analysis (HR = 1.52, 95% CI 1.17–1.97, $P = 0.0016$), but no significant association was found with gender, family history of cancer, MIB-1 score, grade, tumor size, depth or margin. Furthermore, no interaction was evidenced between the risk of multiple malignancies and having received chemotherapy or radiation therapy.

Table 3. Hazard risk of multiple malignancies adjusted for potential confounding variables

Variables	HR	95% CI	*P*-value
Age	1.51	1.17–1.96	0.0019
Tumor size	1.03	0.99–1.07	0.18
MFS	2.34	1.01–5.41	0.048
PMFH	1.85	0.69–4.97	0.22
Other tumors*	1	–	–

*Adjusted hazard risk (HR) referenced to other tumors is presented.
MFS, myxofibrosarcoma; PMFH, pleomorphic malignant fibrous histiocytoma.

Myxofibrosarcoma developed as the first tumor in three patients, the second tumor in seven, the third tumor in two, and the fourth tumor in one (Table 4). The MFSP between the diagnosis of the first and second malignancies ranged from 4 to 275 months (median: 69.0 months). The TPTs were detected within 142 months after the diagnosis of the first tumor. One myxofibrosarcoma of the thigh developed after radiation therapy for a second primary esophageal carcinoma. The fourth primary tumor developed in a patient who had undergone surgical resection three times for carcinomas of the colon and cecum. The patient developed a myxofibrosarcoma of the thigh that was treated by surgery and chemotherapy 120 months after the diagnosis of the SPT. The 5- and 10-year estimated cumulative incidence of multiple malignancies in patients with myxofibrosarcoma were both 16.9% (95% CI 7.8–26.1; Fig. 1). The overall survival time of the 13 patients in the group after the diagnosis of the first tumor ranged from 10 to 408 months (median: 148.0 months). The 5-year survival rate of the group was similar to that of the patients without multiple malignancies (84.6 versus 89.3%, $P = 0.81$).

Pleomorphic MFH occurred as the first tumor in five patients (Table 5), and in one patient it was followed by esophageal carcinoma. The MFSP between the diagnosis of the first and second malignancies varied from 17 to 94 months (median: 74.0 months). The 5-year estimated cumulative incidence of multiple malignancies in patients with pleomorphic MFH was 10.2% (95% CI 0.0–20.6; Fig. 1). The overall survival time of the six patients in this group ranged from 48 to 155 months (median: 113.0 months), and the 5-year survival rate was not significantly different from that of pleomorphic MFH patients without multiple malignancies (50.0 versus 51.6%, $P = 0.32$). One patient died of the first tumor after developing a metastasis, and the other five patients died of the SPT.

Nineteen multiple malignancies were associated with four types of adult STSs: liposarcomas in 11 patients, fibrosarcomas in two, leiomyosarcomas in two and MPNST in one (Table 6). The MFSP between the diagnosis of the primary malignancy

Table 4. Myxofibrosarcoma with multiple malignancies (n = 13)

Patient	Age (years)	Gender	FT	Site	CT	RT	MFSP	SPT	Site	CT	RT	MFSP from SPT	TPT	Site	CT	RT	MFSP from TPT	FPT	Site	CT	RT	Prognosis	OS
1	55	Male	MFS	Thigh	–	–	4	Ad	Stomach	–	–	–	–	–	–	–	–	–	–	–	–	NED	10
2	68	Male	MFS	Buttock	–	–	8	Sq	Pharynx	–	50 Gy	–	–	–	–	–	–	–	–	–	–	DOD	246
3	48	Female	MFS	Leg	–	–	130	Ad	Ovary	CDDP + ADR + CPA CDDP + Taxel	–	–	–	–	–	–	–	–	–	–	–	DOD	177
4	69	Male	Ad	Stomach	–	–	38	MFS	Thigh	–	–	–	–	–	–	–	–	–	–	–	–	DOD	101
5	66	Male	TCC	Bladder	–	–	11	MFS	Chest wall	–	–	5	TCC	Bladder	ADR	–	–	–	–	–	–	NED	156
6	69	Male	Sq	tongue	CDDP 5FU	50 Gy	84	MFS	Leg	–	–	7	Sq	Gingiva	–	–	–	–	–	–	–	NED	91
7	70	Male	Ad	Rectum	–	–	19	MFS	Arm	–	42 Gy	–	–	–	–	–	–	–	–	–	–	DOD	34
8	74	Male	Ad	Prostate	–	–	4	MFS	Arm	–	–	–	–	–	–	–	–	–	–	–	–	NED	24
9	48	Female	Ad	Breast	–	–	85	MFS	Arm	–	–	–	–	–	–	–	–	–	–	–	–	NED	143
10	79	Female	RCC	Kidney	–	–	139	MFS	Arm	–	–	–	–	–	–	–	–	–	–	–	–	NED	148
11	77	Male	Ad	Colon*	–	–	275	Ad	Stomach	–	–	105	MFS	Leg	–	–	–	–	–	–	–	NED	381
12	45	Male	Ad	Stomach	–	–	216	Sq	Esophagus	–	60 Gy	84	MFS	Thigh	–	–	–	–	–	–	–	NED	408
13	62	Male	Ad	Colon	–	–	69	Ad	Cecum	–	–	142	Ad	Colon	–	–	120	MFS	Thigh	CDDP	–	NED	331

FT, first tumor; CT, chemotherapy; RT, radiotherapy; MFSP, malignancy-free survival period (months); SPT, second primary tumor; TPT, third primary tumor; FPT, fourth primary tumor; DOD, died of disease; NED, no evidence of disease; OS, overall survival (months); MFS, myxofibrosarcoma; Ad, adenocarcinoma; Sq, squamous cell carcioma; TCC, transitional cell carcinoma; RCC, renal cell carcinoma; CDDP, cisplatin; ADR, adriamycin; CPA, cyclophosphamide; 5FU, 5-fluorouracil.
*Synchronous tumor.

and the second malignancy ranged from 1 to 141 months (median: 60.0 months). The 5- and 10-year estimated cumulative incidence of multiple malignancies in this group was 5.1% (95% CI 2.2–8.0) and 9.7% (95% CI 3.8–15.7%; Fig. 1), respectively. The overall survival time of the 16 patients from the time of diagnosis of the first tumor ranged from 6 to 223 months (median: 96.5 months). No significant difference in 5-year survival rate was found between the patients with and without multiple malignancies (66.1 versus 71.6%, $P = 0.80$).

DISCUSSION

The objective of this study was to review the incidence of multiple malignancy in adult STS patients. The results of the analysis showed that 9% of the patients had multiple malignancies. The 5- and 10-year estimated cumulative incidence of multiple malignancy was 7.6% (95% CI 4.7–10.4) and 12.3% (95% CI 7.4–18.0), respectively. In addition, the risk of multiple malignancy appeared to be impacted by age at the time of diagnosis of the first tumor and by the histological type of myxofibrosarcoma.

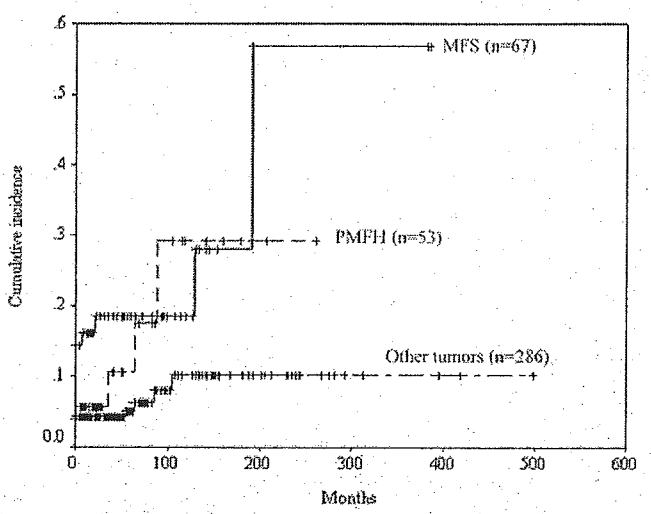

Figure 1. Cumulative incidence of multiple malignancies in STS. MFS, myxofibrosarcoma; PMFH, pleomorphic malignant fibrous histiocytoma. A statistically significant difference is found between the three groups (log rank $P = 0.002$).

The results of this analysis add to the evidence of an association between STS and the risk of multiple malignancy. The results are consistent with the findings in the cohort study Merimsky et al. that assessed the risk of multiple malignancies associated with STS (11). In their study, 28 of 375 adult patients (7.5%) with STS were found to have developed another primary malignant neoplasm either before or after the diagnosis of STS, a significantly higher rate than reported for the occurrence of STS in the general cancer patient population (1.0%). In addition, they also observed an association between primary MFH and the occurrence of renal cell carcinoma. However, Merimsky et al. did not evaluate risk according to histological types of STS, and they included several patients with bone sarcoma in their analysis. Thus, our study expanded on the findings of Merimsky et al. by assessing the impact of histological type.

Previous studies in patients with STS have found frequencies of an SPT ranging from 1.2 to 6.0% (14,15). In contrast, one study that investigated the risk of developing SPT in patients with non-Hodgkin lymphoma yielded a frequency of 15.4% (16). However, the populations in these studies were mainly children or adolescents. In our study, the rate of association of an SPT or TPT with STS was 9.0%, suggesting that the frequency of multiple malignancies is similar in the different age populations. Age at the time of diagnosis was strongly associated with increased risk of multiple malignancies in adult patients with STS.

The results of our study showed that the risk of multiple malignancies was similar when the analysis was conducted separately for patients with pleomorphic MFH and myxofibrosarcoma, the most common types of STS. Multiple malignancies were detected in six patients with pleomorphic MFH, and in five patients where the pleomorphic MFH was preceded by another malignant tumor. Similarly, the other malignancy was detected first in three of the 13 patients (23%) with myxofibrosarcoma and subsequently in the other

Table 5. Pleomorphic MFH with multiple malignancies ($n = 6$)

Patient	Age (years)	Gender	FT	Site	CT	RT	MFSP	SPT	Site	CT	RT	MFSP from SPT	TPT	Site	CT	RT	Prognosis	OS
1	76	Male	PMFH	Shoulder	–	32.5 Gy	64	Ad	Bile duct	MMC	–	–	–	–	–	–	DOD	78
2	76	Male	PMFH	Thigh	–	–	84	Ad	Lung	–	–	–	–	–	–	–	DOD	155
3	53	Male	PMFH	Elbow	VCR ADR	–	6	Sq	Tongue	–	–	–	–	–	–	–	DOD	106
4	47	Male	PMFH	Buttock	–	–	31	Ad	Colon	–	–	–	–	–	–	–	DOD	48
5	76	Male	PMFH	Back	–	50 Gy	121	Ad	Stomach	–	50 Gy	–	–	–	–	–	DOD	138
6	71	Male	Sq	Esophagus	–	–	94	PMFH	Back	–	–	7	Ad	Stomach	–	–	DOD	120

FT, first tumor; CT, chemotherapy; RT, radiotherapy; MFSP, malignancy-free survival period (months); SPT, second primary tumor; TPT, third primary tumor; DOD, died of disease; NED, no evidence of disease; OS, overall survival (months); PMFH, pleomorphic malignant fibrous histiocytoma; Sq, squamous cell carcioma; Ad, adenocarcinoma; VCR, vincristine; ADR, adriamycin; MMC, mitomycin C.

Table 6. Other tumors with multiple malignancies ($n = 16$)

Patient	Age (years)	Gender	FT	Site	CT	RT	MFSP	SPT	Site	CT	RT	MFSP from SPT	TPT	Site	CT	RT	Prognosis	OS
1	62	Female	FS	Thigh	–	–	1	Ad	Uterine	–	–	–	–	–	–	–	DOD	6
2	57	Female	LS (D)	Retroperitoneum	–	40 Gy	29	Ad	Breast	–	–	–	–	–	–	–	DOD	108
3	42	Female	LS (D)	Retroperitoneum	ADR VCR	–	75	Pap	Thyroid	NA	NA	–	–	–	–	–	DOD	78
4	57	Male	LS (M)	Thigh	VCR	–	141	Sq	Larynx	–	60 Gy	–	–	–	–	–	NED	223
5	59	Male	LS (M)	Thigh	–	–	4	Ad	Lung*	–	–	–	–	–	–	–	NED	38
6	61	Male	LS (WD)	Retroperitoneum	–	–	81	Ad	Prostate	SR	62 Gy	–	–	–	–	–	NED	85
7	63	Male	LS (WD)	Retroperitoneum	–	–	8	Ad	Prostate	LA	–	–	–	–	–	–	NED	9
8	70	Female	Ad	Breast	–	–	60	FS	Chest wall	–	–	17	Ad	Stomach	–	–	NED	112
9	60	Male	DLBL	Thyroid	CHOP	–	81	L	Leg	–	–	–	–	–	–	–	NED	117
10	39	Female	Ad	Breast	–	–	60	L	Buttock	CPA, VCR, ADM, DTIC	–	–	–	–	–	–	DOD	212
11	50	Female	Ad	Breast	–	–	105	LS (M)	Thigh	–	50 Gy	–	–	–	–	–	DOD	127
12	64	Male	Ad	Rectum	–	–	50	LS (M)	Leg	–	–	–	–	–	–	–	DOD	61
13	43	Female	Ad	Breast	–	–	102	LS (WD)	Retroperitoneum	–	–	–	–	–	–	–	NED	121
14	63	Female	Ad	Breast	–	–	29	LS (WD)	Retroperitoneum	–	–	–	–	–	–	–	NED	75
15	71	Female	Pap	Thyroid	–	–	2	MPNST	Retroperitoneum	–	–	–	–	–	–	–	NED	15
16	79	Male	TCC	Bladder	–	–	106	Ad	Lung	–	–	12	LS (D)	Retroperitoneum	–	–	DOD	146

FT, first tumor; CT, chemotherapy; RT, radiotherapy; MFSP, malignancy-free survival period (months); SPT, second primary tumor; TPT, third primary tumor; DOD, died of disease; NED, no evidence of disease; OS, overall survival (months); FS, fibrosarcoma; Ad, adenocarcinoma; LS (D), liposarcoma (dedifferentiated); Pap, papillary carcinoma; LS (M), liposarcoma (myxoid); Sq, squamous cell carcinoma; LS (WD), liposarcoma (well differentiated); DLBL, diffuse large B-cell lymphoma; MPNST, malignant peripheral nerve sheath tumor; TCC, transitional cell carcinoma; CHOP, cyclophosphamide, adriamycin, vincristine, prednisolone; ADR, adriamycin; VCR, vincristine; CPA, cyclophosphamide; DTIC, dacarbazine; SR, zoladex; LA, leuplin; NA, not applicable.
*Synchronous tumor.

10 patients (77%). Some investigators consider a pleomorphic MFH to be a high grade tumor that has a substantially high metastatic rate and poor prognosis (17,18). Myxofibrosarcoma is a distinct fibroblastic neoplasm that may recur and has a relatively poor prognosis (19–21). In our study, univariate analysis revealed that no significant association was found between risk of multiple malignancy and survival rate, or familiar history in pleomorphic MFH and myxofibrosarcoma.

A family history of cancer and genetic predisposition to cancer may be associated with a risk of multiple malignancies. A correlation between the incidence of multiple malignancy and familial aggregation has been demonstrated in Li–Fraumeni syndrome (22). Similarly, genetic factors have an impact on the risk of various histological types of SPT (23,24). It was not likely that these factors would profoundly influence the risk related to development of multiple malignancies since there was no significant association between familial history of cancer and the risk of multiple malignancies in our study. Some rare familial syndromes are associated with an excess risk of multiple malignancies. There was a patient with FAP with a germline mutation of the APC gene. This patient developed myxofibrosarcoma of the thigh as a fourth primary tumor after surgical treatment of colon cancers three times.

Despite the fact that the known carcinogenic effects of chemotherapy and radiation therapy are associated with an increased risk of developing SPT (25,26), no interaction was found with having received chemotherapy and radiation therapy according to the results of the multivariate analysis. The lack of agreement between our findings and those of other investigators may be attributable to the small number of patients treated by chemotherapy and radiation therapy: only two patients with second or third primary STS were previously treated by chemotherapy and radiation therapy.

Our results showed that multiple malignancies occurred in 9% of patients with STS, and that the rate of occurrence depended on the histological type. The 5-year survival rate of patients with multiple malignancies according to the histological type of STS was not statistically different from that of the patients without multiple malignancies. Many histological types of multiple malignancies occurred in various organs, suggesting that the whole-body screening to detect other primary malignant neoplasms in addition to local recurrence or distant metastasis should be considered in the management of patients with multiple primary malignancies. Recent prospective studies have highlighted the potential diagnostic role of whole-body [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET) for evaluation of malignant tumors. FDG PET is an accurate non-invasive test for diagnosis of adult STS and has high sensitivity and intermediate specificity for malignancy. We recommend a whole-body FDG PET scan in the search for a second malignancy in patients with multiple primary malignancies.

In summary, the results of our study confirm the incidence of multiple primary malignancies in adult patients with STS, and the histological type of myxofibrosarcoma was found to be associated with an increased risk of multiple primary malignancy. Physicians should be aware of the increased risk of multiple primary malignancies in patients with myxofibrosarcoma, and whole-body screening to detect other malignant neoplasms is desirable.

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Mucin-Producing Adenocarcinoma of the Lung: Thin-Section Computed Tomography Findings in 48 Patients and Their Effect on Prognosis

[Thoracic Imaging: Original Article]

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Abstract

Objective: To determine the prognostic value of thin-section computed tomography (CT) findings in patients with mucin-producing adenocarcinoma (MPA) of the lung.

Methods: The study included 48 patients with pathologically proven MPA who had thin-section CT before treatment. The CT findings were correlated with the histopathologic findings and with disease-free survival on follow-up in all patients.

Results: Computed tomography findings identified in patients with MPA of the lung included an air bronchogram (n = 37, 77.1%), areas of ground-glass attenuation (n = 36, 75.0%), areas of air-space consolidation (n = 36, 75.0%), interlobular septal thickening (n = 33, 68.8%), bubble-like lucencies (n = 23, 47.9%), centrilobular nodules (n = 22, 45.8%), and mucus filling of airways (n = 19, 39.6%). Twenty-two (45.8%) of the 48 patients had intrapulmonary metastases. Centrilobular nodules (odds ratio [OR] = 6.7, 95% confidence interval: 1.1-41.4; $P < 0.05$) and mucus filling of airways (OR = 14.4, 95% 95% confidence interval: 2.0-102.7; $P < 0.01$) on thin-section CT were independently associated with an increased likelihood of intrapulmonary metastases. The 5-year disease-free survival rates were 67.9% and 38.4% for patients without and with intrapulmonary metastases, respectively ($P < 0.05$). The presence of centrilobular nodules (relative risk = 10.5, 95% confidence interval: 1.8-59.3; $P < 0.01$) on thin-section CT was an independent predictor of poor prognosis.

Conclusion: Centrilobular nodules on CT are associated with a higher prevalence of intrapulmonary metastases and a poor prognosis in patients with MPA of the lung.

Mucin-producing adenocarcinoma (MPA) of the lung is a disorder that includes the histologic category of mucinous bronchioloalveolar carcinoma (BAC) and adenocarcinoma with mixed subtypes according to the World Health Organization classification.1

Mucin-producing adenocarcinoma is composed of bronchial, goblet cell-like, tall columnar cells with cytoplasmic mucin and has distinct features, including genetic mutation and antigenic expression by histologic

examination.[2-5]

The computed tomography (CT) findings of mucin-producing tumors of the lung have been described.[6-12] Most published data refer to CT findings resulting from mucinous BAC, although 2 studies have included patients with MPA of the lung in their subject groups.[6,7] Characteristic CT findings of mucin-producing tumors of the lung include multiple cysts, cavitation or bubble-like lucencies, an air bronchogram, an interlobular bulging fissure, a CT angiogram sign, and uniform low attenuation of the pulmonary consolidation. To our knowledge, however, there have been no published findings of large series of patients with MPA of the lung who underwent surgical resection, and the prognostic implications of CT findings have not been evaluated.

The aim of the present study was to correlate thin-section CT findings with histopathologic findings and to determine the prognostic value of thin-section CT findings in patients with MPA of the lung.

MATERIALS AND METHODS

A retrospective review of the pathologic records for the period between January 1996 and January 2004 identified 48 treated patients with MPA of the lung. The study population consisted of 24 men and 24 women, with a mean age of 73.1 years (range: 45-85 years). All patients underwent surgical resection, which comprised wedge resection, lobectomy, or pneumonectomy. Twenty-two (45.8%) of these 48 patients also received chemotherapy. Complete resection or sampling of mediastinal or hilar lymph nodes was performed in all patients. These included high and low ipsilateral paratracheal, subcarinal, and inferior pulmonary ligament lymph nodes as well as any other suspicious lymph nodes identified at surgery. The tumors were classified according to the current international tumor, node, metastasis (TNM) classification for staging lung cancer after surgery.[13] Of these, 6 tumors (12.5%) were classified as stage Ia, 9 (18.8%) as stage Ib, 8 (16.7%) as stage IIa, 3 (6.3%) as stage IIIa, and 22 (45.8%) as stage IV. Clinical records were available for review in all patients. Clinical histories of cases were also reviewed to identify any underlying medical conditions, the presence or absence of symptoms, and cigarette consumption. Our Institutional Review Board does not require its approval or informed consent for review of patient records and images.

Computed tomography was performed on helical or multidetector scanners (X-Vigor or Aquilion V-detector; Toshiba Medical Systems, Tokyo, Japan). The helical technique in 55 patients consisted of 10.0-mm collimation for individual scans of the entire lung (120 kV[peak], 150 mA) and reconstruction using a standard algorithm. Additional thin-section CT images were obtained in 21 patients using 2.0-mm collimation, a 20-cm field of view, 120 kVp and 200 mA per rotation, 1.0-second gantry rotation, and a high spatial frequency reconstruction algorithm. The remaining 27 patients were evaluated on a multidetector CT scanner using axial 2.0-mm × 4 modes (4 images per gantry rotation), 120 kVp, 200 mA, and 0.5-second scanning time. Thin-section CT images in these 27 patients were obtained using 2.0-mm sections reconstructed at 2.0-mm intervals using a high spatial frequency algorithm and were retrospectively retargeted to each lung with a 20-cm field of view. All patients received iodinated nonionic contrast material intravenously, and the scan delay was set at 40 seconds by autoinjector (Autoenhance A-50 or A-250; Nemoto Kyorindo, Tokyo, Japan). All CT examinations were performed after intravenous administration of contrast. Hard copy images were photographed at window settings for the lung (center, -600 Hounsfield units [HU]; width, 2000 HU) and mediastinum (center, 35 HU; width, 400 HU). The time interval between CT and pathologic diagnosis ranged from 0 to 16 days.

The CT images were assessed in random order by 2 independent observers without reference to the clinical findings. The observers assessed the presence of areas of ground-glass attenuation, air-space consolidation, centrilobular nodules, an air bronchogram, mucus plugging, bubble-like lucencies, bulging of the interlobar fissure, cavitation, traction bronchiectasis or bronchiolectasis, intralobular reticular opacities, interlobular septal thickening, and a CT angiogram. Ground-glass attenuation was defined as an area of hazy increased parenchymal attenuation without obscuration of the underlying vascular markings. Areas of air-

space consolidation were considered present when the opacity obscured the underlying vessels. Mucus plugging was defined as tubular attenuation structures resulting from mucus filling of airways. The shape of mucus plugging depends on the branching pattern of involved airways. Bubble-like lucencies were considered present when there was enlargement of multiple cystic air spaces measuring 5 mm or less in diameter within the lesion surrounded by a wall of variable thickness.[14] Bulging of an interlobar fissure was considered to result from expansion of the lobe by the lesion.[15] Cavitation included a circumscribed enlarged air space with a wall of variable thickness.[16,17] Traction bronchiectasis or bronchiolectasis was defined as irregular bronchial dilatation within areas with a parenchymal abnormality. A CT angiogram was considered to have occurred when the enhanced pulmonary vessels could be clearly identified within a lesion of low attenuation relative to the chest wall musculature.[18] The presence of lymphadenopathy and pleural effusions was also noted. Lymphadenopathy was considered present when the short-axis diameter of the nodes was greater than 10 mm. The anatomic distribution was noted to be central if there was a predominance of abnormalities in the inner two thirds of the lung and peripheral if there was a predominance of abnormalities in the outer third of the lung. After initial independent evaluation, the 2 observers reviewed all cases in which they had a discrepant interpretation and reached a final decision by means of consensus.

Surgical specimens were fixed with inflation by transpleural and transbronchial infusion of formalin. The specimens were sectioned transversely in the same plane as that of the CT. All pathologic specimens were stained with hematoxylin-eosin. The presence of mucus retention was assessed by morphologic examination with a histochemical technique using periodic acid-Schiff reagent. The internal characteristics of the tumors seen on thin-section CT were compared with those seen at pathologic examination of the specimens.

Surgical specimens were evaluated by an expert lung pathologist for histologic diagnosis, presence of intrapulmonary metastasis, thickened bronchi or bronchioles, and mucus retention. We defined MPA to indicate classic "diffuse bronchioloalveolar carcinoma" that simulates lobar pneumonia at presentation. Tumor cells of MPA were composed of bronchial, goblet cell-like, tall columnar cells with cytoplasmic mucin. Correlation between the CT and histologic findings was made by consensus between the radiologist, surgeon, and pathologist.

All patients were regularly followed up in our institute. Follow-up CT images were available for all patients. Disease-free survival was calculated from the date of the operation to the date of intrapulmonary metastasis or last contact with the patient. The mean follow-up after surgery was 30.9 months.

Univariate analysis of the thin-section CT findings was performed using the [chi]^2 test and Fisher exact test. The relation of thin-section CT findings and the presence or absence of intrapulmonary metastasis was tested for independent predictors using multiple logistic regression analysis, which determined the odds ratio (OR) after adjusting for the other variables examined. Interobserver variation for the CT findings was quantified as the weighted [kappa]-coefficient of agreement. A [kappa]-value greater than 0 was considered to indicate a positive correlation, a [kappa]-value of 0-0.20 indicated poor agreement, a [kappa]-value of 0.21-0.40 indicated fair agreement, a [kappa]-value of 0.41-0.60 indicated moderate agreement, a [kappa]-value of 0.61-0.80 indicated good agreement, and a [kappa]-value of 0.81-1.00 indicated excellent agreement. Survival curves were estimated using the Kaplan-Meier method. The univariate influence of thin-section CT findings on survival was analyzed by means of the log-rank test. The Cox proportional hazard model was applied to all covariates that had shown statistical significance ($P < 0.05$) at the univariate analysis. The Wald test was used in a backward stepwise selection procedure to identify parameters with significant independent predictive value and to estimate the relative risk (RR) and 95% confidence interval. All analyses were performed using SPSS statistical software (version 11.0, SPSS, Chicago, IL).

Results

Patient Characteristics

The clinical characteristics and outcomes of all patients with MPA of the lung are summarized in Table 1. Twenty-two (45.8%) of the 48 patients had intrapulmonary metastases. The age at presentation was significantly higher in patients with intrapulmonary metastases than in those without intrapulmonary metastases. A statistically significant difference was noted in gender as well as in the proportion of smokers between the patients with and without intrapulmonary metastases. Cigarette consumption was not statistically associated with the presence or absence of intrapulmonary metastases, however. The patients with intrapulmonary metastases were more likely to have a large tumor size than those without intrapulmonary metastases.

	Intrapulmonary Metastasis (−)	Intrapulmonary Metastasis (+)	*P*
No. patients	26	22	
Age (mean/SD, y)	70.0/11.8	76.8/8.1	<0.05†
Age range (y)	45–83	60–85	
Gender			
Male	9	15	<0.05‡
Female	17	7	
Smoker	5	16	<0.0001‡
Nonsmoker	21	6	
Cigarette consumption (pack years/SD)	8.3/3.6	10.9/3.8	0.63†
Tumor size (cm)			
Mean/SD	4.8/2.9	11.5/4.3	<0.0001†
Range	2.1–13.0	5.6–17.5	
Treatment			
Wedge resection	4	0	
Lobectomy*	22	20	
Pneumonectomy*	0	2	
Follow-up duration after initial diagnosis (mo)			<0.0001†
Median	39.0	17.5	
Mean/SD	41.0/16.8	19.0/9.1	
Range	14–75	4–38	
Mortality (%)	7.7	86.4	<0.0001‡

*Complete resection or sampling of mediastinal and hilar lymph nodes was also performed. Patients with intrapulmonary metastasis who underwent a lobectomy or pneumonectomy also received chemotherapy.

Statistical comparisons were performed between the patients with and without intrapulmonary metastasis using the 2-tailed paired *t* test† and χ^2 test‡.

TABLE 1. Clinical Characteristics and Outcomes of the Study Population

CT Features

There was good interobserver agreement for the analysis of the thin-section CT findings (weighted [kappa]-value: 0.68-0.74). The CT findings are summarized in Table 2. The CT findings identified frequently in MPA of the lung on univariate analysis included an air bronchogram (n = 37, 77.1%; Fig 1), areas of ground-glass attenuation (n = 36, 75.0%; see Fig 1; Fig 2), areas of air-space consolidation (n = 36, 75.0%; see Fig 1; Fig 3), and interlobular septal thickening (n = 33, 68.8%; see Fig 1).

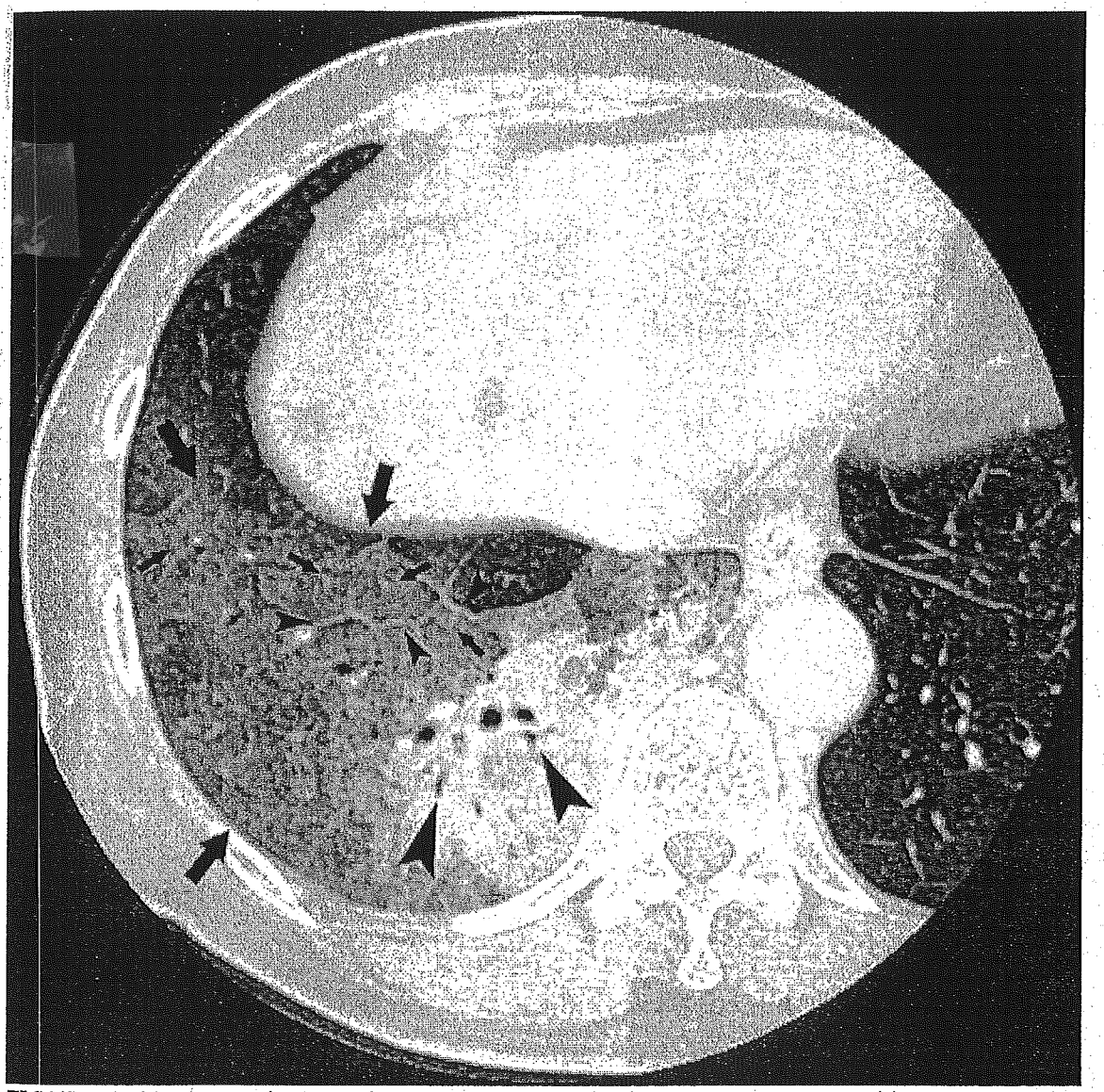

FIGURE 1. Mucin-producing adenocarcinoma of the lung in an 80-year-old woman. A computed tomography image shows a poorly demarcated mass with adjacent areas of ground-glass attenuation (large arrows). Also noted is the presence of an air bronchogram (large arrowheads), interlobular septal thickening (small arrowheads), and intralobular reticular opacities (small arrows).

CT Findings	Metastasis (−) (n = 26)	Metastasis (+) (n = 22)	P
Air bronchogram	81.8	86.4	0.16
Areas of ground-glass attenuation	65.4	86.4	0.09
Areas of air-space consolidation	61.5	90.9	<0.05
Bubble-like lucencies*	46.2	50.0	0.79
Interlobular septal thickening	53.1	27.3	0.89
Centrilobular nodules	15.4	81.8	<0.0001
Mucus filling of airways	7.7	65.4	<0.0001
Bulging of interlobar fissure*	23.1	36.4	0.31
Cavitation	23.1	4.5	0.07
Traction bronchiectasis or bronchiolectasis	26.9	18.1	0.47
Intralobular reticular opacities*	73.1	63.6	0.48

Data are presented as percentages. Differences between 2 groups of intrapulmonary metastasis are compared by the χ^2 test* and Fisher exact probability test.

TABLE 2. Thin-Section CT Findings of Patients With and Without Intrapulmonary Metastasis

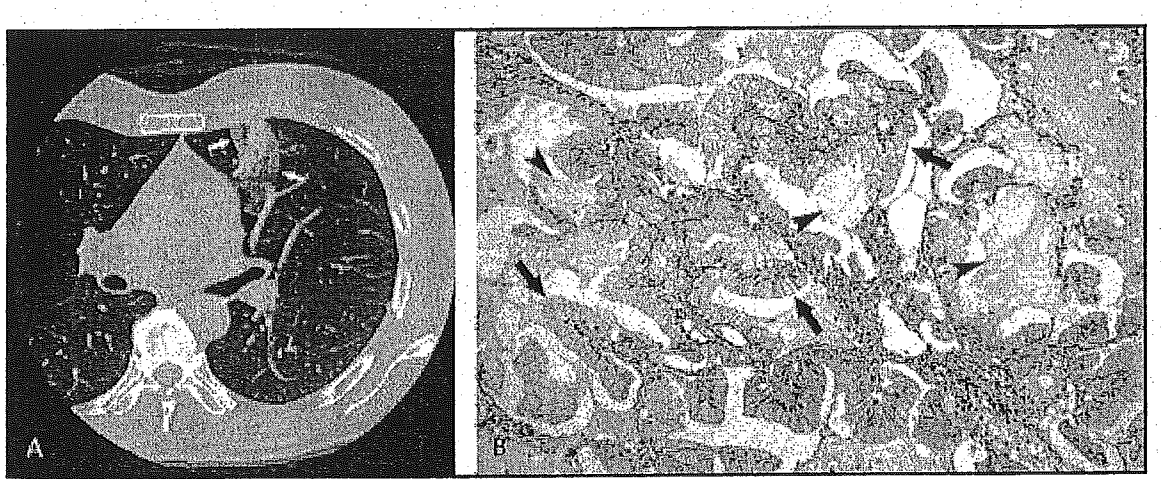

FIGURE 2. Mucin-producing adenocarcinoma of the lung in a 67-year-old woman. A, Thin-section computed tomography image demonstrates areas of ground-glass attenuation (white arrows). B, Pathologic specimen reveals replacement growth of tumor cells (arrows) and the surrounding mucus retention (arrowheads).

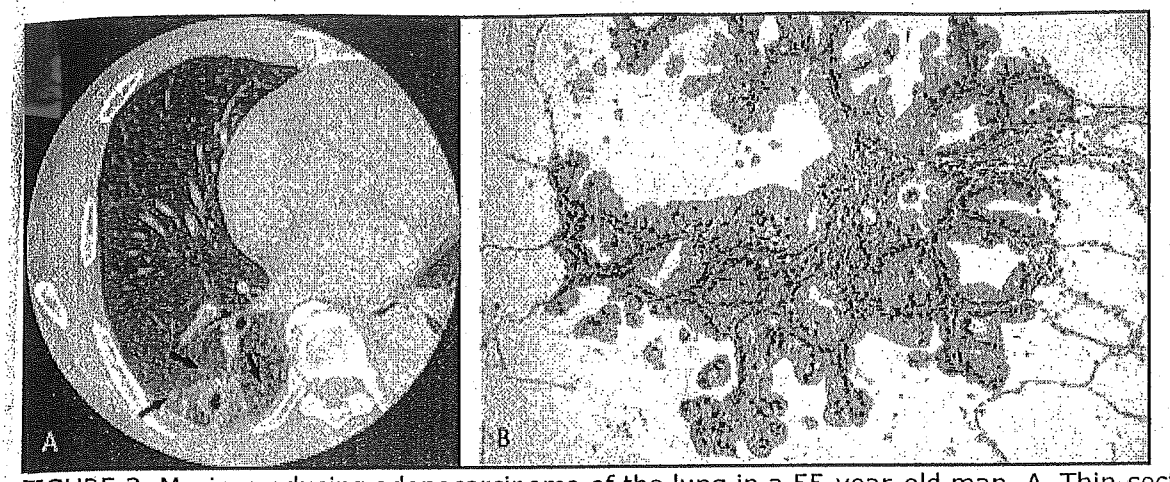

FIGURE 3. Mucin-producing adenocarcinoma of the lung in a 55-year-old man. A, Thin-section computed tomography image shows the tumor with surrounding centrilobular nodules (arrows). B, Microscopic observation reveals intrapulmonary metastasis containing abundant tumor cells and mucin.

Less common CT findings included bubble-like lucencies (n = 23; Fig 5), intralobular reticular opacities (n = 23; see Fig 1), centrilobular nodules (n = 22; Fig 3), mucus plugging (n = 19; Fig 4), bulging of interlobar fissure (n = 14), traction bronchiectasis or bronchiolectasis (n = 11), cavitation (n = 7; Fig 7), and a CT angiogram (n = 4). Mucus plugging, when present, was always superimposed on areas of air-space consolidation or ground-glass attenuation. Pleural effusion was also noted in 2 patients.

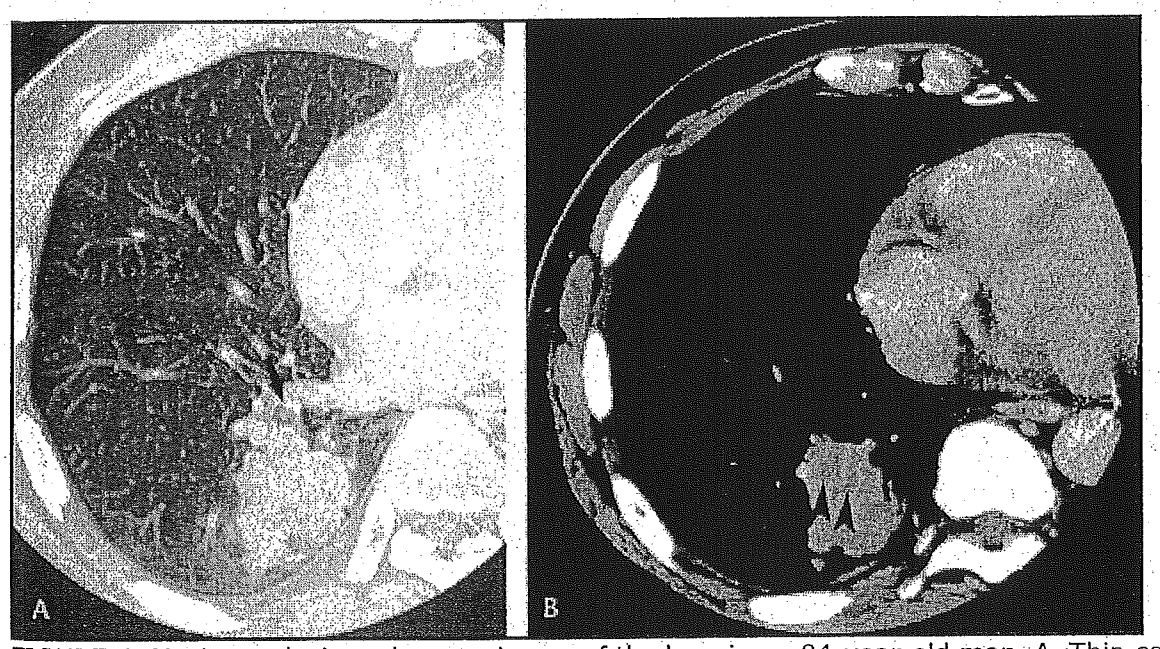

FIGURE 4. Mucin-producing adenocarcinoma of the lung in an 84-year-old man. A, Thin-section computed tomography image shows a poorly demarcated mass with mucus plugging (arrow). B, Thin-section CT image obtained 25 mm below the level of A shows tubular low attenuation of mucus plugging (arrowheads) in the lumen of a dilated peripheral bronchus in the mediastinal window setting.

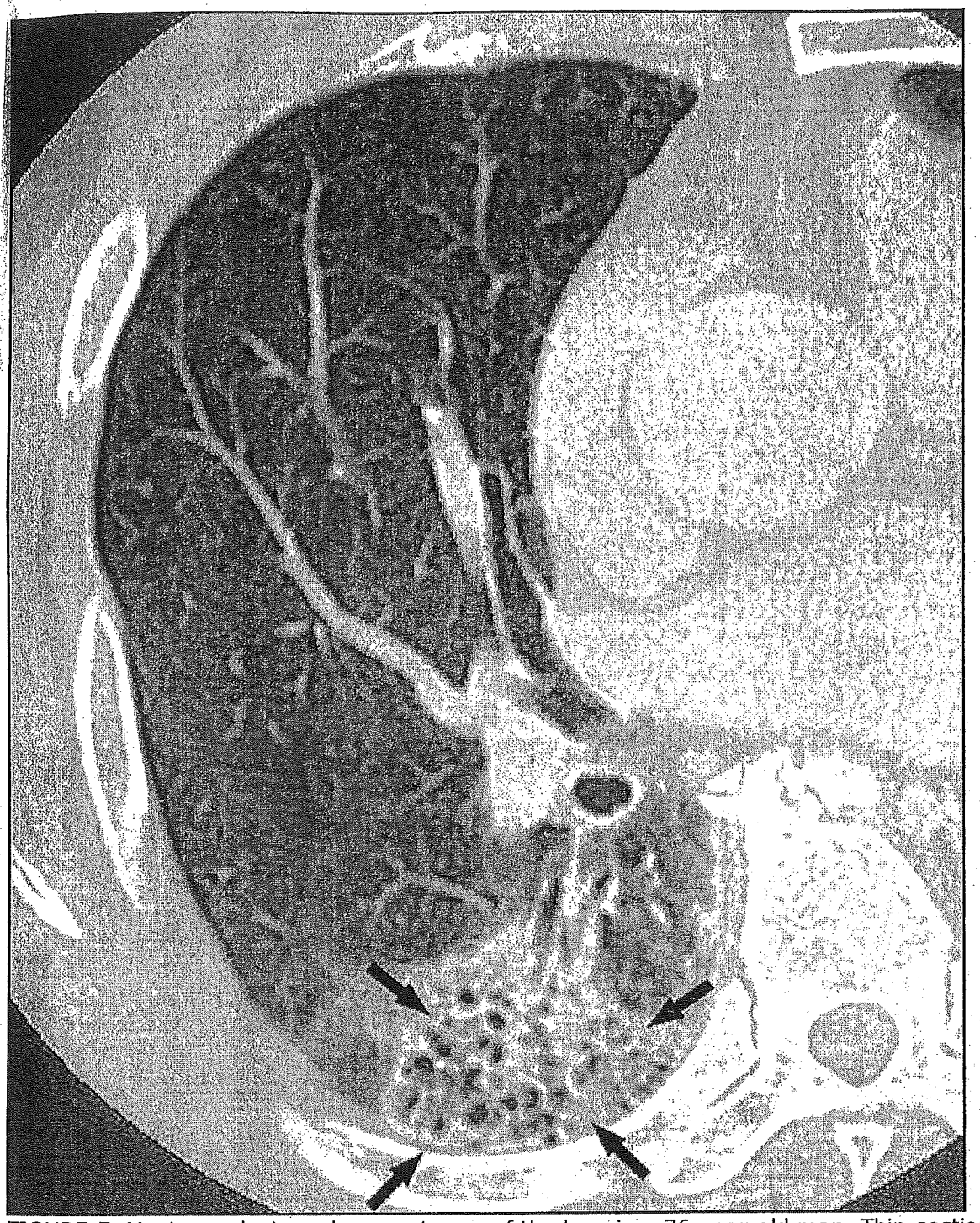

FIGURE 5. Mucin-producing adenocarcinoma of the lung in a 76-year-old man. Thin-section computed tomography image shows areas of air-space consolidation with bubble-like lucencies (arrows).

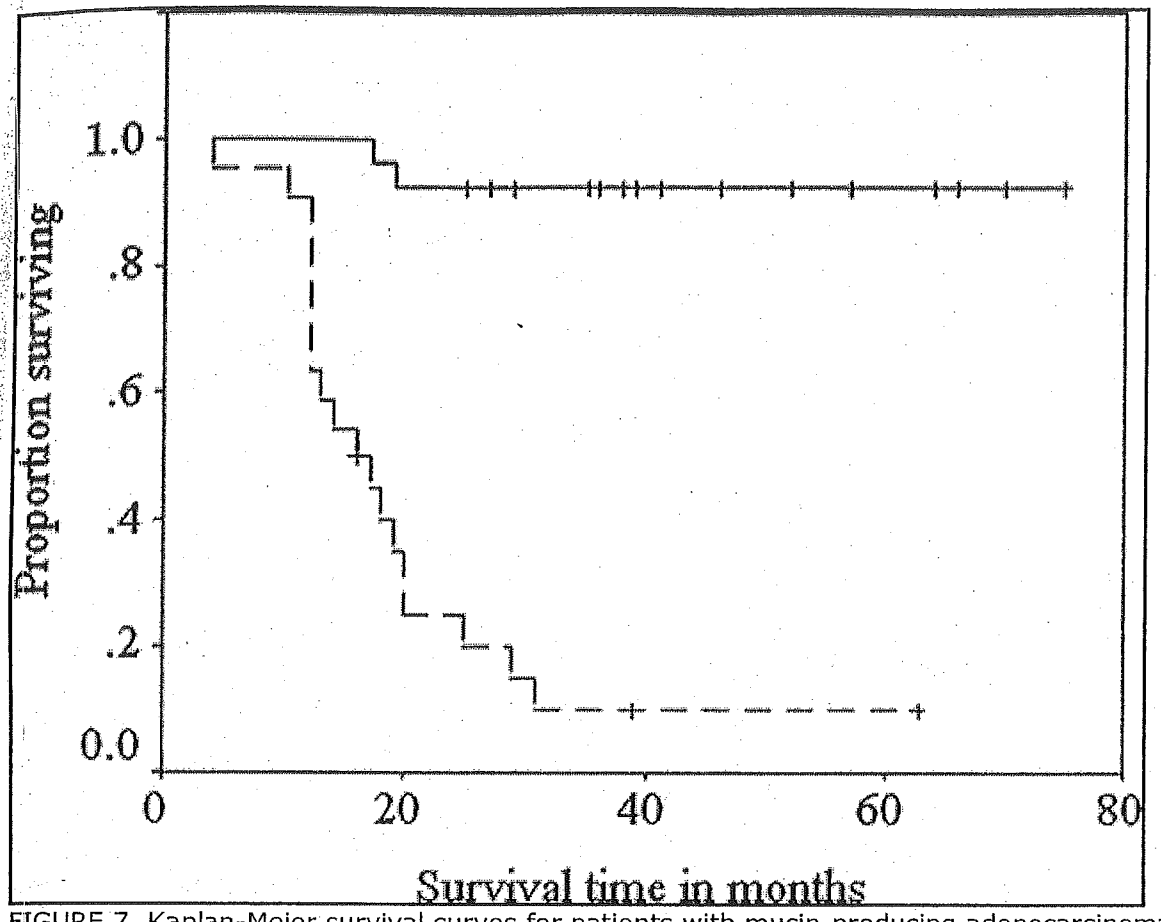

FIGURE 7. Kaplan-Meier survival curves for patients with mucin-producing adenocarcinoma of the lung grouped by the presence (n = 22, dashed line) and absence (n = 26, solid line; $P < 0.0001$) of centrilobular nodules on thin-section computed tomography.

Correlation Between Intrapulmonary Metastases and CT Findings

Univariate analysis demonstrated that areas of air-space consolidation, centrilobular nodules, and mucus plugging were significantly associated with an increased likelihood of intrapulmonary metastases (see Table 2). There was no statistically significant difference in the frequency of areas of ground-glass attenuation, air bronchogram, bubble-like lucencies, bulging of the interlobar fissure, cavitation, traction bronchiectasis or bronchiolectasis, interlobular septal thickening, and intralobular reticular opacities among patients with and without intrapulmonary metastases. Multiple logistic regression analysis demonstrated that the thin-section CT findings independently associated with an increased likelihood of intrapulmonary metastases were centrilobular nodules (OR = 6.7; $P < 0.05$) and mucus plugging (OR = 14.4; $P < 0.05$; Table 3).

CT Findings	OR	95% CI	*P*
Presence of centrilobular nodules (vs. absence)	6.7	1.1–41.4	<0.05
Presence of mucus filling of airways (vs. absence)	14.4	2.0–102.7	<0.01

OR associated with intrapulmonary metastasis is estimated for thin-section CT findings.

95% CI indicates 95% confidence interval.

TABLE 3. Multiple Logistic Regression Analysis of Thin-Section CT Findings Associated With Intrapulmonary

Metastasis

Correlation Between CT and Histopathologic Findings

Tumors with the focal type of lung involvement were well-demarcated nodular tumors growing along alveolar walls and associated with marked mucin production. Tumors with intrapulmonary metastases were multifocal and had poorly defined margins. Areas of ground-glass attenuation on thin-section CT correlated with the replacement growth of tumor cells or mucus (see Fig 2). Mucus resulted in filling of alveolar spaces in all patients. Areas of air-space consolidation corresponded to a mixture of tumor cells, mucus, and decreased air content in alveolar spaces. Bubble-like lucencies on thin-section CT corresponded histologically to a mixture of mucus, goblet type tumor cells, thickened and dilated bronchi or bronchioles, and small amounts of air in alveolar spaces. Thickened and dilated bronchi or bronchioles, which were often accompanied by localized scarring, focal alveolar collapse, and organized pneumonia, were found mainly in the distal periphery of the tumor. Intralobular reticular opacities correlated with the presence of alveoli filled with mucus and the preserved alveolar septa or underlying parenchyma. Interlobular septal thickening on thin-section CT corresponded to infiltration of the interstitium by inflammatory cells or septal edema. The sensitivity and specificity of centrilobular nodules in detecting intrapulmonary metastases were 81.8% (18 of 22 patients) and 84.6% (22 of 26 patients), respectively. Metastatic lesions often contained an aerated bronchiole. In 4 patients (8.3%), the intrapulmonary metastases were minute and were only identified with difficulty on the corresponding CT images. The CT halo sign identified on thin-section CT corresponded to a tumor component with a bronchioalveolar or papillary growth pattern and mucus layer excreted by surrounding tumor cells.

Clinical Outcome and Prognostic Analysis

Follow-up duration and mortality are summarized in Table 1. A statistically significant difference was found in follow-up duration after an initial diagnosis between the patients with and without intrapulmonary metastases ($P < 0.05$). Twenty-six (54.2%) of 48 patients had no evidence of recurrent disease. Twenty-four (92.3%) of 26 patients without intrapulmonary metastases and 3 (38.5%) of 22 patients with intrapulmonary metastases were alive. There was a significantly higher mortality rate of the patients with intrapulmonary metastases compared with the patients without metastases (see Table 1).

Univariate analysis demonstrated that areas of centrilobular nodules, mucus plugging, interlobular septal thickening, and a CT angiogram were significant predictors of poor prognosis in patients with MPA of the lung (Table 4). No significant predictors of poor prognosis were identified in thin-section CT findings, which included areas of ground-glass attenuation, areas of air-space consolidation, an air bronchogram, bubble-like lucencies, bulging of the interlobar fissure, cavitation, traction bronchiectasis or bronchiolectasis, and intralobular reticular opacities. The 5-year disease-free survival rates for those patients not having and having intrapulmonary metastases were 67.9% and 38.4%, respectively ($P < 0.05$; Fig 6). Age, gender, smoking history, and cigarette consumption had no significant prognostic value. Cox proportional hazard analysis demonstrated that the presence of centrilobular nodules (RR = 10.5; $P < 0.01$) on thin-section CT was an independent predictor of poor prognosis (Figs 7,8; Table 5).

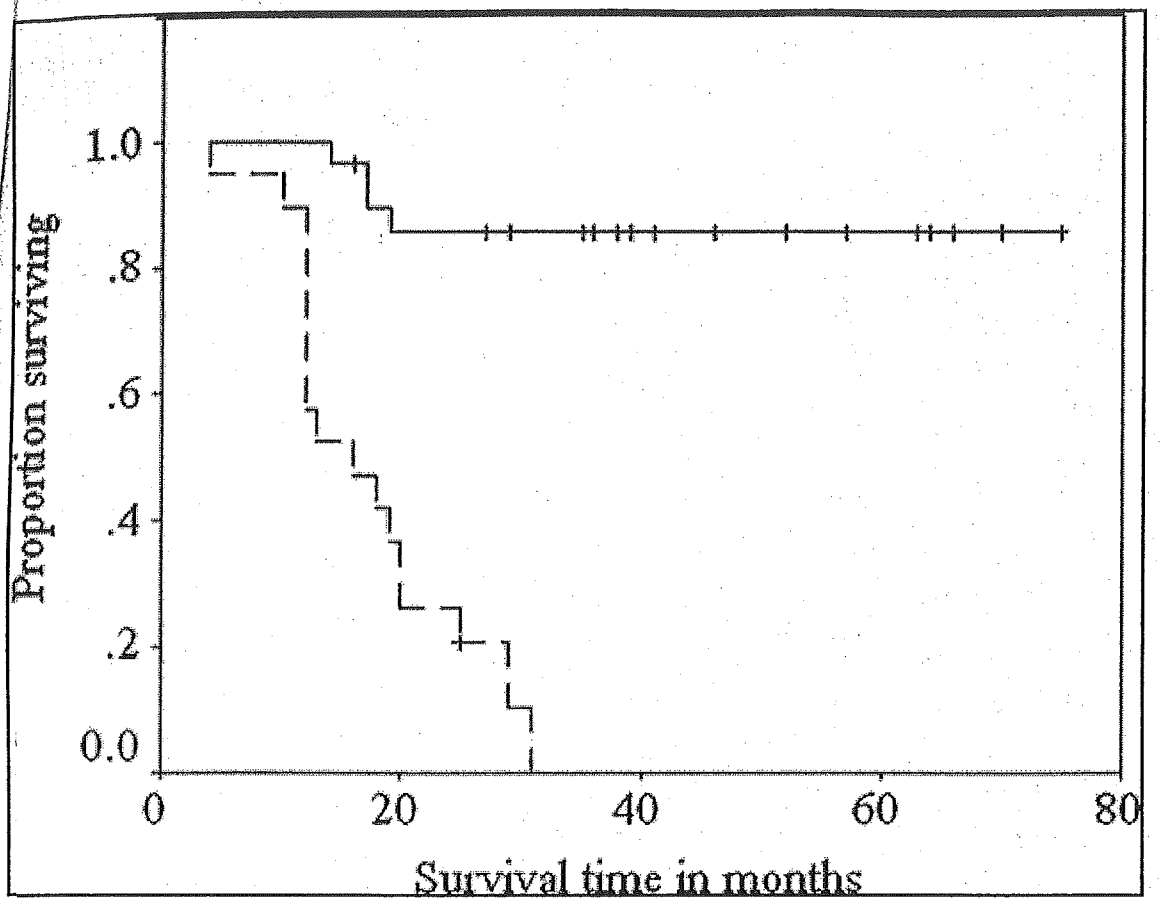

FIGURE 8. Kaplan-Meier survival curves for patients with mucin-producing adenocarcinoma of the lung grouped by the presence (n = 19, dashed line) and absence (n = 29, solid line; $P < 0.0001$) of mucus plugging on thin-section computed tomography.

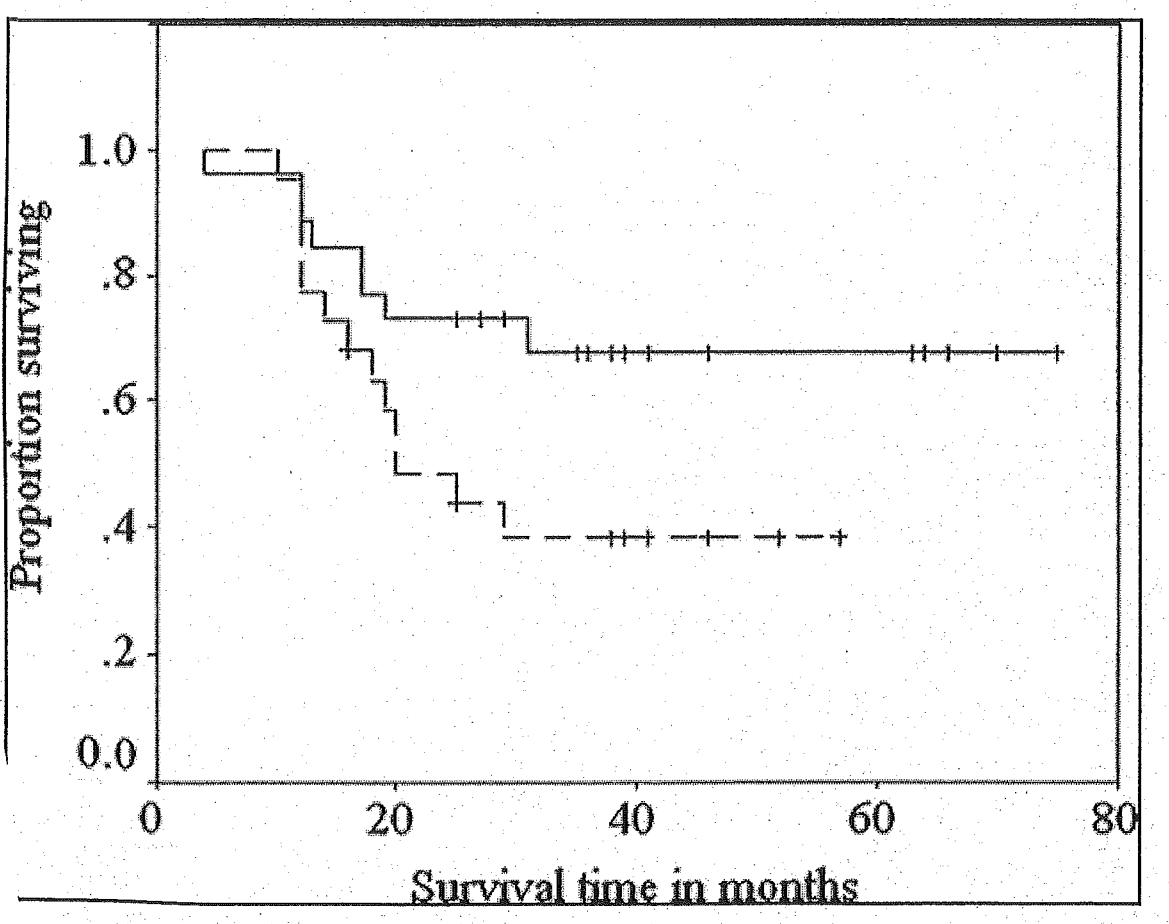

FIGURE 6. Kaplan-Meier survival curves for patients with mucin-producing adenocarcinoma of the lung grouped by the presence (n = 22, dashed line) and absence (n = 26, solid line; $P < 0.05$) of intrapulmonary metastases.

CT Findings	5-Year DFS Rate of Patients With Absent CT Finding (%)	n (%)	5-Year DFS Rate of Patients With Present CT Finding (%)	n (%)	Log Rank P
Air bronchogram	72.7	11 (22.9)	49.4	37 (77.1)	0.33
Area of ground-glass attenuation	66.7	12 (25.0)	49.9	36 (75.0)	0.45
Areas of air-space consolidation	83.3	12 (25.0)	44.9	36 (75.0)	0.06
Bubble-like lucencies	46.7	25 (52.1)	64.5	23 (47.9)	0.31
Interlobular septal thickening	61.9	15 (31.3)	38.1	33 (68.8)	<0.05
Centrilobular nodules	92.3	36 (75.0)	10.0	12 (25.0)	<0.0001
Mucus filling of airways	85.8	29 (60.4)	0.0	19 (39.6)	<0.0001
Bulging of interlobar fissure	59.8	34 (70.8)	42.9	14 (29.2)	0.23
Cavitation	53.4	41 (85.4)	55.6	7 (14.6)	0.43
Traction bronchiectasis or bronchiolectasis	54.4	37 (77.1)	54.6	11 (22.9)	0.91
Intralobular reticular opacities	57.6	43 (89.6)	40.0	5 (10.4)	0.80

Patients were stratified by the presence or absence of each thin-section CT finding on survival.
DFS indicates disease-free survival; MPA, mucin-producing adenocarcinoma.

TABLE 4. Univariate Analysis of Thin-Section CT Findings on 5-Year Disease-Free Survival in Patients With GCA of the Lung

CT Findings	RR	95% CI	P
Presence of centrilobular nodules (vs. absence)	10.5	1.9–59.3	<0.01

RR associated with patient death is estimated for CT findings.
95% CI indicates 95% confidence interval; MPA, mucin-producing adenocarcinoma.

TABLE 5. Cox Proportional Hazard Analysis of Thin-Section CT Findings on 5-Year Disease-Free Survival in Patients With GCA of the Lung

Discussion

In this study, we examined the correlation between thin-section CT findings and histopathologic findings to determine the prognostic value of thin-section CT findings in patients with MPA of the lung. We found that the presence of centrilobular nodules and mucus plugging on thin-section CT was associated with an increased likelihood of intrapulmonary metastases and that the presence of centrilobular nodules was strongly predictive of a poor prognosis.

Several groups of investigators have demonstrated that MPA of the lung has distinct genetic and immunohistochemical features.2-5 Immunohistochemical staining, including lysozyme and epithelial mucinous glycoprotein, has revealed that MPA of the lung has a specific pattern of mucin gene expression different from those of other types of lung adenocarcinoma.4 Mucin-producing adenocarcinoma of the lung also has a greater prevalence of intrapulmonary metastases than other subtypes of lung adenocarcinoma.2-5 These characteristics are at least partly responsible for the poor prognosis of MPA of the lung.

Mucin-producing adenocarcinoma of the lung exhibited a variety of CT features in our study. Characteristic