Cavitated tumor as a clinical subentity in squamous cell lung cancer patients

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Cavity in lung cancer patients is usually attributed to worse prognosis, which could be caused by diagnostic difficulties and late surgery. The aim of this study is to identify cavity as clinical subentity in squamous cell lung cancer (SqCLC) patients. 1094 patients with I^0–III^0 of SqCLC underwent surgery with the purpose of radical lobectomy or pneumonectomy. The patients were divided into two groups: 100 patients with cavity (cSqCLC) and 994 with solid tumor (sSqCLC). The clinical, histological and prognostic features were compared for the both groups. The Cox multivariate analysis of the prognostic factors was performed. The survival curves for both groups were compared. cSqCLC patients showed lower body mass and more frequent hemoptoe. They had larger tumors, located peripherically, rarer nodal involvement and atelectasis. Despite the similar cancer stage and the exploratory thoracotomies ratio, cSqCLC patients lived shorter. The survival curves for both groups were different: in all population, for patients after radical surgery and even after exploratory thoracotomy. We conclude that the cavitation in SqCLC patients can be regarded as a separate subentity related to worse prognosis.

Key words: Lung cancer, squamous cell, surgery, survival, prognosis, cavitation.

The mechanism of cavity formation in lung cancer (LC) patients has remained unclear. Cavitation is believed to be a result of tumor ischemia or infection and necrosis with subsequent expectoration of necrotic masses by drainaging bronchus. There are also other mechanisms leading to cavitation: ectatic changes or alveolar expansion [9, 15, 29, 44, 45, 65, 70, 71]. Radiologically, cavity with fluid level is often regarded as lung abscess [4, 15, 16, 22, 44, 65, 69].

Until World War II only a few case reports, without a deeper insight into this problem, had been published [68]. In the 1950s this issue was under discussion due to the necessity of distinguishing cavitary tuberculosis and lung abscess [17, 53, 58]. The following possibilities were taken into account:

I. Growth of secondary cancer in posttuberculotic cavity lung cyst

II. Cavity or abscess formation in primary lung cancer.

Among patients with lung abscess, diagnosed radiologically, those with LC accounted for 8–52% [15, 17, 53, 69]. 10% of the patients who had lung abscess diagnosed clinically showed LC at autopsy [22, 59]. The worse prognosis for patients with cavity lung cancer (cLC) was attributed to late surgery caused by diagnostic difficulties.

Not until 1966 did Mouroux et al [48] try to identify any clinical, histological and prognostic features confirming cLC as a separate entity specific to cavitated bronchopulmonary tumors. Unfortunately Mouroux based his study on a small group of patients (35 cLC vs 318 solid, sLC) and did not succeed due to non-homogenous material (all cancer types, stages and methods of treatment).

We have not found any further studies on this subject in the literature. Our study is based on histologically pure group of squamous cell lung cancer (SqCLC) patients, treated surgically (I^0–III^0). These patients account for about a half of those operated on for LC. Cavity is quite common in SqCLC patients (cSqCLC) [9, 15, 22, 29, 37, 44, 48, 62]. We compared clinical and radiological features for the patients with cavity and those with solid SqCLC (sSqCLC). We decided to examine whether the worse prognosis in cSqCLC group could be attributed only to diagnostic difficulties or caused by more aggressive clinical course.

Preoperative radio- and chemotherapy [43] are not

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usually used in cSqCLC patients because of the tumor destruction and infection [44]. For this reason it was easier to estimate the results of primary treatment.

The aim of our study was to identify cavity as a clinical subentity among SqCLC.

Patients and methods

One thousand and ninety four consecutive SqCLC patients (1039 men and 55 women) underwent surgery in the years 1956–1996. All patients were operated on for the purpose of radical lobectomy or pneumonectomy. In none of them any other kind of cancer was diagnosed. The patients did not receive chemo- or/and radiotherapy before surgery.

X-ray examination and bronchoscopy were used to diagnose and assess the clinical stage of cancer. We re-examined X-ray pictures and assessed stage of cancer in all 1094 patients, using UICC 1997 criteria [63].

Out of 1094 patients, 841 were operated on radically. As radical we defined lobectomy or pneumonectomy with negative margins confirmed histologically. We also included 34 segmentectomies assessed as radical by a surgeon and pathologist (I^0 SqCLC patients) [47]. Elective mediastinal lymphadenectomy was not performed routinely [28, 49]. One hundred and sixteen (13.8%) patients after radical surgery received adjuvant radiotherapy, 2 had also chemotherapy and 75 (8.9%) were given chemotherapy only. The indication to adjuvant treatment was $pIII^0$ SqCLC, especially pN_2 [5, 13, 14, 24, 25].

All patients were followed-up up to 31 December 1999. We collected the data of all 841 (100%) patients after radical surgery. For 13 patients after exploratory thoracotomy we assumed the date of last contact as the date of death [55].

As a death of cancer we defined the death after exploratory thoracotomy or non-radical surgery as well as unexplained deaths.

For 1094 patients the following data were gathered: sex, age, height, body mass, Body Mass Index (BMI=kg.m^{-2}) [56] and smoking period and the number of cigarettes smoked daily.

At X-ray examination 100 (9%) patients out of 1094 showed tumor cavity, empty or partially filled with fluid [10, 22].

We divided 1094 patients into two groups: with tumor cavity (cSqCLC) and solid tumor (sSqCLC): 100 and 994, respectively. For the both groups we compared: population features, clinical symptoms, radiological features, duration of history, pre-hospital and hospital observation, type of surgery, as well as stage of cancer [18, 19, 21, 39].

The probability of survival and failure was computed by the Kaplan-Meier method [36]. The survival curves were compared in the both groups: I. for all patients (n=1094), II. for patients after radical surgery (n=841), III. for those after exploratory thoracotomy or non-radical resection (n=253).

The log-rank test [52] was applied to compare the differences between the curves. The Cox multivariate analysis [12] was performed to assess the tumor cavitation as a prognostic factor. The Statistica PL 5.1 software was applied. A p-value of less than 0.05 was considered significant.

Results

In both groups of SqCLC patients, men were predominant. In the group of 100 cSqCLC patients there was only one woman and among 994 sSqCLC patients 53 women (p=0.09).

Comparing the two groups, body mass and BMI were lower in cSqCLC group (on average by 3 kg and 1 kg.m^{-2}, respectively; Tab. 1). Hemoptoe was more frequent in this group (Tab. 2). The average duration of symptoms as well as prehospital and radiological observation did not differ significantly for both groups. Only preoperative hospitaliza-

Table 1. Comparison of population features for cSqCLC and sSqCLC patients

Feature	SqCLC	n	$\bar{x} \pm SD$	Me	Range	p
Age (years)	s	994	55 ± 8	55	18–73	0.4211
	c	100	56 ± 7	56	26–69	
Height (cm)	s	870	170 ± 7	170	141–191	0.5288
	c	95	169 ± 6	169	154–184	
Body mass (kg)	s	909	69 ± 10	67	52–105	**0.0111**
	c	98	66 ± 9	65	49–94	
BMI (kg x m^{-2})	s	870	23.9 ± 2.8	23.6	16.5–36.3	**0.0050**
	c	95	22.9 ± 2.8	22.3	17.6–31.5	
Cigarettes per day	s	976	24 ± 10	20	4–60	0.6322
	c	100	24 ± 10	20	10–60	
Smoking period (years)	s	976	34 ± 9	35	3–57	0.2142
	c	100	36 ± 9	36	4–54	

Table 2. Clinical symptoms for cSqCLC and sSqCLC patients

Symptoms n (%)	cSqCLC n=100 (%)		sSqCLC n=994 (%)		p
Without any*	19	(19)	266	(27)	0.0901
cough	48	(48)	529	(53)	0.3727
hemoptoe	47	(47)	338	(34)	**0.0095**
pneumonia	11	(11)	103	(10)	0.3423
fever	35	(35)	302	(30)	0.3404
pain	23	(23)	264	(27)	0.4406
dyspnea	23	(23)	233	(23)	0.9210

*detected accidentally at X-ray examination.

Table 3. Radiological and intraoperative assessment of pulmonary pathology for cSqCLC and sSqCLC patients

Changes within chest	cSqCLC n	n=100 (%)	sSqCLC n	n=994 (%)	p
Radiological					
Tumour located peripherically	64	(64)	324	(33)	**0.0000**
Nodal involvement	31	(31)	432	(44)	**0.0162**
Atelectasis:	15	(15)	355	(36)	**0.0000**
– lobe	15	(15)	345	(35)	–
– lung	–	– 10	(1)	–	
Pneumonia	26	(26)	300	(30)	0.3836
Intraoperative					
Atelectatic and inflammatory	31	(31)	429	(43)	**0.0057**
Cancer involvement:					
– fissura	19	(19)	172	(17)	0.6702
– pericardium	10	(10)	126	(13)	0.4395
– aorta /vcs*	6	(6)	75	(8)	0.7172 (y)
– diaphragm	2	(2)	24	(2)	0.9323 (y)
– chest wall	16	(16)	85	(9)	**0.0142**

*vcs – superior caval vein.

Table 4. Type of surgery for cSqCLC and sSqCLC patients

Type of surgery	cSqCLC n	n=100 (%)	sSqCLC n	n=994 (%)	p
Exploratory thoracot:	18	(18)	235	(24)	0.2061
– segmentectomy	2	(2)	32	(3)	0.7133 (y)
– lobectomy	50	(50)	350	(35)	**0.0032**
– pneumonectomy	18	(18)	287	(29)	**0.0212**
Extended surgery:	12	(12)	91	(9)	0.3531
– pneumonectomy+	7	(7)	75	(5)	0.9883 (y)
– lobectomy+	5	(5)	16	(2)	**0.0485** (y)

Table 5. Stage of cancer: cSqCLC and sSqCLC patients

TNM stage	cSqCLC n	(%)	sSqCLC n	(%)	p
I	37	(37)	331	(33)	
II	35	(35)	297	(30)	0.211
III	28	(28)	366	(37)	

tion was shorter (by one week) for cSqCL patients (p=0.0269).

cSqCLC patients had larger tumor diameter. Tumours located peripherically were twice frequent. Inflammation and atelectatic changes, as well as hilar nodal enlargement were rarer in this group (Tab. 3).

The ratios of exploratory thoracotomies and non-radical resections were similar for both groups. Lobectomies were more frequent in cSqCLC group (Tab. 4). The stage of cancer was similar for both groups (Tab. 5). The 5 and 10-year survivals estimated for all 1094 patients were 31% and 24%, respectively.

Comparing the both groups, cSqCLC patients had 5 and 10-year survivals shorter. They were:

1) In the population of 1094 patients: 21% and 13% vs 32% and 25% for sSqCLC, respectively (Fig. 1)

2) Among 841 patients after radical surgery: 25% and 17% vs 43% and 33% for sSqCLC, respectively (Fig. 2).

The significantly shorter survival was observed in the remaining 253 patients after exploratory thoracotomy or non-radical surgery (Fig. 3).

Cavitation was considered to be a prognostic factor and evaluated along with other clinical factors by the Cox multivariate analysis. Table 6 presents an initial (a) and a final (b) models.

cSqCLC turned out to be an independent, unfavorable prognostic factor.

Discussion

Our group of 1094 SqCLC patients after surgery is one of the most numerous [8, 27, 30, 32, 35, 47, 66] and our study embraces the longest period of the observation in the literature [3, 34, 35, 50].

Most studies consider non-homogenous groups of non-small cell lung cancer (NSCLC) patients, which can influence clinical characteristics, cancer advancement and the results of surgery.

Taking into account the following criteria: the same histological type of cancer (SqCLC), unchanged diagnostic rules and unchanged surgical doctrine, our presented group can be clinically presumed as homogenous and suitable enough to be assessed in our comparative study [19, 21, 39, 46]. Cavitation was not taken into account while indicating patients to surgery, so the choice of the SqCLC patients in our study was accidental. The proportions of cSqCLC and sSqCLC patients in the subsequent decades were similar. Even the introduction of such diagnostic methods as ultrasonography and computed tomography did not influence the resectability in both groups (the ratios of exploratory thoracotomies were falling parallely) [34].

To eliminate the possible beneficial effects of neo-adjuvant treatment in sSqCLC patients (cavitation is regarded as a contraindication), we excluded from our study all patients who received chemo- or radiotherapy before operation [43].

On the other hand, the patients who received this treatment after surgery were included as they histologically showed positive margins or mediastinal nodal involvement (pN_2) [13].

Comparing different types of LC, cavitation is most frequent in SqCLC. Our cSqCLC patients accounted for 9% of

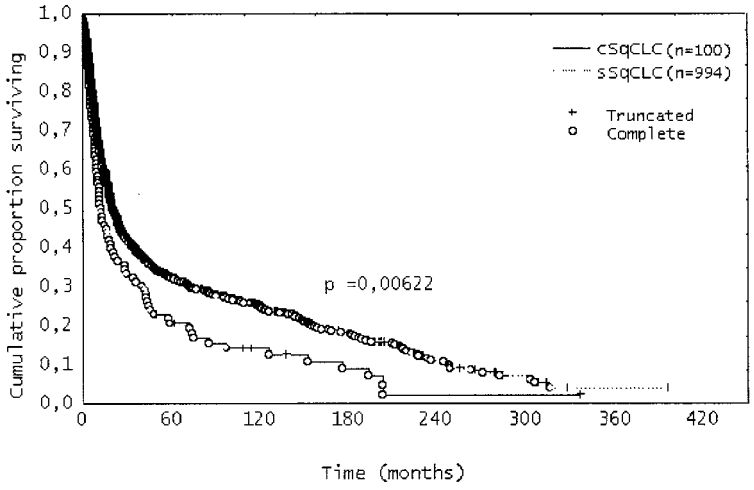

Figure 1. Survival curves for 1094 SqCLC patients operated on between 1956–96.

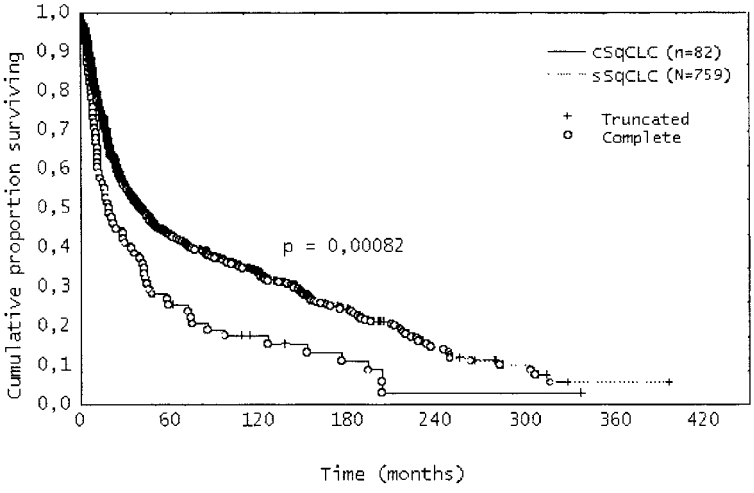

Figure 2. Survival curves for sSqCLC (n=759) and cSqCLC (n=82) patients radically operated on between 1956–96.

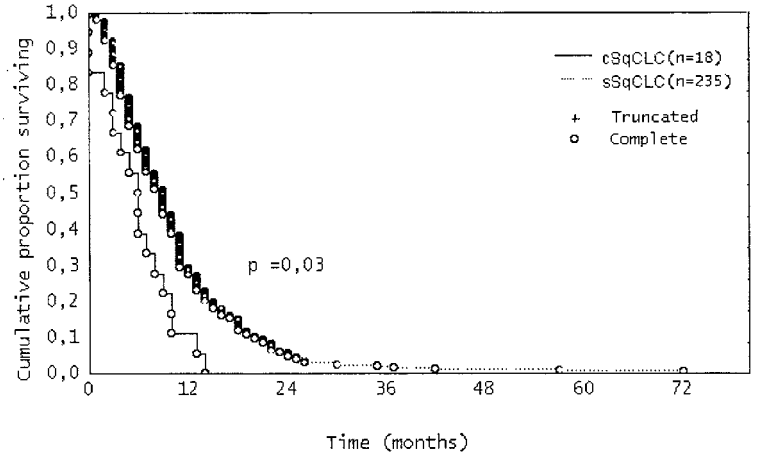

Figure 3. Survival curves for sSqCLC (n=235) and cSqCLC (n=18) patients after explorative thoracotomy or non-radical surgery operated on between 1956–96.

all SqCLC patients operated on, which is in agreement with 6–16% from the literature (Tab. 7).

Cavitation generally was scarcely mentioned in the literature, only while discussing diagnostic difficulties in lung cancer patients. Only Mouroux et al [48] regarded cavity as a possible clinical entity. Unfortunately, they did not manage to indicate any significant differences, either in the clinical course or in the results of treatment in LC patients.

Among our 100 cSqCLC patients, there was only one woman, which was in agreement with women's rate from the literature: 0–10% [10, 15, 22, 71]. Only Mouroux [48] presented the group of 35 patients where women accounted for 22.8%. The author could not explain this fact.

In our study we did not find any correlation between the frequency of cavity and smoking history (the number of smoked cigarettes and smoking duration). Mouroux [48] observed a slightly higher percentage of smokers in cLC patients (94.2% cLC vs 90.5% sLC). This could be explained by the fact that among cLC there were 82.8%) SqCLC patients whereas among sLC only 61% (smokers prevailed in SqCLC group).

Among 1094 patients both body mass and BMI were in agreement with those for the population of healthy men [56]. Comparing cSqCLC and sSqCLC groups, patients with cavity had lower body mass and BMI (on average 3 kg and 0.8 $kg.m^{-2}$, respectively, p=0.021).

Body mass loss is widely regarded as an unfavorable prognostic factor together with such important factors as physical status and cancer stage [18, 39, 51]. The patients who fell below 60% (according to Karnofsky's scale) and 3 points (Zubrod's scale) are not indicated to surgery [1, 2, 41].

The most important criteria while referring for operation are:

I. cancer stage (I^0–III^0 TNM)

II. risk of surgery (ASA) [1].

Surgeons scarcely take into account body mass loss despite the fact that it may result from undetected distant metastases. Among 100 LC patients undergone Positron Emission Tomography (PET), distant metastases were found in 38 with body mass loss <10% and 65 with the loss ≥10% [67].

Among our patients, 19% of cSqCLC and 27% of sSqCLC did not show any symptoms of disease. Neoplasmatic changes were detected accidentally at X-ray examination. These results were in agreement with 12–38% for NSCLC patients from the literature [36, 38]. Mouroux et al [48]

Table 6 (ab). The Cox Multivariate analysis of clinical prognostic factors for 1094 SqCLC patients undergone surgery

(a) initial model Feature	Variant	Relative risk	p
form of cancer	s	1.0000	
	c	1.3603	0.2372
age (years)	≤55	1.0000	
	>55	1.3687	**0.0008**
BMI	≤24	1.0000	
	>24	0.8936	0.2439
T (cm)	≤5	1.0000	
	>5	1.1031	0.3033
N	N_0	1.0000	
	N_{1+2}	1.0817	0.6843
TNM	I	1.0000	
	II+III	1.6183	**0.0166**
(b) final model Feature	Variant	Relative risk	p
N	N_0	1.0000	
	N_{1+2}	1.7331	**0.0000**
age (years)	≤55	1.0000	
	>55	1.4345	**0.0000**
form of cancers	s	1.0000	
	c	1.4638	**0.0017**

Table 7. Cavitation in lung cancer patients

Author	Year	Years of study	cLC n	(%)	Heeds
Good [22]	1960	1953–58	19	(?)	12 SqCLC 4 large cell 3 adeno
Dobrowolski [15]	1968	1957–65	21	(5.8)	9 SqCLC 2 adeno 10 anapl.undiff.
Chaudhuri [9]	1973	1967–70	100	(15.8)	82 SqCLC 4 adeno 3 alveolar 11 undiff.
Lavoie [37]	1977	1970–74	47	(?)	SqCLC
Wallace [65]	1979	1973–77	26	(?)	
Miller [44]	1980	1952–76	47 4	(14.4) (1.6)	SqCLC adeno (autopsy)
Ji [29]	1986	?	100	(?)	
Takashima [61]	1989	?	8 ?	(8.3) (13.9)	SqCLC adeno
Tanigawa [62]	1991	?	? ?	(16.7) (10.3)	SqCLC adeno
Kazerooni [33]	1994	1980–92	4	(13.0)	adeno-plano
Mouroux [48]	1996	1988–92	35	(9.9)	29 (13.0) SqCLC 2 (3.1) adeno
Yamashita [70]	1997	1992–95	5	(13.5)	
Miura 450]	1998	1993–96	7 5	(14.9) (23.8)	adeno. SqCLC (oper)
Our study	2002	1956–96	100	(9.1)	SqCLC

observed similar percentages in 35 cLC and 318 sLC (14.3% and 14.5% respectively).

In patients with operable LC, symptoms usually depend on tumor location: inside or beyond the main bronchi. In SqCLC patients the primary tumor is usually located in main bronchi, especially within bifurcations. This explains the earlier and more frequent symptoms, as well as atelectatic and inflammatory changes [20, 45, 57].

Despite the fact that our cSqCLC patients had tumors located beyond the main bronchi, the tendency to more frequent symptoms was observed (p=0.09). It was caused by more frequent hemoptoe in cSqCLC patients (47% vs 34% for sSqCLC, p<0.0011) [2].

MILLER and MCGREGOR [44] in their autopsy study, based on 877 LC patients confirmed the fact. Massive hemoptoe (history) occurred in almost 50% of cLC patients. The authors also revealed that hemoptoe is more frequent (p=0.0002) in SqCLC than in other types of cancer. Hemoptoe is widely regarded as a symptom, which needs a prompt hospitalization.

Another symptom discussed by MOUROUX [48] was fever. Comparing both groups, fever was more frequent in cLC patients: 28.6% vs 13.5% for sLC (p=0.017). We observed fever in 30% of cSqCLC and 35% of sSqCLC patients.

In our study anamnesis period did not differ for both groups: 5.8 vs 5.6 months for cSqCLC and sSqCLC, respectively. MOUROUX [48] observed shorter duration (3.1 vs 2.7 months for cLC and sLC).

Comparing X-ray pictures for both groups, we observed that cSqCLC patients had: I. larger tumor diameter (on average 1 cm), II. twice frequent peripherical tumor location, III. rarer coexisting atelectatic changes, IV. rarer hilar nodal involvement.

The differences between surgical and pathological measurement remained similar.

The median tumor diameter was 7 cm in cSqCLC patients. Most authors [8, 11, 26, 50] assume 3 cm as a factor of prognostic importance (considered in TNM staging) [63].

We think however, that for SqCLC patients the diameter could be larger and assumed 5 cm [35].

More frequent peripherical tumor location (2/3 cSqCLC vs 1/3 sSqCLC patients) explains rarer atelectatic changes. Central tumor location also influences the radiological assessment of hilar involvement due to overlapping hilar ele-

ments and tumor shadows [60]. In addition, this location is related to more frequent atelectatic and inflammatory changes leading to hilar nodal enlargement. In 44% of sSqCLC patients (vs 31% cSqCLC) hilar nodes were assessed as involved (p=0.0162) [6, 23, 40, 54].

It is astonishing that the presence of potentially infected cavity (abscess-like cSqCLC) was not connected with hilar nodal enlargement.

The advancement of SqCLC for our patients was similar to this for NSCLC in the literature. Until the 1980s III^0 NSCLC patients had prevailed [34, 35, 42] whereas after 1980 the lower stages of cancer were predominant [27, 30]. The changes in TNM classification (1997 eds) [63] caused difficulties in comparing the data because T_3N_0 patients fell from III^0 into II^0 [7].

Among all 1094 patients, the clinical advancement of SqCLC was similar for both groups. cSqCLC patients had larger tumors (T) but less frequent nodal involvement (N) so the differences between the groups were blurred. In sSqCLC central tumor location and related atelectatic and inflammatory changes causing nodal enlargement.

The similar SqCLC advancement for the both groups should have been connected with similar survivals. In fact cSqCLC patients lived shorter. Neither the ratio of exploratory and non-radical surgery, nor the type of radical resection influenced the better prognosis (Tab. 4). We observed the shorter survival in cSqCLC patients both in all population (Fig. 1) and after radical operation (Fig. 2) as well as after exploratory and non-radical surgery (Fig. 3). The survival curves for our 253 patients mirror the natural cancer course [20] and are similar to those shown by VRDOLJAK et al [64] for 130 non-treated NSCLC patients from Croatia.

The shorter survival in cSqCLC group indicates more dynamic cancer course. The Cox multivariate analysis of clinical prognostic factors confirmed the importance of cavity as an unfavorable prognostic factor. It is in accordance with the FIELDING'S [19] and MOUNTAIN'S [46] definition of a prognostic factor.

Our findings show cSqCLC as a possible clinical subentity different from other solid cancers and connected with a worse prognosis. The differences in symptoms, X-ray pictures and clinical course confirm the statement.

Conclusions

In the group of SqCLC, patients with cavity show different clinical and radiological features. In comparison with sSqCLC patients, they have lower body mass and more frequent hemoptoe. Their tumors are larger, usually located peripherically. Nodal involvement, as well as atelectasis is rarer. The prognosis for these patients is worse.

Cavitation can be regarded as a separate subentity in SqCLC group.

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