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ORIGINAL ARTICLE

The clincopathological variables to differentiate the nature of isolated pulmonary nodules in patients who received curative surgery for colorectal cancer

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KEYWORDS
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Summary *Background:* In colorectal cancer (CRC) patients, pulmonary nodules are usually considered lung metastases (LM). However, approximately 10% of LM is presented as a solitary pulmonary nodule which mimics primary lung cancer (PLC). This study aims to determine the distinguishing characteristics of the two pulmonary nodule types during postoperative surveillance of CRC patients.
Methods: Between March 2009 and February 2018, 47 CRC patients with pulmonary nodules from a single institution were retrospectively analyzed. They were divided into two groups, namely CRC with second PLC (CSPLC) and CRC with LM (CRCLM), and their demographic data and clinicopathological features were analyzed.

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Results: When pulmonary nodules are presented, multiple lesions and serum carcinoembryonic antigen (CEA) level >5 ng/mL indicated a higher probability of CRCLM ($p < 0.001$ and $p = 0.028$, respectively). A $CK7^{-}/CK20^{+}/CDX2^{+}/TTF\text{-}1^{-}$ phenotype on immunohistochemistry (IHC) stain suggested CRCLM. Other clinicopathological features showed no significant between-group differences. The median overall survival was considerably longer in the CSPLC group (not reached) than in the CRCLM group (45.41 months, $p = 0.064$).
Conclusions: The detection of a suspicious isolated pulmonary nodule in CRC patients warrants further workup to distinguish between SPLC and LM. Multiple lesions, serum CEA >5 ng/mL when an isolated pulmonary nodule detected, and initial TNM stage IV CRC are more likely related to LM rather than SPLC. Image-guided needle biopsy and IHC stain can reduce the probability of misdiagnosis and rule out LM. CSPLC may have a favorable prognosis owing to early detection and receiving appropriate treatment.

1. Introduction

Between 2006 and 2015, colorectal cancer (CRC) was the most common cancer and the third-most common cause of cancer deaths in Taiwan.[1] Distant metastases, influencing patient survival and changes in treatment strategy, presented in 20%—25% of CRC patients at the initial diagnosis.[2] The most common metastatic site is the liver,[3] and the most common extraabdominal metastatic site is the lung.[4] If pulmonary nodules are detected in CRC patients, such nodules are considered to be lung metastases. However, about 10% of lung metastasis is presented as a solitary pulmonary nodule which mimics primary lung cancer.[5] Thus far, there are no guidelines or consensus regarding treatment strategy for CRC patients with second primary lung cancer (SPLC). We retrospectively analyzed the demographic data and oncological presentations of CRC patients with pulmonary nodules during postoperative surveillance to identifying and differentiate these two pulmonary nodules.

2. Methods

2.1. Patient selection

In this retrospective case note review, we recruited 47 CRC patients with pulmonary nodules after confirmation through pulmonary pathological examination during postoperative surveillance between March 2009 and February 2018 at a single institution in Taiwan. No additional metastatic lesions were noted in any patient. All diagnoses and surveillance followed principles adapted from the National Comprehensive Cancer Network guidelines.[6,7] The patients were divided into two groups: CRC with SPLC (CSPLC) and CRC with lung metastasis (CRCLM). The demographic data and clinicopathological features were compared between CSPLC and CRCLM (Table 1).

2.2. Clinicopathological features and response evaluation

The clinicopathological features comprised sex, age, initial tumor size and location, initial TNM stage, histological type, lymphovascular invasion (LVI) and perineural invasion (PNI) status, serum carcinoembryonic antigen (CEA) level at initial presentation and at pulmonary nodule detection, number of pulmonary nodules, interval to pulmonary nodules (ITP), and overall survival (OS).

2.3. Statistical analysis

ITP was defined as the period between CRC diagnosis and pulmonary nodule identification. OS was defined as the time elapsed between the first treatment and either all-cause death or the final follow-up of the patient. Continuous variables were calculated as means ± standard deviations, and dichotomous variables were calculated as numbers and percentages. All statistical analyses were performed using the Statistical Package for Sciences (version 19.0; SPSS Inc., Chicago, IL, USA). The clinicopathological characteristics of the groups were compared using the Pearson chi-square test, and the survival rates were estimated using the Kaplan—Meier method. The log-rank test was used to determine differences. A p value of <0.05 was considered statistically significant.

3. Results

The clinicopathological data of CRC patients diagnosed with pulmonary nodules are summarized in Table 1. In total, 47 CRC patients (22 men and 25 women; mean age, 64.8 [40.5—86.4] years) were eligible for analysis of pulmonary nodules after the pathological confirmation in this study. Of them, 9 with SPLC and 38 with lung metastases included in the CSPLC and CRCLM groups, respectively. The median follow-up period for all patients was 40.25 (7.62—107.24) months. Except for The CRCLM group had more initial CRC stage IV patients ($p = 0.008$), smoking history, primary CRC tumor size and location, histological type, LVI and PNI status, and initial serum CEA level did not significantly differ between the groups ($p > 0.05$). However, more CRCLM patients exhibited CEA levels of >5 ng/mL at pulmonary nodule presentation than CSPLC patients did ($p = 0.028$). All CSPLC patients exhibited only one nodule, with a significant difference compared with CRCLM patients

Table 1 Clinicopathological profile of 47 colorectal cancer patients with isolated lung nodules.

Variable	All (n = 47) (%)	CSPLC (n = 9) (%)	CRCLM (n = 38) (%)	*p*-value
Gender				0.715
Male	22 (46.8)	5 (55.6)	17 (44.7)	
Female	25 (53.2)	4 (44.4)	21 (55.3)	
Age (year) mean ± SD	64.79 ± 12.48	67.27 ± 12.09	64.20 ± 12.66	0.512
Smoking history				0.074
Non-smoker	35 (74.5)	6 (66.7)	29 (76.3)	
Former smoker	6 (12.8)	3 (33.3)	3 (7.9)	
Smoker	6 (12.8)	0	6 (15.8)	
Primary tumor size (cm)	3.73 ± 2.17	4.18 ± 2.68	3.64 ± 2.07	0.531
Primary tumor location				0.704
Colon	17 (36.2)	4 (44.4)	13 (34.2)	
Rectum	30 (63.8)	5 (55.6)	25 (65.8)	
Initial TNM stage				0.008
I + II + III	14 (29.8)	2 + 2+5 (100)	4 + 6+10 (52.6)	
IV	33 (70.2)	0	18 (47.4)	
Histological type				0.664
WD	4 (8.5)	0	4 (10.5)	
MD	39 (83.0)	8 (88.9)	31 (81.6)	
PD	1 (2.1)	0	1 (2.6)	
Unknown	3 (6.4)	1 (11.1)	2 (5.3)	
Presence of lymphovascular invasion				0.883
Yes	11 (23.4)	2 (22.2)	9 (23.7)	
No	27 (57.4)	6 (66.7)	21 (55.3)	
Unknown	9 (19.1)	1 (11.1)	8 (21.1)	
Presence of perineural invasion				0.336
Yes	13 (27.7)	1 (11.1)	12 (31.6)	
No	25 (53.2)	7 (77.8)	18 (47.4)	
Unknown	9 (19.1)	1 (11.1)	8 (21.1)	
CEA (ng/ml) level at initial CRC diagnosis	17.34 ± 26.02	14.57 ± 20.08	17.96 ± 27.37	0.744
≧5	23 (48.9)	4 (44.4)	19 (50.0)	0.804
<5	21 (44.7)	4 (44.4)	17 (44.7)	
Unknown	3 (6.4)	1 (11.2)	2 (5.3)	
CEA (ng/ml) level at pulmonary nodule presentation	15.40 ± 26.89	10.08 ± 24.27	16.81 ± 27.71	
≧5	20 (42.6)	1 (11.1)	19 (50.0)	0.511
<5	23 (48.9)	8 (88.9)	15 (39.5)	0.028
Unknown	4 (8.5)	0	4 (10.5)	
Numbers of pulmonary nodules				<0.001
Single	16 (34.0)	9 (100)	7 (18.4)	
Multiple	31 (66.0)	0	31 (81.6)	
ITP (months), median	12.22 (5.3—19.14)	9.76 (8.41—11.1)	14.65 (5.56—23.75)	0.236
≧3/<3 months	30 (63.8)/17 (36.2)	8 (88.9)/1 (11.1)	22 (57.9)/16 (42.1)	0.127
≧6/<6 months	27 (57.4)/20 (42.6)	7 (77.8)/2 (22.2)	20 (52.6)/18 (47.4)	0.256
≧12/<12 months	22 (46.8)/25 (53.2)	4 (44.4)/5 (55.6)	18 (47.4)/20 (52.6)	1.000
≧24/<24 months	14 (29.8)/33 (70.2)	3 (33.3)/6 (66.7)	11 (28.9)/27 (71.1)	1.000
Overall survival (months), median	57.86 (35.84—79.88)	Not reached	45.41 (19.86—70.93)	0.064

CSPLC: colorectal cancer with second primary lung cancer; CRCLM: colorectal cancer with lung metastasis.
WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated.
CEA: carcinoembryonic antigen.
ITP: interval to pulmonary nodules.

($p < 0.001$). The median ITP was 12.22 (95% confidence interval [CI] 5.3—19.14) months in all patients; in CSPLC and CRCLM patients, it was 9.76 (95% CI 8.41—11.1) and 14.65 (95% CI 5.56—23.75) months, respectively, without significant difference ($p = 0.236$). However, within the first 6 months of follow-up, a slightly higher proportion of CRCLM patients presented pulmonary nodules. The median OS of the entire study population was 57.86 (95% CI 35.84—79.88) months; the median OS of CSPLC patients was not reached, and the median OS of CRCLM patients was 45.41 (95% CI 19.86—70.93) months; however, the between-group difference was nonsignificant ($p = 0.064$; Fig. 1).

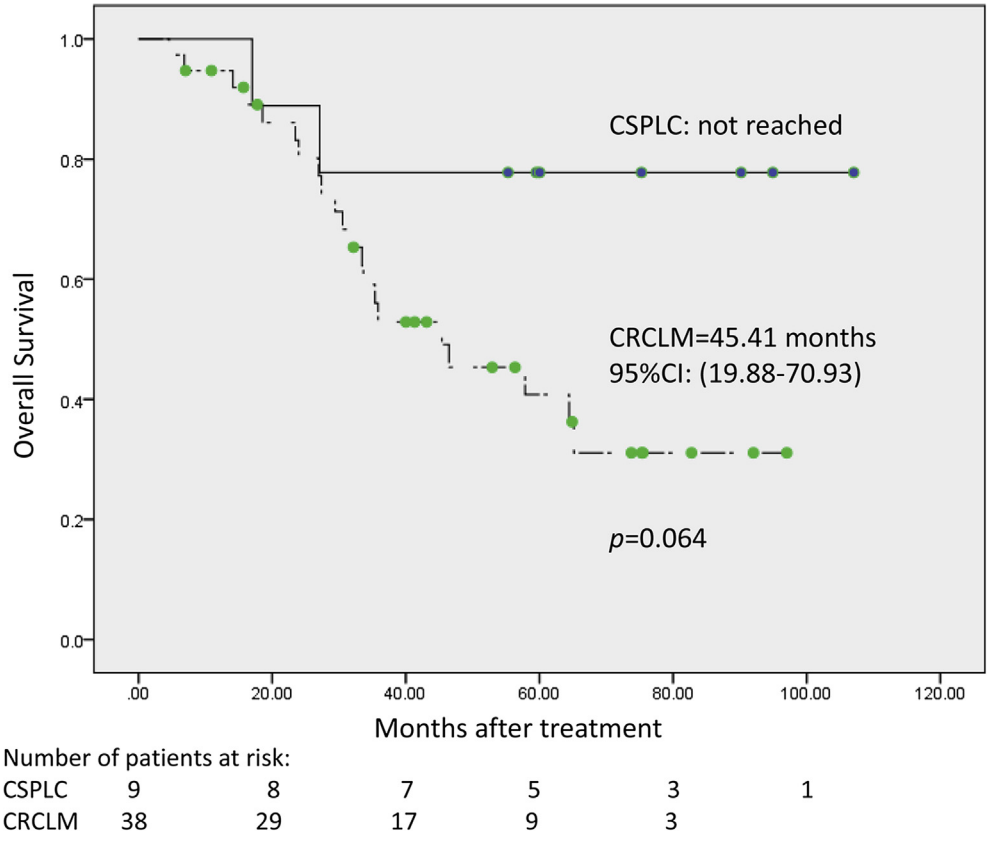

Figure 1 Kaplan—Meier survival analysis of the overall survival of colorectal cancer patients with pulmonary nodules.

In total, 16 (34.8%) of our CRC patients exhibited a solitary pulmonary nodule, of whom 7 (18.9%) were CRCLM patients—higher than that reported previous report (2.8—7.4%).[8] The characteristics and morphology of the solitary pulmonary nodules in all patients are demonstrated in Table 2 and Fig. 2. The maximal diameters of the nodules, irregular or blurred margin of image characters, presence of enlarged mediastinal lymph nodes, and tumor locations (peripheral or central) did not differ significantly between CSPLC and CRCLM patients ($p > 0.05$). When a solitary pulmonary nodule presented, the CRCLM group had a higher proportion of CEA levels of >5 ng/mL than CSPLC group ($p = 0.009$). Moreover, Immunohistochemistry (IHC; $CK7^{+}/CK20^{-}/CDX2^{-}/TTF\text{-}1^{+}$ phenotype suggested SPLC) also showed significant differences between the two groups ($p < 0.05$).

4. Discussion

The incidence of CSLPC is relatively low. Noura et al.[9] reviewed 301 CRC patients between January 1991 and December 1996; only 12.6% of them had second primary extracolonic cancer; the most frequent site of secondary malignancies was the lungs (2.7%), followed by the stomach (2.7%) and liver (2.0%). Kan et al.[10] reported that approximately 17 (1.6%) of 1031 CRC patients exhibited second primary malignancies between January 1998 and December 2004, but the incidence of CSPLC was only 0.1%. Sun et al.[11] studied 1679 CRC patients between January 2000 and June 2010; of them, only 89 (5.3%) had second primary cancer, with incidence of SPLC being only 0.2%. Lee et al.[12] reported the incidence of second primary malignancies following CRC was 4.3% and that of SPLC was 0.9%; the incidence of CRCLM was 10%—20%, and that of lung metastasis was considerably lower than that of liver metastasis.[13] The rare incidence of CSPLC might lead physicians to misdiagnose CRC pulmonary nodules as lung metastases, leading to administration of unsuitable surgical strategy or chemotherapy to these patients. Therefore, in these cases, using an appropriate diagnostic strategy is important.

When detecting pulmonary nodules through chest radiography or computed tomography (CT) at initial diagnosis or during the postoperative surveillance period, the American College of Chest Physicians guidelines suggests that thorough medical history and malignancy risk assessment is necessary, and the medical history review should include current or past smoking status, age, extrathoracic cancer history, and time since quitting smoking. Changes in any of these factors, except for time since quitting smoking, can increase the risk of malignant pulmonary nodules. In our investigation, we noted no significant sex and age differences among the patients. Most of our patients were nonsmokers or had quit smoking after CRC diagnosis. Thus, a thorough medical history review may not provide helpful information in patients with existing extrathoracic malignancies.

Chest CT is the most common and useful tool in evaluation the pulmonary nodules which has advantages such as, high specificity and sensitivity in detection, providing

Table 2 Characteristics of solitary pulmonary nodule.

Variable	CSPLC (n = 9) (%)	CRCLM with single nodule (n = 7) (%)	*p*-value
Maximal diameter of pulmonary nodule (cm)	2.68 ± 1.79	2.84 ± 2.19	0.870
CEA (ng/ml) level at pulmonary nodule presentation			
≧5	1 (11.1)	6 (85.7)	0.009
<5	8 (88.9)	1 (14.3)	
Image characters			
Irregular or blurred margin			
Yes	8 (88.9)	5 (71.4)	0.550
No	1 (11.1)	2 (28.6)	
Presence of enlarged mediastinal lymph node			
Yes	4 (44.4)	3 (42.9)	1.000
No	5 (55.6)	4 (57.1)	
Tumor location			
Peripheral	7 (77.8)	6 (85.1)	1.000
Central	2 (22.2)	1 (14.3)	
IHC staining			
CK7 positive/negative/ND	7 (77.8)/0/2 (22.2)	1 (14.3)/2 (28.6)/4 (57.1)	0.030
CK20 positive/negative/ND	0/6 (66.7)/3 (33.3)	3 (42.9)/0/4 (57.1)	0.011
CDX2 positive/negative/ND	0/6 (66.7)/3 (33.3)	4 (25.0)/0/3 (42.9)	0.007
TTF-1 positive/negative/ND	6 (66.7)/2 (22.2)1 (11.1)	1 (14.3)/1 (14.3)/5 (71.4)	0.040

CSPLC: colorectal cancer with second primary lung cancer; CRCLM: colorectal cancer with lung metastasis.
IHC: immunohistochemistry.

specific information about the location, size, and attenuation characteristics.[14] Pulmonary nodule size is a strong indicator of whether it is benign or malignant. Approximately 80% of nodules >20 mm in size are malignant, whereas only 1% of such nodules are 2–5 mm in size.[15,16] Morphological characteristics of the nodules also provide indications for distinguishing nodule types. Benign nodules have with a smooth border, calcification (concentric, central, or popcorn pattern), solid density, and size < 5 mm, whereas malignant lesions may have irregular or spiculated border, no or eccentric calcification, nonsolid or ground-glass density, and size > 10 mm.[14,17] Quint et al.[18] evaluated 149 patients with extrathoracic malignancies and solitary pulmonary nodules and found that a solitary nodule is more likely diagnosed as primary lung cancer than as metastasis of other cancers in elderly people or smokers. The authors also found that a smooth margin indicated benign lesions or metastases, whereas an irregular or blurred margin with enlarged mediastinal lymph nodes suggested primary lung cancer. In our study, we found multiple pulmonary nodules mostly indicated metastasis. We also analyzed the tumor size and morphological features of the pulmonary nodules between CSPLC patients ($n = 9$) and CRCLM patients with solitary nodular metastasis ($n = 7$); however, no significant differences were noted. The findings clarify the reason physicians easily misdiagnose metastasis; identifying a solitary pulmonary nodule as primary lung cancer or metastasis is difficult.

CEA is a serum marker associated with CRC. Although CEA lacks sensitivity and specificity in diagnosing CRC, it aids in surgical treatment planning, posttreatment surveillance, and prognosis assessment. Therefore, serum CEA levels should be obtained preoperatively in most CRC patients, according to the American Society of Clinical Oncology guidelines.[19] Here, in all patients, serum CEA levels were measured at initial diagnosis of CRC and at pulmonary nodule detection, but no significant difference in CEA levels was noted between two groups. However, CRCLM patients had a significantly higher proportion of >5 ng/mL serum CEA ($p = 0.028$) when pulmonary nodule presented. Moreover, CRCLM patients with single nodule had an even higher proportion ($p = 0.009$). Thus, serum CEA levels >5 ng/mL when pulmonary nodule presented may aid in correctly identifying pulmonary nodules as lung metastasis, rather than SPLC.

Quint et al.[18] found that a longer the ITP more likely indicate a diagnosis of primary lung cancer, but they provided no clear cutoff duration. Here, we analyzed the ITP and found no statistically significant difference between groups. We set a cutoff of 3 months as the first interval for surveillance and performed subgroup analysis. During the initial 3-month surveillance, the incidence of pulmonary nodules in CRCLM patients (42%) was slightly higher than that in CSPLC patients (11%, $p = 0.127$). A 3-month cutoff may be appropriate to distinguish primary lung cancer and lung metastasis; a large-scale analysis is warranted for validation.

The most accurate method to diagnose pulmonary nodules is to obtain a specimen through surgery or image-guided needle biopsy for pathological examination. If the whole specimen can be obtained, histological differences may provide the answer. However, to verify the etiology before surgical planning, needle biopsy is the only method to obtain the specimen. The small volume of the biopsy specimen can impede the determination of histological differences; IHC may resolve this issue. Kummar et al.[20] noted that IHC was an effective differential diagnosis method because primary lung cancer presents a $CK7^{+}$/

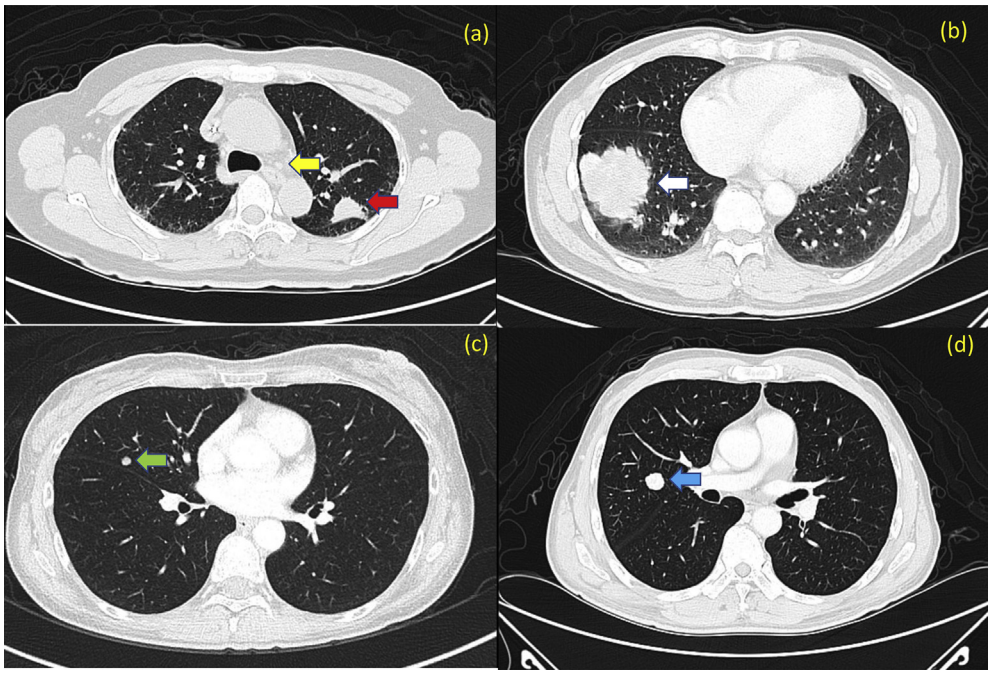

Figure 2 Morphology of pulmonary nodules on chest CT: (a) CSPLC patient with a single solitary nodule with irregular margin (red arrow) and enlarged mediastinal lymph node (yellow arrow). (b) CRCLM patient with a single solitary nodule with irregular margin (white arrow). (c) CRCLM patient has multiple lung nodules with smooth margin (green arrow). (d) CRCLM patient has a single solitary nodule with smooth margin (blue arrow).

$CK20^-$ phenotype, whereas metastatic adenocarcinoma shows a $CK7^-/CK20^+$ phenotype. In their 102 tumor samples, the CK7/CK20 phenotype was used to differentiate lung cancer and metastatic colorectal adenocarcinoma in 95% of cases, suggesting that cytokeratin staining is a cost-effective screening tool. *CDX2* is a homeobox gene, encoding a transcription factor that plays a vital role in the development and differentiation of intestinal epithelial cells. Levine et al.[21] reported that CDX2 is a highly useful IHC marker for differentiating primary pulmonary adenocarcinoma from colorectal adenocarcinoma metastasized to the lungs in fine-needle aspiration specimens. TTF-1 is crucial for normal lung function and morphogenesis and is expressed consistently and uniformly throughout life in the terminal respiratory unit, comprising peripheral airway cells and small-sized bronchioles. Yatabe et al.[22] reported TTF-1 expression was maintained in 72% of adenocarcinoma cases exhibiting a high correlation with surfactant apoprotein and morphologic resemblance to terminal respiratory unit cells. Thus, we assumed that the

Table 3 Clinicopathologic data of 9 colorectal cancer with second primary lung cancer patients.

No.	Age (year)	TNM stage (CRC)	Adjuvant therapy for CRC	TNM Stage (lung cancer)	Pathology (lung)	Procedure	Adjuvant therapy for lung cancer	OS (Month)	Surveillance
1	75	T3N1aM0	FOLFOX4	T1aN0M0	Adenocarcinoma	Wedge resection	None	55.59	Survived
2	84	T3N0M0	UFUR	T4N0M1a	Adenocarcinoma	Lobectomy	Target therapy (Iressa)	17.35	Dead
3	68	T1N0M0	None	T2NxM1a	Adenocarcinoma	Wedge resection	Target therapy (Iressa)	76.55	Survived
4	53	T1N0M0	None	T1aN0M0	Adenocarcinoma	Lobectomy	None	90.15	Survived
5	61	T2N1aM0	FOLFOX4	T1aN0M0	Adenocarcinoma	Wedge resection	None	59.83	Survived
6	84	T3N1bM0	FOLFOX4	T4N2M0	Adenocarcinoma	CT-guided biopsy	None	60.55	Survived
7	54	T3N0M0	None	T1aN0M0	Adenocarcinoma	Wedge resection	None	107.24	Survived
8	56	T1N1M0	FOLFOX6	T2aN0M0	Adenosquamous carcinoma	Lobectomy	Chemotherapy (navelbine + cisplatin)	27.20	Dead
9	67	T3N1M0	FOLFOX4	T2aN0M1b	Squamous cell carcinoma	CT-guided biopsy	Chemotherapy (gemcitabine + cisplatin)	95.01	Survived

CRC: colorectal cancer.
CT: computed tomography.

IHC results showing a $CK7^+/CK20^-/CDX2^-/TTF\text{-}1^+$ phenotype indicated primary lung cancer, whereas a $CK7^-/CK20^+/CDX2^+/TTF\text{-}1^-$ phenotype indicated a CRC metastasis. Accordingly, most of our CSPLC patients presented the $CK7^+/CK20^-/CDX2^-/TTF\text{-}1^+$ phenotype, whereas CRCLM patients presented the $CK7^-/CK20^+/CDX2^+/TTF\text{-}1^-$ phenotype. Thus, these markers are powerful tools for identifying the etiology of pulmonary nodules.

When CRCLM is diagnosed, chemotherapy combined with biological agents is the main treatment and prolongs survival. However, when CSPLC is diagnosed, no guideline or evidence-based study suggests treatment strategy. In Taiwan, lung cancer was the third-most common cancer and the most common cause of cancer death in 2015.[1] In Taiwan, 24.65%, 4.5%, 14.2%, and 54.4% patients have lung cancer of stage I, II, III, and IV, respectively.[1] Here, stage I, II, III, and IV lung cancer was noted in 44.4%, 0%, 22.2%, and 33.3% of our CSPLC patients, respectively; 77.8% (7/9) of the patients had received the surgical intervention (with curative intent or for diagnosis). The 5-year overall survival rate of the CSPLC patients was 78% which was higher than the CRCLM group (30%). A higher proportion of CSPLC patients were in the early clinical stage because of the early detection of suspicious pulmonary nodules through regular surveillance. Early detection, immediate surgical resection and appropriate adjuvant therapy may prolong survival and improve prognosis. The clinicopathologic data of the 9 CSPLC patients are presented in Table 3.

When encountering a CRC patient with a solitary pulmonary nodule, a thorough medical history review, chest CT evaluation, and serum CEA levels are necessary. For multiple pulmonary nodules, serum CEA levels >5 ng/mL at pulmonary nodule presentation may indicate metastasis. If the possibility of SPLC cannot be excluded, complete surgical resection or image-guided needle biopsy (when the patient is unsuitable for surgery) may be needed. Further treatment strategy is dependent on the pathological outcome. If distinguishing between primary and metastatic cancer is difficult because of a small nodule or a small biopsy specimen volume, an IHC phenotype of $CK7^+/CK20^-/CDX2^-/TTF\text{-}1^+$ indicates primary lung cancer. After the confirmation of diagnosis, disease severity and symptoms should be considered to select appropriate treatment strategy.

This study has limitations. First, we used a relatively small sample size and a retrospective and nonrandomized design. Moreover, the incidence of SPLC is relatively low (0.1—2.7%) according to previous publications.[9–12] Thus, such small sample numbers may lead to difficulty in statistical comparison. Second, we could not obtain specimens of the all pulmonary nodules in the CRCLM patients; thus, we could not exclude the possibility of multiple primary lung cancer or mixed malignancies. Therefore, a prospective, randomized, large-scale study is warranted to validate our current findings.

5. Conclusion

CSPLC has a relatively low incidence. The detection of suspicious isolated pulmonary nodules in CRC patients warrants further workup to distinguish between CSPLC and CRCLM because the treatment strategy is quite different between them. Though the medical history review and chest CT evaluation provide little clinical information to distinguish between CSPLC and CRCLM, CRC patients presenting multiple pulmonary nodules or initial TNM stage IV have a higher correlation to LM. Moreover, when an isolated pulmonary nodule is detected, the serum CEA >5 ng/mL may indicate CRCLM rather than CSPLC. Image-guided needle biopsy plus IHC stain may reduce the probability of misdiagnosis and rule out LM (phenotype: $CK7^-/CK20^+/CDX2^+/TTF\text{-}1^-$). Finally, CSPLC may have a favorable prognosis owing to early detection and receiving appropriate treatment.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.08.002.

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