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REVIEW ARTICLE

Clear cell sugar tumor of the lung; a systematic review for a rare entity

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Summary

Purpose: *The diagnosis and management of patients with a clear cell sugar tumor of the lung (CCSTL) is challenging in the clinical practice due to its rarity.*

Methods: *We performed a systematic review on this field according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We sought eligible articles in Medline through January 1st, 2019.*

Results: *Overall, 104 CCSTL cases were identified and included in the present study. The median age at diagnosis was 52 years (interquartile range 42.5-62.5), whereas the cases were almost equally distributed among males (n=48) and females (n=49). Most of the tumors were asymptomatic (60.7%) and had a benign clinical course (73.3%). Complete tumor resection with a curative intent was the treatment of choice and pathology along with immunohistochemical indices established the diagnosis. However, long-term follow up is recommended, especially among patients with underlying genetic diseases, because disseminated disease may become evident many years following the resection of the primary lesions. Furthermore, an extensive workup for excluding metastasis from another occult primary site is necessary. The updated classification of lung neoplasms has enabled the more frequent reporting of CCSTL cases in the last decade. Interestingly, our time trend analysis showed an increase in malignant cases throughout the years.*

Conclusions: *Both collaborative multicenter studies and basic research on the underlying pathogenetic mechanisms are deemed necessary in order to optimize the diagnosis and personalize the management of patients with this rare entity.*

Key words: *lung neoplasms, clear cell sugar tumor, perivascular epithelioid tumor, systematic review*

Introduction

Lung cancer constitutes the most commonly diagnosed carcinoma and one the leading causes of cancer-related mortality worldwide. Screening of high risk populations with low dose computed tomography (CT) has demonstrated a survival benefit [1,2]. However, the population screening in a large scale has also resulted in an increase in the diagnoses of benign pulmonary neoplasms and nodules with non-specific characteristics [2]. A better understanding of the presentation and the clinical course of these benign entities is considered essential for physicians, in order to efficiently rule out the presence of malignancy and, simultaneously, avoid overtreatment.

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Clear cell sugar tumors of the lung (CCSTL) are rare neoplasms with indolent biologic course that belong to the family of perivascular epithelioid cell tumors (PEComas). There is a slight predominance for females. This tumor can occur at any time throughout life with a mean age at diagnosis of 57 years. CCSTL consists of epithelioid clear cells containing large amounts of glycogen that are immunoreactive for melanocytic markers [3,4]. The diagnostic features of this entity are not well established, due to its rarity. Typically, CCSTLs present as peripherally located "coin lesions", and they are usually found on chest imaging as incidentalomas [5,6]. However, they may be misinterpreted as metastatic lesions originating from renal cell carcinoma (RCC) [7]. CT-guided fine needle aspiration (FNA) and core biopsy are commonly implemented for diagnostic purposes [8-10], whereas wide excision of the lesions constitutes the main therapeutic approach.

Taking all the above into consideration, our aim was to collect and critically present all available literature data regarding CCSTL. To the best of our knowledge, this is the first systematic review in this field.

Methods

Search strategy and eligibility of studies

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was formulated and agreed upon in advance by the study team as per institutional guidelines. Potentially eligible articles were identified in the MEDLINE bibliographical database with end of search date January 1st, 2019. The search strategy included the following algorithm: ("sugar tumor" OR "sugar tumour" OR "sugar cell tumor" OR PEComa OR "perivascular epithelioid cell tumor" OR ("clear cell" AND (tumor OR tumour OR neoplasm OR neoplasms) AND (lung OR pulmonary). There were language restrictions, since only full articles written in English, French, German or Spanish were included. Potentially eligible articles included prospective and retrospective studies, case reports and case series pertaining to humans. Manuscripts not stating authors' names were excluded. Furthermore, manuscripts not referring to the term "sugar tumor" without describing pathologic characteristics of CCSTL were not included due to reporting reasons. CCST without lung involvement were also excluded. Inclusion criteria were applied by reviewing the articles in full-text. Additional articles were identified from the reference lists of retrieved articles, relevant reviews, meta-analyses and expert opinion articles, in a snowball procedure, as previously described [11]. Two reviewers (INS and DIT) carried out the literature search and selection of studies working independently. In case of discrepancies, a third reviewer (TK) provided input in order to reach consensus.

Data abstraction

The data abstraction for each eligible article included pubmed number and number of reported cases; for each case separately the following data were abstracted: gender, age, country, risk factors, clinical symptoms, blood test abnormalities, tumor markers, diagnostic tests (imaging studies, fine needle aspiration/biopsy, other biopsies) and description of their findings, way of ascertainment that the reported tumor was primary and not metastatic, tumor location, surgical treatment, total resectability or residual disease, postoperative complications, revision surgeries, benign or malignant histologic features and clinical course, tumor size, nodal status, presence and site of metastases, stage, differentiation, grade, immunohistochemical indices, radiotherapy, chemo/immunotherapy or targeted therapy, other treatments, overall survival (OS), relapse-free survival (RFS), and follow-up period following diagnosis. Two separately working reviewers (INS and DIT) performed the data abstraction, whereas a third reviewer (IGT) also participated in case of discordances.

Statistics

Descriptive statistics were presented as median (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Bivariate analyses included Kruskal-Wallis one-way analysis of variance for continuous and chi-squared test or Fisher's exact test for categorical variables, as appropriate. The level of statistical significance for all tests was set at α=0.05. All statistical analyses were performed with the SPSS, v25 (IBM Corp. Armonk, NY, USA) statistical package.

Results

Selection of studies

2218 records were retrieved from the search strategy. Following removal of duplicates and exclusion of non-eligible articles based on title and abstract screening, 107 entries remained. Ten publications were excluded due to reporting reasons pertaining to non-clear histopathology data. Thirty-one articles were excluded due to language; the majority of them were written in Japanese and Chinese. Two articles were included from the snowball procedure. Overall, 68 articles [6-10,12-75] encompassing 104 cases were deemed eligible for inclusion in the present systematic review. The flow chart of the selection of studies is depicted in Figure 1.

Description of eligible studies

The characteristics of individual cases are described in Supplementary Table 1. Overall, the median age of the patients was 52 years (IQR 42.5-62.5

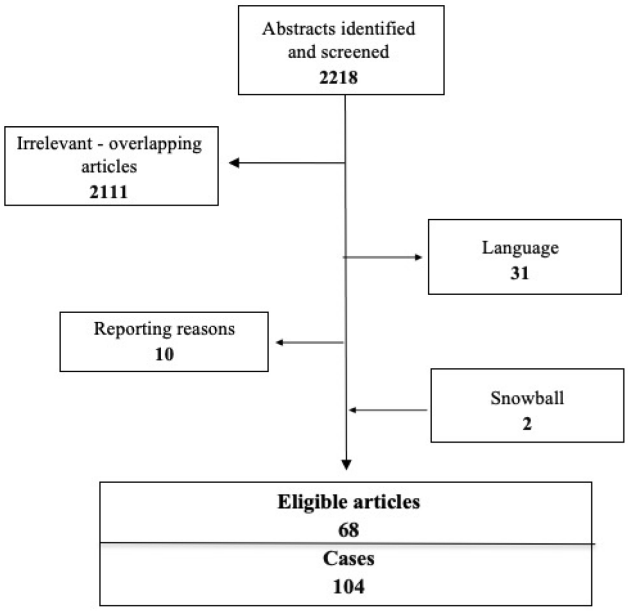

Figure 1. Flowchart of the selection of studies.

years). The reported cases were equally distributed between males and females (49.5% and 50.5%, respectively). The majority of the reports were stemming from the USA (43.3%) and Asia (34.6%). Most of the patients were asymptomatic at the time of diagnosis (60.7%), whereas the most commonly reported symptoms were cough (n=15), dyspnea (n=9), non-specific chest pain (n=9), hemoptysis (n=8) and weight loss (n=5). Among 31 cases with data on smoking history, smoking was reported as a potential predisposing factor in 24 cases, whereas 7 patients were non-smokers. Two patients had a history of systemic hereditary syndromes including the Birt-Hogg-Dube syndrome [29] and tuberous sclerosis [23]. Interestingly, another patient had a concurrent diagnosis of $JAK2^{V617F}$ positive essential thrombocythemia. No specific blood test abnormalities or changes in tumor marker levels were reported. Imaging studies (chest x-ray and/or CT) almost unanimously revealed a well-demarcated, "coin"-like lesion that was enhanced following the administration of intravenous contrast agent. Although bronchoscopy and bronchoalveolar lavage were not always diagnostic, FNA and core biopsy or surgical excision of the lesion established the diagnosis of CCSTL in all cases. Regarding histopathology, CCSTLs were characterized by an abundant vacuolated, granular, or clear cytoplasm that showed positive staining by the periodic acid–Schiff (PAS) method. This material was digested by diastase, which was indicative of the underlying high concentration in glycogen (sugar). Mitoses were rather rare and the Ki67 index was low in all occasions reported. However, there were some cases

Table 1. Demographics of the entire study cohort (n=104)

Demographics	*n (%)*
Age (median, IQR), years	52 (42.5-62.5)
Sex	
Male	48 (49.5)
Female	49 (50.5)
Reporting year	
1971-1990	27 (26)
1991-2007	24 (23)
2008-2018	53 (51)
Geographic area	
Asia	36 (34.6)
USA	45 (43.3)
Europe	20 (19.2)
Other	3 (2.9)
Symptomatic	
No	51 (60.7)
Yes	33 (39.3)
Tumor location	
RLL	21 (25.3)
RML	3 (3.6)
RUL	15 (18.1)
LLL	27 (32.5)
LUL	15 (18.1)
Multiple	2 (2.4)
Type of resection	
Lobectomy	33 (38.4)
Wedge	37 (43)
Segmentectomy	8 (9.3)
Pneumonectomy	2 (2.3)
Enucleation	6 (7)
Type of lesion	
Benign	66 (73.3)
Malignant	24 (26.7)
Tumor size (median, IQR), cm	2.5 (1.6-3.0)
LNM	
N0	20 (80)
N1	3 (12)
N2	2 (8)
Metastatic disease at Px	
No	36 (90)
Yes	4 (10)
Immunohistochemistry	
HMB-45+	46 (90.2)
S-100+	24 (50)
Vimentin+	21 (60)
CD34+	13 (68.4)
Follow-up (median, IQR), mo	24 (7.7-36.0)

*Percentages are derived from patients with available data on the variable of interest. RLL: right lower lobe; RML: right median lobe; RUL: right upper lobe; LLL: left lower lobe; LUL: left upper lobe; LNM: lymph node metastasis; IQR: interquartile range

demonstrating a high proliferative potential [6,22]. In the majority of the CCSTL cases, positivity in the immunohistochemistry markers HMB-45 (90.2%), S-100 (50%), vimentin (60%) and CD34 (68.4%) and negativity in cytokeratins (90%) were used to confirm the diagnosis. Overall, the benign tumors were more common (73.3%) compared with those with a malignant clinical course (26.7%). Interestingly, a case of malignant CCSTL with lung-to-lung metastasis without the involvement of lymph nodes or other metastatic sites was reported [43]. Another case of documented hepatic metastatic disease 10 years following the resection of the primary tumor is also remarkable [75]. The presence of malignant features rendered the differential diagnosis complex [37,51,60,71]. Median tumor size was 2.5 cm (IQR 1.6-3.0 cm) and 80% of the cases did not present with lymph node involvement, whereas metastatic disease at presentation was reported in only four cases. The tumor was located at the right lower lobe (RLL) in 21% of the cases, right median lobe (RML) in 3%, right upper lobe (RUL) in 15%, left lower lobe (LLL) in 7%, left upper lobe (LUL) in 15%, whereas 2% of the patients presented with lesions in multiple lung locations. A detailed description of the approach used in order to exclude other primary sites of clear cell tumor was reported only in 52 (50%) cases. Abdominal imaging studies including ultrasonography, CT and/or pyelogram were the commonest modalities described. The use of positron emission tomography (PET) with or without concurrent CT was also reported in nine cases. The preferred types of surgery were wedge resection (43%) and lobectomy (38.4%), followed by segmentectomy (9.3%), enucleation (7%) and pneumonectomy (2.3%). Complete resection was feasible in all cases, whereas no major postoperative complications were reported. In case of tumor recurrence, re-excision was usually performed. Systemic treatment with chemotherapy or targeted agents has been also reported [22,33,39], whereas only one case-report reported the use of a single course of radiotherapy as a therapeutic modality in localized disease [46]. After a median follow-up of 24 months (IQR 7.7-36.0) among 51 patients with available data, 49 (96.1%) patients remained alive, whereas two (3.9%) patients were dead, both due to the underlying malignant CCSTL. The demographics of the entire study cohort are summarized in Table 1.

Time trend analysis

Taking into consideration that the eligible cases covered a wide timeframe from 1971 to 2018, we opted to perform an exploratory time trend analysis (Table 2). Half (51%) of the reported cases were published during the last decade (2008-2018), whereas the rest were approximately equally distributed during 1971-1990 (26%) and 1991-2007 (23%). The time trend analysis revealed three factors (geographic area, type of lesion and positivity in vimentin) that showed statistically significant changes over time. The number of CCSTL reports stemming from Asia is increasing during the last years (p<0.001) (Figure 2). Although benign lesions are more frequently encountered during the whole time frame, malignant cases show an increase during the most recent time periods (p=0.01) (Figure 3). It is also rather intriguing that among the CCSTL cases with data on immunohistochemical staining with vimentin, the percentage of those with a positive staining raised steadily during the decades (p=0.001). Although most of those published before

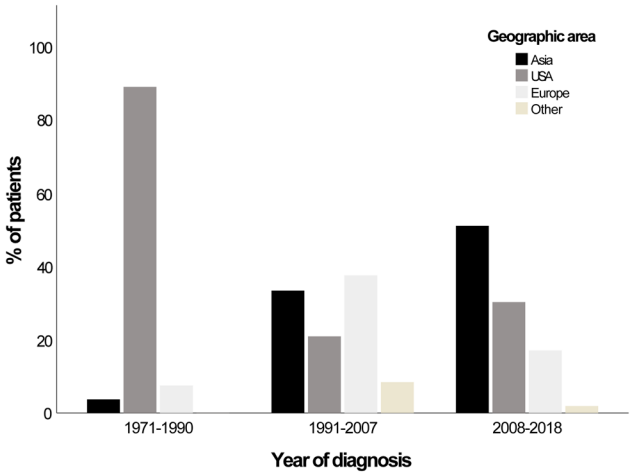

Figure 2. Distribution of the eligible cases according to the geographic area (Asia, USA, Europe, other) in three time periods (1971-1990, 1991-2007, 2008-2018) (p<0.001).

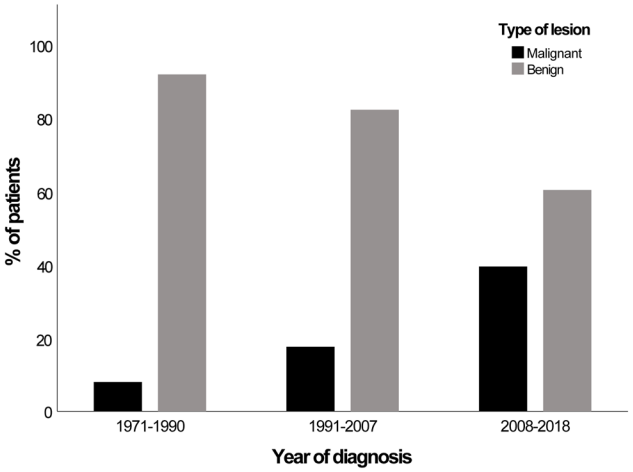

Figure 3. Distribution of the eligible cases according to the type of lesion (benign or malignant) in three time periods (1971-1990, 1991-2007, 2008-2018) (p<0.001).

Table 2. Exploratory time trend analyses

Variables	*Year of diagnosis*			*p value*
	1971-1990 *n (%)*	*1991-2007* *n (%)*	*2008-2018* *n (%)*	
Age	55 (45-62)	49 (32-60)	53 (44-64)	0.38
Sex				0.47
Male	11 (40.7)	11 (47.8)	26 (55.3)	
Female	16 (59.3)	12 (52.2)	21 (44.7)	
Geographic area				<0.001
Asia	1 (3.7)	8 (33.3)	27 (50.9)	
USA	24 (88.9)	5 (20.8)	16 (30.2)	
Europe	2 (7.4)	9 (37.5)	9 (17)	
Other	0	2 (8.3)	1 (1.9)	
Symptomatic				0.074
No	21 (77.8)	10 (47.6)	20 (55.6)	
Yes	6 (22.2)	11 (52.4)	16 (44.4)	
Tumor location				0.79
RL	11 (42.3)	10 (47.6)	18 (50)	
LL	15 (57.7)	10 (47.6)	17 (47.2)	
Bilobar	0	1 (4.8)	1 (2.8)	
Type of resection				0.527
Lobectomy	8 (34.8)	6 (26.1)	19 (47.5)	
Wedge	10 (43.5)	11 (47.8)	16 (40)	
Segmentectomy	2 (8.7)	4 (17.4)	2 (5)	
Pneumonectomy	0	1 (4.3)	1 (2.5)	
Enucleation	3 (13)	1 (4.3)	2 (5)	
Type of lesion				0.01
Benign	23 (92)	14 (82.4)	29 (60.4)	
Malignant	2 (8)	3 (17.6)	19 (39.6)	
Tumor size, cm	2 (1.5-3.0)	2.4 (1.4-3.4)	2.6 (2.0-3.9)	0.43
LNM				0.65
N0	-	6 (85.7)	14 (77.8)	
N1	-	1 (14.3)	2 (11.1)	
N2	-	0	2 (11.1)	
Metastatic disease at Px				0.093
No	12 (92.3)	15 (100)	9 (75)	
Yes	1 (7.7)	0	3 (25)	
Immunohistochemistry				
HMB-45+	-	16 (88.9)	30 (90.9)	0.58
S-100+	4 (44.4)	8 (44.4)	12 (57.1)	0.68
Vimentin+	2 (22.2)	5 (45.5)	14 (93.3)	0.001
CD34+	-	3 (42.9)	10 (83.3)	0.095

RL: right lobe; LL: left lobe; LNM: lymph node metastasis; Px: presentation

1990 reported a negative vimentin staining, the majority of those published from 2008 onwards reported a positive vimentin staining.

Discussion

Clear cell sugar tumors of the lung are rare tumors with indolent course [3,4]. Patient characteristics, diagnostic procedures and the optimal therapeutic approach are not well established. Herein, we have synthesized available literature data and we have provided original and intriguing results.

We observed that CCSTLs occur more commonly during the 6th decade of life, which is in agreement with the previously reported data regarding PEComas [76]. We have not found any gender predominance, which may denote a common pathophysiology background in both men and women. Although no definitive risk factors were reported in the included studies, the co-existence of CCSTLs with tuberous sclerosis and Birt-Hogg-Dube syndrome is worth noting. The incidence of PEComas in general has been associated with tuberous sclerosis and a shared underlying genetic background has been identified [76]. Mutations in members of family of the tuberous sclerosis complex (TSC), which is a tumor suppressor, ultimately result in aberrant cell proliferation that is primarily mediated by the mTOR signaling cascade. Regarding the Birt-Hogg-Dube syndrome, mutations in the FLCN gene result in a malfunctioning folliculin protein, which acts as a tumor suppressor. As a result, multiple pulmonary cysts are formed and there is also a potential for carcinogenesis [77]. Therefore, surveillance among these patient groups might be valuable in terms of prevention. Furthermore, most of the included patients with CCSTL were asymptomatic or experienced minor and/or non-specific symptoms at diagnosis, which underlines the key role of imaging [6, 12, 17, 21, 24, 29-31, 34, 36, 38, 39, 42, 43, 45, 47, 48, 53, 56, 59, 62, 63]. CCSTLs present in CT scans as homogenous lesions that are usually enhanced with intravenous contrast agent in the delayed phase. The non-specific imaging characteristics necessitate the histopathology examination. Cytology with minimally invasive techniques may be preferred for patients with comorbidities, however, its diagnostic value is rather debatable. Therefore, bronchoscopic, CT-guided or even open biopsy is usually implemented to establish the diagnosis.

Although the biopsy results are usually highly suggestive or even pathognomonic for the benign pathologic nature of the CCSTL, complete resection is subsequently performed to rule out the presence of any malignant components. A large tumor size more than 2.5cm may be also indicative of an aggressive behavior [74]. Complete excision is also important for the differential diagnosis and the evaluation of several immunohistochemical indices, especially in cases with a prior inconclusive histology. Furthermore, it is essential to perform an imaging workup in order to ascertain the primary site of CCSTL. In our study, only half of the eligible cases provided a detailed description of such an approach. Taking into consideration that metastasis from clear cell RCC should be excluded primarily, abdominal imaging is of outmost importance. The presence of an underlying genetic syndrome such as tuberous sclerosis should further raise the suspicion of renal tumors [77, 78]. Ideally, PET-CT should be the gold standard, in terms of evaluating a solitary pulmonary lesion.

Regarding surgical management, several approaches have been reported in the literature with lobectomy and wedge resection being the most commonly used. However, due to the rarity of the neoplasm there are no clinical trials, prospective or retrospective studies including a large number of cases and an adequate time of follow-up to reach firm conclusions about the optimal surgical approach. In our study, a survival analysis evaluating the surgical modalities was not possible because of the limited available follow-up of the patients and the absence of survival events. Therefore, total excision of the lesion with curative intent should be currently considered the mainstay of treatment for localized CCSTL [22]. Local external radiation or observation could be also considered for older patients or those with comorbidities who are unfit for surgery. Regardless the therapeutic approach, the need for long-term imaging follow up has to be highlighted especially among patients with putative risk factors, taking into consideration that disseminated disease may become evident may years following the primary resection [55,75].

Chemotherapy has to be considered for patients with metastatic disease. As aforementioned, PEComas are characterized by the upregulation of the mTOR signaling pathway [76]. Thus, targeted therapy with mTOR inhibitors is a rational approach. Indeed, a few available case reports and case series have shown promising results with the administration of either temsirolimus, everolimus or sirolimus in patients with malignant PEComas. Interestingly, in a recent comparative analysis mTOR inhibitors have shown a prolonged PFS benefit compared with antiangiogenetic agents and anthracycline- or gemcitabine-based regimens, which may be considered in subsequent lines of therapy [79, 80]. Taking into consideration that CCSTL is an orphan disease, we pledge for the off-label administration of mTOR inhibitors in metastatic CCSTL. Further genomic

studies in the field could enable the use of other targeted agents tailored to each patient.

The importance of novel agents is confirmed by the results of our time trend analysis. Although most reported cases of CCSTLs refer to benign neoplasms, there is a significant increase in the reporting of malignant cases throughout the years. It is intriguing to hypothesize that exposure to potentially oncogenic environmental factors in the context of the modern lifestyle may contribute to the more frequent development of a malignant phenotype. Moreover, a possible explanation might be the advances in histopathology that allow for a more accurate diagnosis of CCSTL with malignant features compared to the past. The integration of genetic, clinical and radiological indices in the pathologic classification of lung tumors has enabled the detailed sub-classification and easy recognition of rare subtypes such as the CCSTL. This may at least partially explain the fact that half of the included cases have been reported during the last decade. Furthermore, it may explain the increase in vimentin positive cases that has been shown throughout the years. Regarding the latter, this observation may be also related to the increase in malignant CCSTLs and the presence of mesenchymal stem cells in these lesions.

Several limitations of our study have to be discussed. As aforementioned, survival analyses were not possible due to a lack of reported events and adequate follow-up. Furthermore, the reporting of data was not uniform across the included studies and, thus, any comparisons among the cases should be made with caution. In this context, our analysis based on case reports and case series should be considered rather exploratory. No prospective studies were identified in order to provide more robust results in terms of level of evidence. It should be also noted that a documented exclusion of other primary sites of CCSTs was provided in only half of the cases; therefore, a possible misclassification of metastatic CCSTs as primary CCSTLs can be entirely ruled out. Another source of misclassification could be the evolving classification of lung neoplasms throughout the years. Last but not least, the observed increase in the number of reported cases stemming from Asia in the last decade may not be indicative of an increase in incidence; it may reflect that Asian authors have been publishing in English instead of Chinese or Japanese. Unfortunately, we could not include the cases written in Asian in our study due to language restrictions, as described in the "selection of studies" section.

Among the strengths of our study is the novelty of our approach, the extensive literature search including the "snowball" procedure, along with the inclusion of studies written in English, German, Spanish and French.

In conclusion, we have provided an extensive overview of the CCSTL characteristics based on 104 cases reported worldwide from 1971 to 2018. Both collaborative multicenter studies and basic research on the underlying pathogenetic mechanisms are deemed necessary in order to optimize the diagnosis and personalize the management of patients with this rare entity.

Conflict of interests

The authors declare no conflict of interests.

References

1. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment, Mayo Clin Proc 2019;94:1623-40.
2. Usman Ali M, Miller J, Peirson L et al. Screening for lung cancer: A systematic review and meta-analysis, Prev Med 2016;89:301-14.
3. Hornick JL, Fletcher CD. PEComa: what do we know so far? Histopathology 2006;48:75-82.
4. Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F. PEComas: the past, the present and the future, Virchows Arch 2008;452:119-32.
5. Chen YB, Guo LC, Huang JA, Ji C, Ling CH. Clear cell tumor of the lung: a retrospective analysis, Am J Med Sci 2014;347:50-3.
6. Kalkanis A, Trianti M, Psathakis K et al. A clear cell tumor of the lung presenting as a rapidly growing coin lesion: is it really a benign tumor? Ann Thorac Surg 2011;91:588-91.
7. Masur Y, Becker HP, Fackeldey V. Sugar tumor. Rare differential diagnosis of pulmonary clear cell tumor after renal carcinoma. Urologe A 2013:42:1250-4.
8. Edelweiss M, Gupta N, Resetkova E. Preoperative diagnosis of clear cell "sugar" tumor of the lung by computed tomography-guided fine-needle biopsy and core-needle biopsy. Ann Diagn Pathol 2007;11:421-6.
9. Kim WJ, Kim SR, Choe YH et al. Clear cell "sugar" tumor of the lung: a well-enhanced mass with an early washout pattern on dynamic contrast-enhanced computed tomography. J Korean Med Sci 2008;23:1121-4.
10. Policarpio-Nicolas ML, Covell J, Bregman S, Atkins K. Fine needle aspiration cytology of clear cell "sugar" tumor (PEComa) of the lung: report of a case. Diagn Cytopathol 2008;36:89-93.

11. Ntanasis-Stathopoulos I, Tsilimigras DI, Georgiadou D et al. Squamous cell carcinoma of the pancreas: A systematic review and pooled survival analysis. Eur J Cancer 2017;79:193-204.
12. Adachi Y, Kitamura Y, Nakamura H et al. Benign clear (sugar) cell tumor of the lung with CD1a expression. Pathol Int 2006;56:453-6.
13. Ahrens WA, Folpe AL. CD1a immunopositivity in perivascular epithelioid cell neoplasms: true expression or technical artifact? A streptavidin-biotin and polymer-based detection system immunohistochemical study of perivascular epithelioid cell neoplasms and their morphologic mimics. Hum Pathol 2011;42:369-74.
14. Arafah MA, Raddaoui E, Alsheikh A, Hajjar WM, Alyousef F. Mimicry of sugar tumor and minute pulmonary meningothelial-like nodule to metastatic lung deposits in a patient with rectal adenocarcinoma. Ann Saudi Med 2013;33:400-3.
15. Ayadi-Kaddour A, Ben Slama S, Braham E et al. Clear cell tumor of the lung. A case report with review of the literature. Rev Pneumol Clin 2006;62(6 Pt 1):395-8.
16. Becker NH, Soifer I. Benign clear cell tumor ("sugar tumor") of the lung, Cancer 1971;27:712-9.
17. Bonetti F, Pea M, Martignoni G et al. Clear cell ("sugar") tumor of the lung is a lesion strictly related to angiomyolipoma--the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology 1994;26:230-6.
18. Calio A, Mengoli MC, Cavazza A et al. Cathepsin K expression in clear cell "sugar" tumor (PEComa) of the lung. Virchows Arch 2018;473:55-9.
19. Chang M, Lim D, Genovesi M. Clear cell "sugar" tumor of the lung: a case report and review of the literature. AME Case Rep 2018;2:40.
20. Das S, Cherian SV, Das N et al. A 52-year-old smoker with an incidental pulmonary nodule. Chest 2012;141:1346-50.
21. Drebber U, Ortmann M, Kasper HU et al. Clear cell tumor of the lung], Pathologe 2005;26:378-82.
22. Eldessouki I, Gaber O, Riaz MK, Wang J, Abdel Karim N. Clinical Presentation and Treatment Options for Clear Cell Lung Cancer: University of Cincinnati A Case Series and Literature Review of Clear Cell Lung Cancer. Asian Pac J Cancer Prev 2018;192373-6.
23. Flieder DB, Travis WD. Clear cell "sugar" tumor of the lung: association with lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis. Am J Surg Pathol 1997;21:1242-7.
24. Gaffey MJ, Mills SE, Askin FB et al. Clear cell tumor of the lung. A clinicopathologic, immunohistochemical, and ultrastructural study of eight cases. Am J Surg Pathol 1990;14:248-59.
25. Gaffey MJ, Mills SE, Frierson HF, Jr. Askin FB, Maygarden SJ. Pulmonary clear cell carcinoid tumor: another entity in the differential diagnosis of pulmonary clear cell neoplasia. Am J Surg Pathol 1998;22:1020-5.
26. Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung. Immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644-53.
27. Garzon JC, Lai FM, Mok TS et al. Clear cell carcinoma of the lung revisited. J Thorac Cardiovasc Surg 2005;130:1198-9.
28. Gora-Gebka M, Liberek A, Bako W, Szumera M, Korzon M, Jaskiewicz K. The "sugar" clear cell tumor of the lung-clinical presentation and diagnostic difficulties of an unusual lung tumor in youth. J Pediatr Surg 2006;41:e27-9.
29. Gunji-Niitsu Y, Kumasaka T, Kitamura S et al. Benign clear cell "sugar" tumor of the lung in a patient with Birt-Hogg-Dube syndrome: a case report. BMC Med Genet 2016;17:85.
30. Han B, Jiang G, Wang H, He W, Liu L, Song N. Benign clear cell tumor of the lung. Ann Thorac Surg 2010;89:2012-4.
31. Harbin WP, Mark GJ, Greene RE. Benign clear-cell tumor ("sugar" tumor) of the lung: a case report and review of the literature. Radiology 1978;129:595-6.
32. Hashimoto T, Oka K, Hakozaki H et al. Benign clear cell tumor of the lung. Ultrastruct Pathol 2001;25:479-83.
33. Hayashi T, Haba R, Kushida Y et al. Cytopathologic findings and differential diagnostic considerations of primary clear cell carcinoma of the lung. Diagn Cytopathol 2013;41:550-4.
34. Hernandez Gonzalo D, Salinas Martin MV, Borderas Naranjo F. Benign clear cell tumor of the lung. A case report and diagnostic features. Cir Esp 2008;83:330-1.
35. Hirata T, Otani T, Minamiguchi S. Clear cell tumor of the lung. Int J Clin Oncol 2006;11:475-7.
36. Hoch WS, Patchefsky AS, Takeda M, Gordon G. Benign clear cell tumor of the lung. An ultrastructural study. Cancer 1974;33:1328-36.
37. Kavunkal AM, Pandiyan MS, Philip MA et al. Large clear cell tumor of the lung mimicking malignant behavior. Ann Thorac Surg 2007;83:310-2.
38. Kim HY, Choi JH, Lee HS, Choi YS, Kim A, Kim HK. Sclerosing Perivascular Epithelioid Cell Tumor of the Lung: A Case Report with Cytologic Findings. J Pathol Transl Med 2016;50:238-42.
39. Kitada M, Ozawa K, Sato K, Hayashi S, Miyokawa N, Sasajima T. Clear cell carcinoma of the lung. Gen Thorac Cardiovasc Surg 2010;58:87-90.
40. Klein JS, Goldin HM, Keegan C, Shiomoto G, Israel SR, Bronson DM. Clear-cell carcinoma of the lung in a patient treated with cyclosporine for epidermolysis bullosa acquisita. J Am Acad Dermatol 1991;24(2 Pt 1):297.
41. Kosjerina Z, Kuhajda I, Koledin M, Koledin B, Stojanovic M, Pocuca M. Clear cell "sugar" tumor of the lung - case report. Cent Eur J Med 2013;8:41-4.
42. Liebow AA, Castleman B. Benign clear cell ("sugar") tumors of the lung. Yale J Biol Med 1971;43:213-22.
43. Lim HJ, Lee HY, Han J, Choi YS, Lee KS. Uncommon of the uncommon: malignant perivascular epithelioid cell tumor of the lung. Korean J Radiol 2013;14:692-6.
44. Lin XY, Zhang H, Tang N et al. Expression and diagnostic implications of carbonic anhydrase IX in several tumours with predominantly clear cell morphology. Histopathology 2015;66:685-94.
45. Makek M, Ruttner JR. Benign clear cell tumor ("sugar tumor") of the lung. Case report and review of the literature (author's transl). Langenbecks Arch Chir 1979;348:177-81.

46. McNamee CJ, Simpson RH, Pagliero KM, Meyns B, Hamilton-Wood C. Primary clear-cell carcinoma of the lung. Respir Med 1993;87:471-3.
47. Mizobuchi T, Masahiro N, Iwai N, Kohno H, Okada N, Nakada S. Clear cell tumor of the lung: surgical and immunohistochemical findings. Gen Thorac Cardiovasc Surg 2010;58:243-7.
48. Nakanishi K, Kawai T, Suzuki M. Benign clear cell tumor of the lung. A histopathologic study. Acta Pathol Jpn 1988;38:515-22.
49. Nehra D, Vagefi PA, Chang H et al. Clear cell sugar tumor of the lung masquerading as tuberculosis in a pediatric patient. J Thorac Cardiovasc Surg 2010;139:e108-9.
50. Neri S, Ishii G, Aokage K et al. Multiple perivascular epithelioid cell tumors: clear cell tumor of the lung accompanied by angiomyolipoma of the liver. Ann Thorac Cardiovasc Surg 2014;20 (Suppl):453-6.
51. Olivencia-Yurvati AH, Rodriguez AE. Clear cell "sugar" tumor of the lung: benign or malignant? Int Surg 2015;100:924-6.
52. Panizo-Santos A, Sola I, de Alava E, Lozano MD, Idoate MA, Pardo FJ. Angiomyolipoma and PEComa are immunoreactive for MyoD1 in cell cytoplasmic staining pattern. Appl Immunohistochem Mol Morphol 2003;11:156-60.
53. Papla B, Demczuk S, Malinowski E. Benign clear-cell "sugar" tumor of the lung--a case report. Pol J Pathol 2003;54:183-5.
54. Rao Q, Cheng L, Xia QY et al. Cathepsin K expression in a wide spectrum of perivascular epithelioid cell neoplasms (PEComas): a clinicopathological study emphasizing extrarenal PEComas. Histopathology 2013;62:642-50.
55. Sale GF, Kulander BG. Benign clear cell tumor of lung with necrosis. Cancer 1976;37:2355-8.
56. Sanai Raggad S, Zouaoui A, Mehiri N et al. Sugar tumor. Tunis Med 2011;89:202-5.
57. Santana AN, Nunes FS, Ho N, Takagaki TY. A rare cause of hemoptysis: benign sugar (clear) cell tumor of the lung. Eur J Cardiothorac Surg 2004;25:652-4.
58. Sen S, Senturk E, Kuman NK, Pabuscu E, Kacar F. PEComa (clear cell "sugar" tumor) of the lung: a benign tumor that presented with thrombocytosis. Ann Thorac Surg 2009;88:2013-5.
59. Shiran MS, Tan GC, Arunachalam N, Sabariah AR, Pathmanathan R. Clear cell "sugar" tumour of the lung: a case report. Malays J Pathol 2006;28:113-6.
60. Song Y, Chen F, Zhang C, Lin X. Spindle cell subtype of pulmonary clear cell tumor with prominent calcification and malignant potential. Thorac Cancer 2017;8:530-4.
61. Suemitsu R, Takeo S, Uesugi N, Inoue Y, Hamatake M, Ichiki M. A long-term survivor with late-onset-repeated pulmonary metastasis of a PEComa. Ann Thorac Cardiovasc Surg 2010;16:429-31.
62. Takanami I, Kodaira S, Imamura T. The use of transbronchial lung biopsy to establish a diagnosis of benign clear cell tumor of the lung: report of a case. Surg Today 1998;28:985-7.
63. Termeer A, Arkenbout PM, Lacquet LK, Cox AL. Benign clear cell tumour of the lung--intermediate filament typing as a tool in differential diagnosis. Eur Respir J 1988;1:288-90.
64. Tsilimigras DI, Bakopoulos A, Ntanasis-Stathopoulos I et al. Clear cell "sugar tumor" of the lung: Diagnostic features of a rare pulmonary tumor. Respir Med Case Rep 2018;23:52-4.
65. Vijayabhaskar R, Mehta SS, Deodhar KK, Pramesh CS, Mistry RC. PEComa of the lung. J Cancer Res Ther 2010;6:109-11.
66. Xu Q, Lu C, Li L, Xu K. Clear cell tumor of the lung: Two case reports and a review of the literature. Medicine (Baltimore) 2016;95:e4492.
67. Yamamato T, Yazawa T, Ogata T, Akaogi E, Mitsui K. Clear cell carcinoma of the lung: a case report and review of the literature. Lung Cancer 1993;10:101-6.
68. Yan B, Yau EX, Petersson F. Clear cell 'sugar' tumour of the lung with malignant histological features and melanin pigmentation-the first reported case. Histopathology 2011;58:498-500.
69. Yazak V, Sargin G, Yavasoglu I et al. Lung Clear "Sugar" Cell Tumor and JAK V617F Positive Essential Thrombocythemia: a Simple Coincidence? Mediterr J Hematol Infect Dis 2013;5:e2013021.
70. Ye T, Chen H, Hu H, Wang J, Shen L. Malignant clear cell sugar tumor of the lung: patient case report. J Clin Oncol 2010;28:e626-8.
71. Yeon EK, Kim JI, Won KY, Lee HN. Growth pattern change of a benign clear cell 'sugar' tumor of the lung: Serial imaging surveillance over seven years. Oncol Lett 2018;15:8652-4.
72. Yousem SA. Immunohistochemical and molecular characterization of clear cell carcinoma of the lung. Hum Pathol 2013;44:2467-74.
73. Zarbis N, Barth TF, Blumstein NM, Schelzig H. Pecoma of the lung: a benign tumor with extensive 18F-2-deoxy-D-glucose uptake. Interact Cardiovasc Thorac Surg 2007;6:676-8.
74. Wang GX, Zhang D, Diao XW, Wen L. Clear cell tumor of the lung: a case report and literature review. World J Surg Oncol 2013;11:247.
75. Sale GE, Kulander BG. 'Benign' clear-cell tumor (sugar tumor) of the lung with hepatic metastases ten years after resection of pulmonary primary tumor. Arch Pathol Lab Med 1988;112:1177-8.
76. Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. Ann Diagn Pathol 2015;19:359-68.
77. Dal Sasso AA, Belem LC, Zanetti G et al. Birt-Hogg-Dube syndrome. State-of-the-art review with emphasis on pulmonary involvement. Respir Med 2015;109:289-96.
78. Henske EP, Jozwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers 2016;2:16035.
79. Sanfilippo R, Jones RL, Blay JY et al. Role of Chemotherapy, VEGFR Inhibitors, and mTOR Inhibitors in Advanced Perivascular Epithelioid Cell Tumors (PEComas). Clin Cancer Res 2019;25:5295-300.
80. Subbiah V, Trent JC, Kurzrock R. Resistance to mammalian target of rapamycin inhibitor therapy in perivascular epithelioid cell tumors. J Clin Oncol 2010;28:e415.

Supplementary Table 1. Patient characteristics of the included studies

Id	*S*	*Age*	*CS*	*L*	*Surgery*	*Revision*	*(B)/ (M)*	*T(cm)*	*N*	*Immunohistochemical indices*		*Other treatments*	
										Positive	*Negative*	*CT*	*RT*
1	F	38	A	LLL	LM	none	B	2.5	N0	vimentin, microphthalmia transcription factor, S100, CD1a, CD10, CD63 and folliculin	cytokeratin, α-smooth muscle actin, HMB45, Melan-A, and PNL-2.	NO	NO
2	M	24	S	RLL	TM,SM	none	B	3×2.5	NR	HMB-45,Melan-A, Syn, CD56, PLAP and PAS	SMA, S-100, cytokeratin, EMA, CD10, CgA, CD117	NO	NO
2	M	59	S	RUL	LM	none	B	2.2×1.5	NR	Melan-A, S-100	HMB-45, CK, EMA, SMA, Des, P63, CK5/6	NO	NO
3	M	51	A	RUL	W	NR	B	1	NR	HMB-45, Melan-A, Vimentin, Ki-67, SMA, CD34, PAS and diastase PAS	S-100, CD56, Synaptophysin, Chromogranin, TTF-1, Surfactant, Napsin, Cytokeratin, p63, CD68, mucicarmine and alcian blue staining	NR	NR
4	NR	NR	NR	NR	NR	NR	5M	NR	NR	CA IX	CA IX	NR	NR
5	M	38	S	LLL	TM,W	NR	B	3,4	NR	HMB-45(strong), vimentin, CD34, S-100, PAS	cytokeratin, desmin, CD68, EMA, RCC, TTF-1	NR	NR
6	M	74	NR	RUL	LM	NR	M	4.4	N2	(all PAS) CK7(6/6), TTF-1(4/6)	(diastase PAS) TTF-1 (2/6), P40 (6/6), CK5/6 (6/6)	NR	NR
6	M	69	NR	LLL	LM	NR	M	9	N1	NR	NR	NR	NR
6	M	48	NR	LUL	lLM	NR	M	4	N0	NR	NR	NR	NR
6	F	52	NR	LUL	LM	NR	M	2	N2	NR	NR	NR	NR
6	F	68	NR	LLL	LM	NR	M	5	N0	NR	NR	NR	NR
6	F	75	NR	RUL	LM	NR	M	2.5	N1	NR	NR	NR	NR
7	M	63	A	LLL	LM,TM	W	M	9×12	N0	SMA, S-100 and CD56	cytokeratin AE1/AE3, HMB45, CD10, CD34, chromogranin and synaptophysin	NR	NR
8	F	44	S	RUL	E	none	B	3.5	NR	HMB-45, NSE and focal S100 antigen	synaptophysin	NO	NR
9	M	38	NR	RML	W	none	B	1.8×1.5×1.3	NR	PAS staining/ HMB-45, SMA, Vimentin	diastase PAS staining/ S100, desmin, AE 1/3, epithelial membrane antigen(EMA), and CD117	NR	NR
10	M	45	NR	NR	NR	NR	B	NR	NR	Cathepsin k, HMB-45, Melan-A, SMA, TFE3	NR	NR	NR
11	M	52	S	RUL	W	NR	B	0.9	NR	HMB-45 and vimentin	cytokeratin AE1/AE3, pancytokeratin, cytokeratin 7, epithelial mem brane antigen, and CD10	NR	NR

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Id	S	Age	CS	L	Surgery	Revision	(B)/ (M)	T(cm)	N	Immunohistochemical indices		Other treatments	
										Positive	Negative	CT	RT
12	M	53	NR	RUL	LM	NR	M	2.2×1.5×1	NR	diffuse and strong membranous staining for CK(AE1/AE3), CK7, and CA19-9, CK5/6	Napsin A, CK20, CDX2, TTF-1, alpha-fetoprotein, chromogranin A, synaptophysin, CD10, and CD56	YES	NR
13	F	75	S	LLL	LM	NR	M	2.8 ×2.2×2.0	free	S100 protein, muscle specific actin (clone HHF35), anti-melanoma associated antigen (clone HMB45), and vimentin.	cytokeratin (AE1 / 3), epithelial membrane antigen (EMA), smooth muscle actin (SMA), desmin, Factor VIII, CD34, neuron specific enolase (NSE), chromogranin and synaptophysin	NR	NR
14	F	75	A	LLL	TM	NR	B	10	NR	HMB-45, S-100	NR	NO	NO
15	M	41	A	LLL	TM,W	NR	NR	2	NR	HMB-45	paired box gene 2, renal cell carcinoma markers, CD-10, and CD-34	NR	NR
16	NR	NR	NR	NR	NR	NR	NR	NR	NR	CD1a	CD1a negative with additional biotin blocking	NR	NR
17	F	50	S	RLL	LM	NR	M	4	N0	HMB45, PNL2, and A013	vimentin, AE1/AE3, or CAM5.2	NR	NR
18	M	51	A	LUL	W,LM,TM	NR	B	NR	NR	(HMB)-45, vimentin, neuron-specific enolase, and CD34, S-100	cytokeratin, desmins, CD68, and thyroid transcription factor-1.	NR	NR
19	M	15	S	RLL	LM	none	B	3×3×2	N0	HMB-45	cytokeratin,epithelial membrane antigen (EMA), synaptophysin,chromogranin, S-100, thyroid ranscription factor-1,surfactant protein, CD31, desmin, mucin, CK-7,C-kit and smooth muscle actin	NO	NO
20	F	65	A	LLL	W	NR	B	1×0.9	N0	Vimentin, HMB-45, Melan-A, CD34, Ki-67 <1%	Cytokeratin (AE1, AE3), Cytokeratin 7, Cytokeratin 20, EMA, Ber-Ep4, S-100, α-SMA, Desmin, Caldesmon	NO	NO
21	F	71	A	RML	LM	none	M	2.5	N0	TTF-1, CK7, PAS staining	αβ-crystallin, Leu M1	YES	NR
22	F	44	S	RUL	PM	none	NR	3×4	NR	periodic acid-Schiff, s100, HMB45 , vimentin and CD34	musine, cytoceratin and CD68.	NR	NR
23	F	10	S	LUL	TM,LM	none	B	2.7×2.7×2	N0	periodic acid–Schiff, (HMB)-45,melan A	cytokeratin, S-100, and smooth muscle actin	NR	NR
24	M	64	NR		TM,W	none	B	1.2×1	N0	PAS staining, HMB-45 and S-100	cytokeratin	NR	NR
25	M	53	A	RLL	SM	NR	B	3	NR	HMB-45, S-100	NR	NR	NR

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Id	S	Age	CS	L	Surgery	Revision	(B)/ (M)	T(cm)	N	Immunohistochemical indices		Other treatments	
										Positive	Negative	CT	RT
26	M	64	S	RLL	W	NR	NR	2.2×2×1.9	N0	HMB-45, Melan-A, CD34	EMA, AE1/AE3, RCC, and S-100	NR	NR
27	F	26	A	RLL	TM,LM	NR	NR	3.7×3.7×5.2	N0	PAS, HMB-45, neurone specific enolase	S-100 protein, CD34	NR	NR
28	M	46	A	LML	TM,SM	NR	B	2.8	N0	PAS, HMB-45, MART-1, vimentin, CD68, and CD34, CD10 antigen	Pancytokeratin cocktail (AE1/AE3, CAM5.2, Cytokeratin MNF116, Keratin 8 and 18), S-100, Desmin, TTF-1	NR	NR
29	F	76	S	LLL	TM,SM	NR	B	2.5	N0	PAS sensitive-diastase, HMB-45, Vimentin and CD34, Ki-67	c-Kit, S-100, Cytokeratin, Myosin, Actin and CD99	No	No
30	M	18	S	RLL	TM,PM	NR	B	12×10	NR	(HMB-45) and S-100	cytokeratin 7, epithelial markers, cytokeratins, and epithelial membrane antigen	NR	NR
31	F	28	S	RLL	LM	NR	B	2.5	NR	HMB-45, S-100	KL1, EMA	NR	NR
32	F	45	NR	RUL	TM	NR	NR	1.5	NR	HMB-45, vimentin and CD34	S-100 protein, epithelial membrane antigen (EMA), and thyroid transcription factor-1 (TTF-1).	NR	NR
33	M	60	A	LLL	W	NR	B	1.4×1.2×1.2	NR	CD1a, S-100 protein (focal), NSE (focal), Melan-A (focal), HMB-45 (focal), Cathepsin 45 (focal)	Ki67<1%, cytokeratin (detected by AE1/ AE3), epithelial membrane antigen (EMA), vimentin, CEA, CA19-9, CD68, lysozyme, α-smooth muscle actin, surfactant apoprotein A, myoglobulin, CD34, CD57, CD68, CD117, chromogranin A, or calretinin, and factor VIII-related antigen	NR	NR
34	M	16	S	LL	TM,W	NR	B	2.5×3.5×3	NR	HMB-45	cytokeratin, LCA, CD34, CD68	NR	NR
35	M	37	S	RUL	LM	NR	NR	4.7	N0	cytokeratins CK7 and AE1/ AE3 and transcriptional protein p63	thyroid transcription factor-1, chromogranin and synaptophysin.	NR	NR
36	F	52	A	RLL	TM,SM	NR	B	2.2	NR	HMB-45	Cytokeratins MNF-116 and CK-7, S-100, NSE, CD57	NR	NR
37	M	48	S	LLL	TM,SM	NR	B	2	NR	S-100 and HMB-45	Carcinoembryonic antigen, cytokeratin 7 and 20, chromogranin and synaptophysin	NR	NR
38	M	68	A	RLL	W	NR	NR	1.2	NR	HMB45 and NSE , S-100 and alfa-1-antichymotrypsin. Ki67 ,CD56, Vimentin	TTF-1, chromogranin and CD117	NR	NR

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Id	S	Age	CS	L	Surgery	Revision	(B)/ (M)	T(cm)	N	Immunohistochemical indices		Other treatments	
										Positive	Negative	CT	RT
39	M	62	A	LLL	W	NR	B	NR	NR	NSE, S-100	Cytokeratin, HMB-45	NR	NR
40	NR	NR	NR	NR	NR	NR	NR	NR	NR	HMB-45, muscle-specific actin, strong MyoD1	Markers for epithelial cells, cytokeratins (AE3/AE1, CAM 5.2) and epithelial membrane antigen	NR	NR
41	F	26	A	RLL	W	NR	B	1.2×1.2×1.2	NR	S-100 protein, vimentin, neuron-specific enolase, and epithelial membrane antigen staining	keratin, neurofilament, chromogranin, carcinoembryonic antigen, and EMB-45	NR	NR
42	M	55	S	RLL	LM	NR	NR	2×1.5×1.5	N1	Cytokeratin, epithelial membrane antigen, LeY	vimentin, desmin, myosin, S-100 protein, and neuron specific enolase; Lex and sialyl Lex-i	NR	hNR
43	F	53	NR	LUL	W	NR	B	2	NR	cytokeratin , neuron-specific enolase and chromagranin	oil-red-O and periodic acid-Schiff. Epithelial membrane antigen, vimentin, synaptophysin, S-100 protein, glial fibrillary acid protein, and with HMB-45	NR	NR
44	F	32	S	Nd	W	NR	NR	1	NR	PAS, HMB-45	Cytokeratin, TTF1, proSPB, proSPC, desmin, smooth muscle actin, muscle-specific actin, and S-100 protein	NR	NR
45	F	57	A	NR	W	NO	B	2.2	N0	HMB45, HMSA-1, actin, vimentin	HMSA-5, chromogranin, desmin, s-100, keratin	NO	NO
46	M	28	A	RLL	LM	NR	B	2	NR	NR	NR	NR	NR
46	F	51	S	RLL	LM	NR	B	2.5×2×2	NR	NR	NR	NR	NR
46	F	50	S	RUL	LM	NR	B	1.5	NR	NR	NR	NR	NR
46	M	29	A	RUL	LM	NR	B	2.5×3	NR	NR	NR	NR	NR
46	F	59	S	LLL	LM	NR	B	2.5×3	NR	NR	NR	NR	NR
46	M	59	A	LUL	W	NR	B	2	NR	NR	NR	NR	NR
46	M	55	A	LUL	W	NR	B	1.5	NR	NR	NR	NR	NR
46	F	64	A	LLL	E	NR	B	2	NR	NR	NR	NR	NR
46	F	45	A	RLL	E	NR	B	6.5×6×2	NR	NR	NR	NR	NR
46	F	46	A	LLL	E	NR	B	2.5×2.5×2	NR	NR	NR	NR	NR
46	F	57	A	RUL	NR	NR	B	2.5×2.5×1.5	NR	NR	NR	NR	NR

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Id	*S*	*Age*	*CS*	*L*	*Surgery*	*Revision*	*(B)/ (M)*	*T(cm)*	*N*	*Immunohistochemical indices*		*Other treatments*	
										Positive	*Negative*	*CT*	*RT*
46	M	45	S	LLL	NR	NR	B	2	NR	NR	NR	NR	NR
47	F	62	A	NR	TM	NR	B	NR	NR	NR	NR	NR	NR
48	F	46	A	LLL	LM	NR	B	2.5	NR	NR	NR	NR	NR
49	M	28	A	LLL	W	NO	B	NR	NR	S-100 protein	neural and markers for epithelial, muscular, vascular, histiocytic and endocrine cell origins	NO	NO
50	F	61	A	LUL	TM	NR	B	3	NR	Vimentin	Keratin	NR	NR
51	M	51	S	NR	W	NR	M	NR	NR	NR	NR	NR	NR
52	F	57	A	LUL	W	NR	B	2	NR	NSE, S-100	Cytokeratin, vimentin, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR
52	M	36	A	LUL	W	NR	B	1.5	NR	NSE, S-100, LEU-7, SYN	Cytokeratin, vimentin, chromogranin, epithelial membrane antigen, neurofilament	NR	NR
52	F	55	A	RML	W	NR	B	0.7	NR	NR	Cytokeratin, vimentin, neuro-specific enolase, S-100, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR
52	M	61	A	RUL	W	NR	B	1	NR	NR	Cytokeratin, vimentin, neuro-specific enolase, S-100, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR
52	F	67	A	RLL	W	NR	B	2	NR	NSE, S-100	Cytokeratin, vimentin, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR
52	F	32	A	RLL	W	NR	B	1	NR	NR	Cytokeratin, vimentin, neuro-specific enolase, S-100, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR

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Id	S	Age	CS	L	Surgery	Revision	(B)/ (M)	T(cm)	N	Immunohistochemical indices		Other treatments	
										Positive	Negative	CT	RT
52	F	66	S	LLL	LM	NR	M	4.5	NR	NR	Cytokeratin, vimentin, neuro-specific enolase, S-100, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7	NR	NR
52	M	31	A	LLL	W	NR	B	1.5	NR	Vimentin	Cytokeratin, vimentin, neuro-specific enolase, S-100, chromogranin, synaptophysin, epithelial membrane antigen, neurofilament, LEU-7, muscle-specific actin, desmin, collagen type IV , factor VIII-related antigen	NR	NR
53	F	71	A	LLL	W	NR	B	NR	NR	S-100, HMB45, HMB50, NKIC3	CK, EMA, NSE, CRN, SYN, NF, LEU-7	NR	NR
54 55	F	66	S	LLL	TM	NR	M	12×7	NR	NR	NR	NR	NR
56	M	65	A	RLL	LM	NR	NR	2	NR	NR	NR	NR	NR
57	M	69	A	LUL	NR	none	B	3	NR	NR	NR	NR	NR
58	F	53	S	RLL	TM,LM	NR	NR	1×1	N0	HMB-45, vimentin, S-100 protein, CD-117	αSMA, CK-7, AE1/AE3, CD-10, chromogranin and TTF-1.	NR	NR
59	F	39	A	LUL	VATS W	none	B	1.1×1	N0	NR	NR	no	no
60	F	75	S	RLL	W	NR	B	0.4×0.3×0.3	NR	PAS, CD34, vimentin, HMB-45, melan-A, S-100	cytokeratin-coctail, CK7, vimentin, SMA, NSE, synaptophysin, CD68	no	no
61	F	35	S	RUL	LM	NR	M	3	N0	PAS, low molecular weight cytokeratin (AEl), epithelial membrane antigen (HMFG), CEA.	mucin, SlOO protein, vimentin, high molecular weight cytokeratin (AE3 and Dako-Keratin), a-feto protein or human chorionic gonadotrophin.	NR	1 course
61	M	69	S	RUL, RML	LM	NR	M	8	N0	PAS, low molecular weight cytokeratin (AEl), CEA.	mucin	NR	NR
62	F	49	A	RLL	W, TM	NR	B	2.5×2×2	NR	PAS, Alcian blue, PAM, type IV collagen, HMB45, NCAM 123C3	Grimelius, keratin, epithelial membrane antigen (EMA), vimentin, neuron-specific enolase (NSE), Leu7 (CD57), chromogranin A, CD34, alpha-smooth muscle actin, factor VIII, and S-100 protein. Their MIB1 index was less than 0.5% and p53 (clone, DO7)	NR	NR

Continued on the next page

Id	*S*	*Age*	*CS*	*L*	*Surgery*	*Revision*	*(B)/ (M)*	*T(cm)*	*N*	*Immunohistochemical indices*		*Other treatments*	
										Positive	*Negative*	*CT*	*RT*
63	M	59	A	LUL, LLL , RLL , LLL	LM	LM	M	NR	NR	NR	NR	NR	NR
64	F	49	S	RLL	LM		M	4×3×2		HMB-45, Melan A, CD34, vimentin, CD1a, smooth muscle actin (SMA)	EMA, synapto- physin, chromogranin, S-100, thyroid transcription factor- 1, surfactant protein A, CD31, desmin, mucin, CK7, and CD117.	no	no
65	M	46	A	RML	VATS	NR	B	5.5	NR	HMB45, MART-1, SMA and desmin	pancytokeratin cocktail AE1/AE3, cytokeratin7, cy-tokeratin20 and EMA	no	no
66	M	62	A	NR	E	NR	B	2.6	NR	Cathepsin K, CD68 (PG-M1 and KP1), HMB45	MITF, TTF1, and PAX8; TFE3 or TFEB rearrangement	NR	NR
66	M	53	A	LUL	TM, E	NR	B	1.5	NR	Cathepsin K, CD68 (PG-M1 and KP1), HMB45	MITF, TTF1, and PAX8; TFE3 or TFEB rearrangement	NR	NR
66	M	20	A	NR	NR	NR	B			Cathepsin K, CD68 (PG-M1 and KP1), HMB45	MITF, TTF1, and PAX8; TFE3 or TFEB rearrangement	NR	NR
66	M	34	NR	NR	NR	NR	B	NR	NR	Cathepsin K, CD68 (PG-M1 and KP1), HMB45	MITF, TTF1, and PAX8; TFE3 or TFEB rearrangement	NR	NR
66	M	46	A	NR	NR	NR	B	NR	NR	Cathepsin K, CD68 (PG-M1 and KP1), HMB45	MITF, TTF1, and PAX8; TFE3 or TFEB rearrangement	NR	NR
67	M	58	A	LLL	W	NR	B	2.7	NR	(HMB)-45, vimentin, and CD34	cytokeratin AE1/AE3, and epithelial membrane antigen	NR	NR
68	F	61	S	NR	NR	NR	M	NR	NR	NR	NR	yes	yes
68	F	52	S	NR	VATS	NR	B	NR	NR	NR	NR	no	no
68	F	71	A	NR	VATS	NR	B	NR	NR	NR	NR	no	no
68	F	74	A	NR	VATS	NR	B	NR	NR	NR	NR	no	no
69	F	61	A	LUL	VATS, W	NR	B	3×2.5× 2.5		HMB45/MART- 1, Vimentin, CD34	pan-cytokeratin, CAM5.2, SOX10, Thyroid transcription factor-1 (TTF-1), S-100, AE1/3, SMA, Calponin, GFAP, Desmin, TTF-1, P40 and PAX-8	NR	NR

Id: Identity, S: Sex, F: female, M: Male, CS: Clinical symptoms, A: asymptomatic, S: symptomatic, L: location, LLL: left lower lobe, LUL: left upper lobe, RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LM: lobectomy, TM: thoracotomy, SM: segmectomy, W: wedge, E: excision, NR: not reported, B: benign, M: malignant, T: tumor size, N: lymph nodes