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Lung Cancer in Combined Pulmonary Fibrosis and Emphysema: A Large Retrospective Cohort Analysis

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Abstract

Background

Combined pulmonary fibrosis and emphysema (CPFE) is characterized by upper lobe emphysema and lower lobe fibrosis. Our study aim was to determine the incident risk, presenting characteristics, and outcome of lung cancer (LC) diagnoses in a cohort of CPFE patients over time.

Materials and Methods

We conducted a retrospective cohort study assessing patients with radiologic CPFE followed over a median of 76 months (range 1- 237). Interval development of LC and clinicopathologic characteristics of those with and without LC was compared and survival analysis performed.

Results

LC occurred in 26 of 230 (11.6%) CPFE patients dominated by non-small cell lung cancer (88%, N =23) with squamous cell carcinoma comprising the majority (N = 13(57%)). There was a predominance of lower lobe (62%) and sub-pleural radiologic presentation (64%). Survival was reduced for the whole cohort by LC even after adjusting for a priori covariables of age, sex, smoking pack years, presenting forced vital capacity (FVC%), and radiologic honeycombing. Univariable predictors of increased mortality after LC diagnosis included honeycombing (HR 3.03 (1.16-7.91), P = 0.02) and later stage presentation (HR 4.77 (1.8-14.94) P = 0.001), with those able to undergo surgical resection having better survival (HR 0.29 (0.09-0.87) P = 0.02).

Conclusion

LC occurred in 26 of 230 (11.6%) CPFE patients and was dominated by squamous cell carcinoma presenting in a lower lobe peripheral distribution. Surgical resection appeared to improve survival in selected patients with earlier stage disease. Further studies are needed to develop a relevant screening program for CPFE patients.

Take Home Message

Lung cancer is common in CPFE patients followed over time, with possibly better survival in those diagnosed at earlier stages and successfully resected. Further studies to formulate a disease-specific cancer screening protocol are needed.

Abbreviations

COPD = chronic obstructive pulmonary disease
CPFE = combined pulmonary fibrosis and emphysema
CT = computed tomography
DLCO = diffusion capacity for carbon monoxide
FEV1 = forced expiratory volume in the first second
FVC = forced vital capacity
HR = hazard ratio
IPF = idiopathic pulmonary fibrosis
LC = lung cancer
NSCLC = non-small cell lung cancer
RVSP = right ventricular systolic pressure
TLC = total lung capacity

Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a clinical entity characterized by heavy smoking history, pulmonary hypertension, hypoxemia, and relatively normalized spirometry and lung volumes in the context of severely impaired gas exchange (1). Radiologically, CPFE presents as upper lobe predominant emphysema and lower lobe lung fibrosis.(2) Mortality is significant in CPFE with a median survival reported between 2.1 and 8.5 years and five-year survival of 38% to 55% (3). CPFE has been recognized as an important risk factor for the development of lung cancer (LC) and appears associated with a generally worse prognosis (4, 5). Chronic lung injury with CPFE may influence the development and progression of lung cancer, perhaps related to the triple effects of smoking, emphysema, and pulmonary fibrosis, all known factors associated with lung cancer development.

Although there have been descriptive studies, the association between newly diagnosed CPFE and LC risk has not been well elucidated. The majority of prior studies began with diagnosed LC cohorts (6-11), with the largest series to date comprising 4,313 LC patients from 9 institutions reporting 265 cases (6.1%) with associated CPFE (7). Only 3 studies have reported the incidence of LC in CPFE beginning with baseline CPFE prior to LC diagnosis (5). A recent study evaluated LC risk in a series of 48 CPFE cases noting 12 (25%) going on to develop LC (4). A second study found 22 of 47 (46.8%) CPFE patients with incident LC (12), while a third and smaller study found 6 out of 29 (20.6%) developing subsequent LC (13). A recent meta-analysis describing LC in CPFE reported squamous cell carcinoma as the most common subtype (42.3%), followed by adenocarcinoma (34.4%) (5). LC in CPFE patients appeared to exhibit advanced pathological staging with relatively short survival [7, 9–14]. There is a single study to

date reporting the location of presenting LC lesions in CPFE (6). The aim of our study was to report the frequency of incident LC cases in a large retrospective cohort of CPFE patients (CPFE-LC) and describe presenting clinical features, management strategies, and predictors of outcome.

Materials and Methods

We conducted a retrospective cohort study of patients diagnosed with CPFE from January 1st 1995 to December 31st 2017, at Mayo Clinic Rochester, a 1264 bed tertiary care center. Institutional research review board approval was obtained (IRB 16-009700) and only patients providing informed consent for general study participation at the time of initial clinical visit were included. Data abstraction was performed by study investigators using a computerized query tool that allowed systematic search of clinical data stored in the enterprise data trust, using the terms 'fibrosis' and 'emphysema' in the descriptive notes of chest computed tomography (CT) scans (N= 256). Those without record of informed consent for de-identified cohort research were excluded (N=12). All patients greater than 18 years of age with radiologically confirmed CPFE were included for review. Clinically reported cases without available confirmatory CT imaging were excluded (N= 14). CT scans were read by expert radiologists at the time of diagnosis and reviewed by the authors to confirm radiologic CPFE, defined as at least 10% or more of total involvement of both emphysema and lung fibrosis on imaging in any distribution. Fibrosis was defined as the presence of reticular or honeycomb change in any distribution, with or without traction bronchiectasis, and emphysema as low attenuation areas without a

parenchymal lining (cystic changes) either in a centrilobular or subpleural distribution, as defined by standard Fleischner criteria (14). Further manual data abstraction from the electronic medical record was performed. Study variables included age at CPFE and LC diagnosis, sex, reported presence of finger clubbing, smoker pack-years, pulmonary function testing (PFT), known causes of lung fibrosis, treatment of underlying lung disease, use of home oxygen, right ventricular systolic pressure (RVSP) on transthoracic echocardiogram (TTE), and interval diagnosis of LC. Specific PFT parameters included percent predicted total lung capacity (TLC %), forced vital capacity (FVC %), forced expiratory volume in the first second (FEV1%), and diffusing capacity for carbon monoxide (DLCO %). Summary PFT patterns were categorized as normal, obstructive, restrictive, mixed (obstruction and restriction), nonspecific (defined as isolated or proportionate decline in FEV1 and FVC with normal FEV1/FVC ratio and normal TLC), and isolated low DLCO. For patients diagnosed with LC, additional variables were collected including histologic subtype, LC staging according to 2016 IASLC criteria(15), broad treatment categories (chemotherapy +/- radiation vs surgical resection alone as adjunct), and survival and cause of death, if applicable or available. All LC cases had pathology reports available for review as initially diagnosed by subspecialty pathologists at Mayo Clinic Rochester, in accordance with the 2004 WHO international classification of lung and pleural tumors(16). Timing of LC diagnoses was defined as the date of clinician review for LC or final pathology report.

Statistical Analysis

Statistical analysis was performed using JMP Software (Version 13.0, SAS Institute, Cary NC). Data were presented as mean and standard deviation (SD) or median and 25-75%

interquartile range for continuous variables and as counts and percentages for categorical variables. For comparison of baseline characteristics between those with and without LC, Chi-square or Fisher's exact test were used for categorical variables and one-way ANOVA for continuous variables. Follow-up for all-cause mortality was obtained in all cases and survival time was defined in months from the date of the first available chest CT with radiologic CPFE (signifying a first date of CPFE diagnosis based on radiologic definition) to the date of death or United States Social Security Death Index (USSDI) search date 6/15/2018 if still alive. All living and transplanted patients were censored from the date of USSDI search or date of transplant. Survival was compared between those with and without LC diagnosis, using Kaplan Meier and Log rank, censored for live or transplanted patients. Cox proportional hazards regression was performed to determine predictors of death for the whole cohort with univariable analysis followed by multivariable adjustment of positive predictors (P values < 0.05) for *a priori-selected* covariables of age, sex, smoker pack years, FVC% at presentation, and presence of honeycombing, avoiding stepwise selection or spurious adjustments. Only univariable Cox regression analysis for predictors of survival after LC diagnosis was performed for the CPFE-LC cohort, given the smaller sample size (N= 26). For the purposes of modeling predictors, missing data for selected continuous variables was imputed with multivariate normal imputation using least squares prediction and shrinkage from non-missing variables (done specifically for smoker pack years, RVSP, FVC%, FEV1%, and DLCO %). Two-sided P values less than 0.05 were considered statistically significant.

Results

Two hundred and thirty patients with radiologically defined CPFE and clinical follow-up were reviewed for interval development of lung cancer. Median follow-up for the whole cohort was 75.6 months (95% CI 60-103) from the date of radiologic CPFE diagnosis to date of death, transplant, or last known alive (USSDI search 6/15/2018). LC was diagnosed in 26 (11.6%) patients over the observation period. Baseline demographic and clinical findings for CPFE-LC and non-LC patients are presented in Table 1). There were no presenting differences between those with and without LC except for greater overall percent mortality in those with subsequent LC diagnosis (50% vs 81%, P = 0.003). There were also more males in the cohort overall (173 (75 %)) and all were active or former smokers. Pack-years of smoking were similar between those with and without LC (50 vs 56, P = 0.08). Presence of finger clubbing was 20% and 27% respectively for each cohort along with similar use of directed therapy for CPFE and home oxygen. RVSP as seen on TTE was elevated similarly (median 49 mmHg (IQR 39-63) vs 49 mmHg (IQR 32-66.5). PFT findings were also comparable by individual parameters as well as final summary pattern, with nearly equivalent distributions of obstructive, restrictive, and isolated DLCO findings (P = 0.86). Secondary causes of ILD were found in 42 cases, comprised of 40 autoimmune or connective-tissue disease and two biopsy-proven desquamative interstitial pneumonia. All secondary cases were clinically diagnosed by multidisciplinary team discussion involving rheumatology and/or pathology team members at the time of diagnosis.

Cancer characteristics at the time of diagnosis for CPFE-LC patients are presented in Table 2. Non-small cell lung cancer (NSCLC) was more common (N =23 (88%)) with a predominance of squamous cell carcinoma in 57% of cases, followed by adenocarcinoma (N= 8

(35%)) and large cell carcinoma (N=1 (4%)). Three cases of small cell lung cancer were noted (all presenting with limited staging) with one patient having both small cell and adenocarcinoma. Another patient had both MALToma and adenocarcinoma. At the time of diagnosis, 13 cases (56.6%) were potentially resectable based on Stage I through IIIA presentations, 4.3% were stage IIIB and the remainder were stage IV (N = 9 (39%). Unfortunately stage IV disease was the most common single presenting stage. The majority of LC originated in the lower lobes (62%, N=16) and a similar number (64%) were sub-pleural and within 2 cm of the pleural edge. Surgical resection was offered alone or in combination with chemotherapy or radiation in 8 (31%) patients. Overall mortality was 81%, caused by the underlying primary cancer in 55%, followed by infectious complications from treatment in 15%. Figure 1 demonstrates Kaplan-Meier survival curves from the date of CPFE diagnosis stratified by those with and without LC, noting decreased survival in those with LC (Log rank 0.0275). Median survival was 49 months (95% CI 31-98) for those with LC compared to 86 months (95% CI 70-107) for those without. Eight CPFE patients without LC underwent eventual lung transplantation.

Time to LC diagnosis in those with CPFE-LC and yearly interval incidence of LC for the whole cohort are presented in Figure 2. Median time to LC diagnosis was 31 months (95% CI 17-45), ranging from half a month to 144 months after initial CPFE diagnosis.

Univariable and multivariable adjusted predictors of all-cause mortality for the whole CPFE study cohort using Cox proportional hazards regression analysis are presented in Table 3. Independent predictors of death included age (unit HR 1.04 (95% CI 1.02-1.06); P = <0.0001), use of supplemental home oxygen (HR 2.09 (95% CI 1.24-3.51); P = 0.005), RVSP (HR 1.02 (95% CI 1.01-1.03); P < 0.0001), DLCO% (HR 0.98 (95% CI 0.96-0.99); P =0.0011), radiologic honeycombing (HR 2.18(95% CI 1.49-3.19), P < 0.001), and LC diagnosis (HR 2.25 (95% CI

1.36-3.72), P =0.0015). Among those subsequently diagnosed with LC (N= 26), univariable predictors of mortality from the date of cancer diagnosis included the presence of radiologic honeycombing (HR 3.03 (1.16-7.91), P = 0.02), late or non-resectable cancer staging at presentation with the inclusion of SCLC (HR 4.77 (1.8-14.94), P = 0.001), and feasibility of surgical resection (HR 0.29 (0.09-0.87), P = 0.02) (Table 4).

Discussion

Our study of 230 patients represents the largest single center cohort to date of presenting CPFE patients meeting both clinical and radiological criteria set forward by Cottin et al in 2005 (1) followed over time for subsequent development of LC. Prior studies have focused on large cohorts of already established LC patients reviewed retrospectively for the presence of CPFE, leaving incident risk of LC in CPFE previously unexplored in a systematic manner. Baseline functional and demographic characteristics of our CPFE cohort were similar to those described previously in terms of preserved lung volumes and normal range FEV1% (17-20). LC diagnoses occurred in 26 of 230 CPFE patients (11.6%) with squamous cell carcinoma being the most common histopathology. Disease staging at presentation was dominated by later presentation in the majority of cases (39% stage IV). Age, subsequent diagnosis of LC, use of supplemental oxygen, and pulmonary hypertension were independent predictors of mortality after adjustment for a priori covariables. Honeycombing was the only unadjusted baseline predictor associated with worse survival among those with subsequent LC. Successful surgical resection of earlier stage disease in our study was associated with improved outcome in likely highly selected patients.

Both emphysema and pulmonary fibrosis have been recognized as independent risk factors for the development of LC. Radiologic emphysema appears to be associated with idiopathic pulmonary fibrosis (IPF) in approximately 30% of patients (17, 21). Data from the COPD Gene Study Group suggests the presence of interstitial shadowing or radiologically overt interstitial pneumonia on computed tomography (CT) in approximately 5-10% of those with COPD (22, 23). Increased incidence of LC has been identified in large epidemiologic cohorts of pulmonary fibrosis, ranging between 4.4 to 4.9% of cases in the United Kingdom (24, 25), and 4.8% of cases from a review of incident deaths in the United States between 1979 and 1991.(26) The incidence of LC is approximately 1% per year in those with COPD (27). Lung cancer risk appears greater in CPFE (6.1- 46.8 %) than in either IPF (4.4 -4.9%) or COPD alone.(4, 7, 26, 28) LC was diagnosed in 11.6 % of our 230 CPFE cases while three prior studies reviewing smaller sample sizes found new cases occurring in 25% to 47% of their respective cohorts (4, 12, 13). Studies enrolling patients with diagnosed lung cancer as their primary study cohort also found significant incidence of associated CPFE,(12) including some demonstrating greater frequency of LC in CPFE than lone fibrosis (6, 29).

Squamous cell carcinoma and later stage disease were the primary features of CPFE-LC seen in our cohort. These findings are compatible with those of previous studies (4, 8, 10, 12, 29, 30). Zhang and colleagues reviewed the incidence of LC in CPFE and non-CPFE resected patients, and found a greater incidence of squamous cell carcinoma with higher tumor grade than in those with fibrosis alone. They also found disease extending more commonly from contiguous areas of histologic fibrosis independent of tumor location (6). In our study, incident tumors had no laterality but were dominated by a sub-pleural lower lobe distribution. Radiologic honeycombing in our cohort occurred similarly in those with and without LC, and was an

independent predictor of survival in both cohorts. Kawasaki et al. analyzed the relationship between cancer location and regions of IPF, and reported that 50% of new cancer diagnoses occurred in areas of fibrotic parenchyma (31). Such findings support the hypothesis that cancer development may be related to areas of fibrosis more than emphysema, explaining the radiologic distribution of peripheral and lower lobe predominance as seen in our cohort and others. Zones of fibrosis and emphysema are often radiologically separated (upper lobe emphysema and lower lobe fibrosis) in typical CPFE, though overlap of histologic findings at any one location cannot be excluded (2, 32). Paraseptal emphysema has also been reported at the lung bases near fibrotic lesions and may contribute to tumorigenesis (2, 33). In all, the development of LC in patients with CPFE may be distinct from those with fibrosis or emphysema alone, though further research is needed to distinguish true areas of histologic fibrotic change from emphysema as a determinant of tumor risk.

Lung cancer was associated with greater mortality in our CPFE cohort even after correction for a priori covariables. We also found successful surgical resection of earlier stage disease in highly selected patients may improve outcomes despite concern for increased surgical risk. Mimae et al in contrast found CPFE was associated with increased postoperative mortality and complications after lung resection, particularly among those with greater severity of radiologic fibrosis (7, 8). Presence of radiologic honeycombing also appeared to contribute to poorer outcomes in those with LC in our cohort. Honeycombing may confer a sense of more advanced fibrosis and deter surgical resection among those with potentially resectable disease, though in our limited data set of diagnosed patients, frequency of radiologic honeycombing did not differ among earlier or later stage disease. Falsely preserved FEV1 and FVC values and ratios in patients with CPFE may make lung volume assessment of pre-operative risk unreliable.

Surgical risk appears associated with severity of radiologic fibrosis(7) which may serve as a potential parameter for considering resection in those with earlier stage disease, though further research is needed. Lastly, pulmonary hypertension has also been previously reported as increasing surgical risk in those undergoing major lung resection, and may contribute to increased peri-operative morbidity (34). RVSP in our study trended towards being predictive of mortality in those diagnosed with LC, but was no different between those undergoing resection vs those who were eligible but did not receive it. LC staging appears to drive surgical resection more than suspicion for pulmonary hypertension, though cannot be confirmed with this limited data set.

We also assessed contributing factors to overall survival among those with CPFE. Multivariable analysis revealed age, elevated RVSP, home oxygen use, DLCO%, and presence of radiologic honeycombing were predictive of poorer outcome. Kishaba et al did not find FVC% to be predictive of survival (35) while Choi et al did (3). Finger clubbing has been described as a predictor of mortality in one prior study while pulmonary hypertension has been well described as contributing to poorer survival among CPFE patients (1, 35). CPFE should be suspected in smokers with interstitial lung disease and preserved lung volumes but severely reduced DLCO. Recognition of radiologic disease and closer monitoring of associated complications may allow for earlier detection of malignancy and opportunity for resection in the setting of other predictors of disease outcome. No recommendations currently exist regarding more specific or regular cancer screening in CPFE despite their apparent increased risk. Careful consideration should be given in weighing the potential benefit of earlier detection against related comorbidities and risk of surgical resection, where mortality as exemplified in our smaller study may be improved in carefully selected patients with earlier stage disease.

There are several limitations to our study. Despite a large sample size, a single-center retrospective cohort can only assess correlation but not causation. Selection bias may be present as not all eligible subjects had timed or serial radiographic and pulmonary function data available for analyses. Additionally we only included patients with available CT for review. A smaller number of subsequently diagnosed CPFE-LC allowed for only univariable analysis and cause of death was not known in approximately 15% of the cohort. Despite these limitations, CPFE patients in our study were representative and characteristic of those reported in prior studies.

Conclusion

Lung cancer in CPFE was most commonly squamous cell carcinoma presenting in older heavy male smokers with a predominance of peripheral and lower lobe radiologic presentations. Despite underlying fibrosis and emphysema, carefully selected earlier stage patients undergoing surgical resection still achieved mortality benefit. Weighing the risks of surgical resection after earlier detection with associated baseline comorbidities and other predictors of CPFE survival remain difficult. Further study is needed to understand factors associated with increased risk of LC in CPFE, perhaps to determine a more disease-specific cancer screening program for these patients.

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Table 1 Baseline characteristics in CPFE with and without LC diagnosis

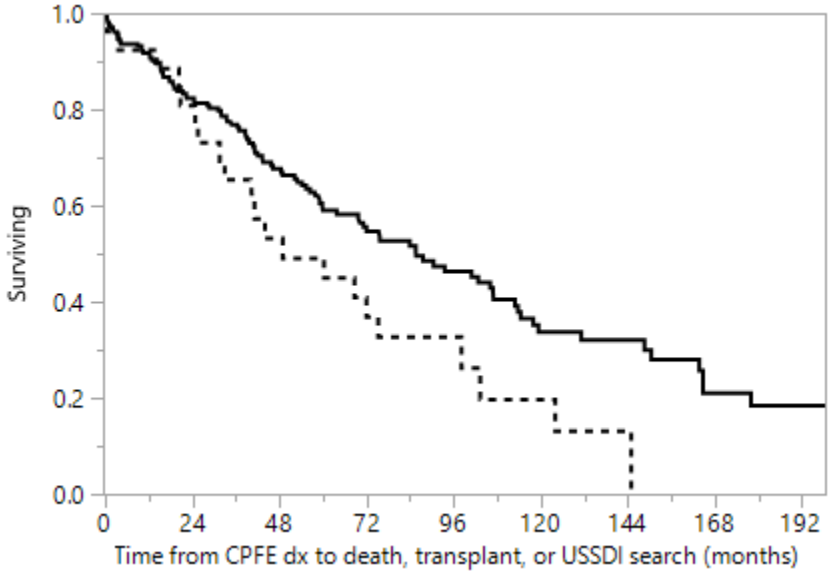
Variable	**CPFE** (N= 204)	**CPFE-LC** (N=26)	**P value**
Age at diagnosis of CPFE, mean ± SD (95% CI)	68 ± 9.1 (67-70)	66 ± 7.1 (63-69)	0.18
Males (%)	155(76)	18 (69)	0.45
Smoking status - N (%) Active Former	 12 (5.5) 192 (94)	 2 (8) 24 (92)	0.31
Smoker pack years, mean ± SD(95% CI)	56 ± 24.6 (46-66)	50 ± 28.3 (46-54)	0.08
Finger Clubbing N (%)	40 (20)	7 (27)	0.39
LABA Use N (%)	117 (57)	11 (42)	0.15
Systemic Steroid N (%)	70 (34)	10 (38)	0.68
Immunosuppressive agents N (%)	15 (7.4)	1 (4)	0.51
Home Oxygen N (%)	155 (76)	16 (62)	0.11
RVSP mmHg, median(IQR)	49(39- 63)	49 (32 – 66.5)	0.40
PFT findings			
TLC % , mean ± SD (95% CI)	84.1± 16.7 (81-87)	91.2 ± 16.1 (82-100)	0.12
FVC%, mean ± SD (95% CI)	80.8 ± 18.5 (78-84)	85.8 ± 18.2 (78-94)	0.22
FEV1%, mean ± SD (95% CI)	75.8 ± 18.9 (73-79)	76.7 ± 16.3 (70-84)	0.83
FEV1/ FVC, mean ± SD (95% CI)	73.5 ± 11.5 (72-75)	71 ± 12.3(66-76)	0.31
DLCO%, mean ± SD (95% CI)	42.9 ± 16.9 (40-45)	49.6 ± 16.9 (42-58)	0.09
PFT pattern Normal Obstructive Restrictive Isolated low DLCO Nonspecific Mixed	(N= 188) 9 (4) 46 (23) 63 (31) 60 (29) 9 (4) 1 (0.5)	(N= 23) 1 (4) 7 (30) 5 (22) 6 (26) 3 (13) 1 (4)	0.86
Radiologic features			
Presence of Honeycombing N (%)	74 (36)	9 (35)	1.0
Distribution of Emphysema Centrilobular Subpleural Mixed	 81 (40) 32 (16) 91 (45)	 9 (35) 3 (12) 8 (31)	0.90

Lung Transplantation N (%)	8 (4)	0 (0)	0.88
All-cause mortality N (%)	103 (50)	21 (81)	**0.003**

Table 2 CPFE Lung Cancer Characteristics (N= 26)

Histology	
NSCLC / small cell (%/%)	23/3 (88/12)
Adenocarcinoma N (%)	8 (35)
Squamous cell N (%)	13 (57)
Large cell N (%)	1 (4)
Other N (%)	1 (4)
Clinical Staging	
NSCLC	
Stage I N (%)	5 (21.7)
Stage II N (%)	5 (17.4)
Stage IIIA N (%)	3 (17.4)
Stage IIIB N (%)	1 (4.3)
Stage **IV** N (%)	9 (39)
Small cell lung cancer	
Limited disease N (%)	3 (100)
Location	
Left/ Right N (%)	12/11 (52/48)
Left lower lobe N (%)	8 (31)
Right lower lobe N (%)	8 (31)
Left upper lobe N (%)	3 (12)
Right upper lobe N (%)	3 (12)
Other (right middle lobe, lingula, hilar only) N (%)	4 (15)
Located within 2 cm of pleural edge N (%)	16 (64)
Treatment	
No therapy (direct hospice or palliation)	4 (15)
Chemotherapy alone	1 (4)
Radiation alone (including SBRT)	7 (27)
Chemotherapy and radiation	6 (23)
Surgical resection alone	6 (23)
Surgical resection + chemo or radiation	2 (8)
Cause of Death	
Deaths, N (%)	21 (81)
Primary cancer N (%)	12 (55)
Infection N (%)	3 (15)
Acute exacerbation of ILD N (%)	1 (5)
Unrelated to CPFE and/or lung cancer N (%)	2 (10)
Unknown	3 (15)

Figure 1 Kaplan-Meier analysis comparison of CPFE with CPFE-LC

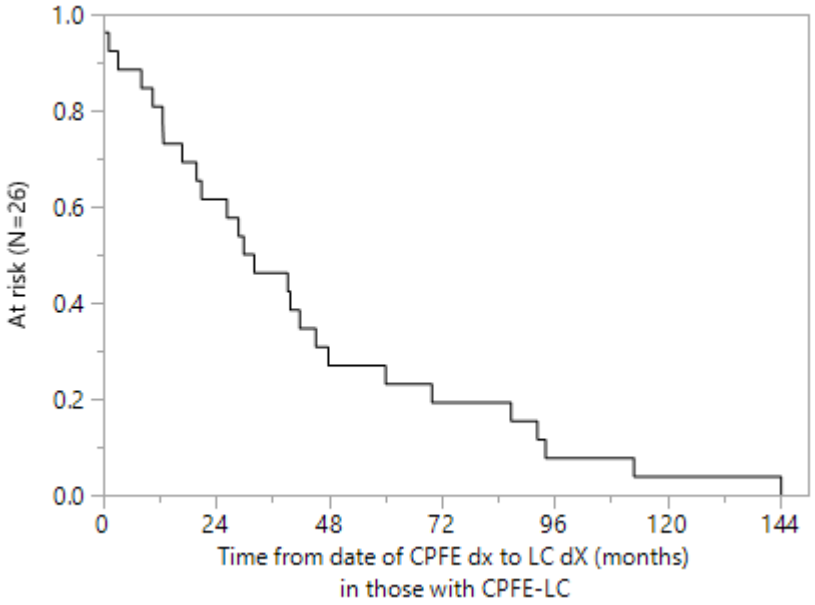


Log Rank: **0.0275**
Solid line: CPFE
Dash line: LC- CPFE

Legend:

Survival was poorer from the time of initial CPFE diagnosis for those with subsequent LC (median survival 49 months (95% CI 31-98) compared to those without (median survival 86 months (95% CI 70-107) (Log rank 0.0275).

Figure 2 Kaplan-Meier time to LC diagnosis



Interval risk for the whole cohort (N =230)

Time (months)	0	12	24	36	48	72	84	96	120	144
Interval alive at risk for LC	230	210	179	136	107	66	55	44	25	17
Interval LC cases	0	5	5	4	5	2	0	3	1	1
Cumulative LC cases	0	5	10	14	19	21	21	24	25	26

Legend:
Median time to LC diagnosis was 31 months (95% CI 17-45). Frequency of new LC diagnoses appeared greatest in the first 4 years of CPFE diagnosis based on interval risk for the whole cohort.

Table 3 CPFE univariable and multivariable Cox regression predictors of all-cause mortality for the whole cohort (N= 230)

Variable	Univariable HR (95% CI)	P value	Multivariable¶ HR (95% CI)	P value
Age at CPFE diagnosis (years)*	1.04 (1.02-1.06)	<0.0001	1.04 (1.02-1.06)	<0.0001
Male sex (%)	1.25 (0.83-1.90)	0.28	-	-
Pack years *	1.00 (0.99-1.01)	0.22	-	-
Finger Clubbing	1.23 (0.82-1.86)	**0.32**	-	-
Home Oxygen use	1.98 (1.21-3.28)	**0.004**	2.09 (1.24-3.51)	**0.005**
RVSP (mmHg) *	1.02 (1.01-1.03)	**<0.0001**	1.02 (1.01-1.03)	**<0.0001**
FVC%*	0.99 (0.99-1.01)	0.78	-	-
FEV1%*	0.99 (0.99-1.01)	0.89	-	-
DLCO% *	0.97 (0.96-0.99)	**<0.0005**	0.98 (0.96-0.99)	**0.0011**
Presence of Honeycombing	2.07 (1.44-2.97)	**0.0001**	2.18 (1.49-3.19)	**<0.001**
Lung cancer diagnosis	1.69 (1.05-2.71)	**0.039**	2.25 (1.36-3.72)	**0.0015**

¶ Adjusted for age, sex, pack years, FVC%, and presence of honeycombing

*Unit hazard ratios for linear predictors

Table 4) Univariable Cox regression predictors of death in CPFE-LC patients (N=26)

Variable	**Univariable HR (95% CI)**	**P value**
Age at CA diagnosis (years)	1.03 (0.96-1.09)	0.43
Male sex (%)	0.91 (0.35-2.61)	0.53
Pack years	1.01 (0.98-1.02)	0.51
Finger Clubbing	1.15 (0.40-2.86)	0.78
Home Oxygen use	1.32 (0.52-3.57)	0.56
RVSP (mmHg)	1.03 (0.99-23.97)	0.05
FVC%	0.98 (0.95-1.01)	0.16
FEV1%	0.99 (0.97-1.02)	0.39
DLCO%	0.97 (0.93-1.00)	0.14
Presence of Honeycombing	3.03 (1.16-7.91)	**0.02**
Adeno vs others	1.95 (0.72-4.81)	0.17
Stage at presentation (late or non-resectable (Stage III and IV, with small cell) vs potentially resectable NSCLC (Stages I and II)	4.77 (1.8-14.94)	**0.001**
Surgical resection performed	0.29 (0.09-0.87)	**0.02**