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Treatment and outcome of lung cancer in idiopathic interstitial pneumonias

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Abstract. *Background:* Idiopathic interstitial pneumonias (IIP) are associated with an increased lung cancer (LC) risk. However, data on the prognostic and therapeutic impact are limited. We therefore aimed to analyze the outcome of IIP patients with LC under different treatment modalities. *Methods:* Patients with IIPs diagnosed in a tertiary interstitial lung diseases (ILD) center were reviewed for LC diagnosis. *Results:* Of 265 patients with idiopathic pulmonary fibrosis (IPF), 142 with non-specific interstitial pneumonia (NSIP), and 71 with cryptogenic organizing pneumonia (COP), 16%, 4%, and 6% were affected by LC, respectively. Patient characteristics were: IPF: 93% male, median age 67 years, forced vital capacity (FVC) 82%, diffusion capacity for Carbon monoxide (DLCO) 41%, mean survival 20 months. NSIP: 67% male, median age 70 years, FVC 72%, DLCO 43%, mean survival 35 months. COP: 50% male, median age 66 years, FVC 93%, DLCO 77%, mean survival 88 months. Significant treatment-related toxicities occurred in 55% IPF, 20% NSIP und 0% COP patients. 30-days postoperative mortality was 25% in IPF, and 0% in NSIP/COP while rate of radiation pneumonitis was 24% in IPF. *Conclusions:* LC is a frequent comorbidity in IIP, with a higher incidence and reduced survival in IPF compared to other IIPs. LC treatment is associated with significant toxicity, specifically in IPF. Interdisciplinary evaluation of therapeutic options in IIP patients diagnosed with LC is therefore mandatory. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 266-274)*

Key words: idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis, lung cancer, comorbidity, therapy, prognosis

Introduction

Both lung cancer (LC) (1) and idiopathic interstitial pneumonias (IIP) including idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (NSIP), and idiopathic cryptogenic organizing pneumonia (COP) are major global health issues associated with high morbidity and mortality, especially in IPF. The mortality rate and incidence in IPF increased in recent decades in both

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men and women (2, 3). Historically, Averill Liebow initiated the separation of idiopathic interstitial pneumonias into clinically and histologically distinct groups based on morphological characteristics which was currently updated (4, 5). Current concepts describe IPF as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in the elderly, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). The definition of IIP requires the exclusion of other forms of interstitial lung diseases (ILD) e.g. associated with environmental exposure, medication, or systemic disease (6).

It is well known that IPF patients have an increased risk to develop syn- or metachronous pulmonary neoplasms and the incidence of LC in IPF patients is increasing – also with time after IPF first diagnosis (7, 8). While having this high incidence compared to the normal or even smoking population, LC is much harder to identify on radiological imaging since the interstitial lung disease, especially those with fibrotic changes, superimposes the lung parenchyma and seriously interferes with the detection of lesions indicating LC. Furthermore, radiological patterns like consolidations as well as ground-glass opacifications might belong to both diseases (IIP and LC, e.g. lepidic adenocarcinoma). Mortality due to LC has been reported with 10.4% in IPF patients (9). The reported prevalence of LC in IPF patients is up to 48.2 % compared to LC patients in the age-matched general population without IPF (9.1%, $p < 0.001$) (10-12); even double and triple carcinomas have been described (11). The incidence of LC among IPF patients is higher in males and the mean age of onset of IPF with LC is higher compared to IPF without LC (11). However, data on the incidence and course under treatment of LC in other IIPs as NSIP and COP are very sparse (13) or lacking, respectively. Moreover, although the combination of IPF and LC is frequently observed and treatment is challenging, only limited data were published and evidence-based treatment guidelines are missing so far. In order to shed more light on LC treatment in IIP and to provide a basis for future treatment decisions, we retrospectively analysed respective patients treated in a tertiary ILD referral centre.

Patients and Methods

We retrospectively reviewed the database of the interstitial and rare lung disease outpatient clinic, Thoraxklinik and the Institute of Pathology, both University of Heidelberg, Germany, between 2004 and 2011 for cases with syn- or metachronous LC in IIP. The study was approved by the ethics committee of the medical school of the University of Heidelberg (IRB approval number S-318/2013). All patient records were anonymized and de-identified prior to analysis. Only patients with completely available clinicopathological data including sex, age, smoking status, time of LC diagnosis, time of IIP diagnosis, therapy, complications, and outcome were included. IIP was diagnosed in a multidisciplinary team according to the current ATS/ERS/JRS/ALAT statements and re-evaluated for this retrospective analysis (6, 14). Only patients with a definitive diagnosis of IPF, NSIP or COP were included. LC was proven histopathologically and treatment was discussed in a multidisciplinary board.

Statistics

Overall survival (OS) was analyzed using the Kaplan-Meier method, with a log-rank test to probe for significance. Statistical analyses were performed using SPSS Statistics 19 (IBM, Ehningen, Germany). P-values <0.05 were considered significant.

Results

Patient characteristics

We retrospectively screened >8000 LC patients as well as 478 patients with IIPs, i.e. 265 patients with IPF, 142 with NSIP, and 71 with COP. All IIP cases were discussed in our multidisciplinary team (MDT) for interstitial lung diseases; for inclusion into this retrospective analysis, IPF cases had to have definitive IPF and all NSIP and COP cases were rated idiopathic according to the MDT. Thereby we identified syn- or metachronous LC in 42 IPF patients (16%), 6 NSIP patients (4%), and 4 COP patients (6%) (Table 1). Overall, 45/52 patients were male ($p=0.018$). IPF was diagnosed before LC in 55% (mean interval 36 months) and synchronously

Table 1. Clinicopathologic data of all patients

	IPF (n=42)	NSIP (n=6)	COP (n=4)
Age [range]			
Age at IIP diagnosis [range]	67 [44-84]	68 [62-76]	70 [66-76]
Age at LC diagnosis [range]	70 [44-84]	69 [62-81]	66 [55-72]
Sex			
male	93%	67%	50%
female	7%	33%	50%
Smoking history	93%	83%	75%
pack years [rangel]	40 [5-100]	63 [50-70]	31 [10-53]
Lung function parameters [range]			
FVC l / % predicted	3.3 [1.5-4.9] 82 [44-118]	2,6 [1,3-5,3] 72 [52-107]	3 [2,1-4,9] 93 [69-141]
FEV1 % predicted	2.4 [1.3-3.5] 83 [44-122]	2,1 [1,3-4,3] 73 [52-116]	2 [0,7-4,2] 81 [25-163]
TLC % predicted	5.3 [2.4-7.9] 84 [38-105]	4,9 [3,5-6,6] 80 [57-90]	6,7 [4,2-9,2] 114 [89-138]
DLCO-SB % predicted	41 [18-98]	43 [27-53]	77 [77-77]
PO2 mmHg	67 [48-85]	60 [52-67]	71 [56-85]
Syn- or metachronous diagnoses			
metachronous, IIP diagnosis first	55%	50%	25%
(median interval)	(36 months)	(49 months)	(5 months)
metachronous, LC diagnosis first	7%	33%	50%
(median interval)	(5 months)	(22 months)	(105 months)
synchronous	36%	17%	25%
n.d.	2%		
Histology of LC			
SCLC	19% (n=8)	33% (n=2)	0%
NSCLC	81% (n=34)	67% (n =4)	100% (n=4)
SQCC	36% (n=15)	33% (n=2)	25% (n=1)
ADC	31% (n=13)	17% (n=1)	75% (n=3)
ADSQ	7% (n=3)	0%	0%
LCNEC	5% (n=2)	17% (n=1)	0%
SC	2% (n=1)	0%	0%
Tumor stage (UICC)			
cis	3% (n=1)	0%	0%
I	12% (n=4)	17% (n=1)	75% (n=3)
II	12% (n=4)	0%	25% (n=1)
III	38% (n=13)	17% (n=1)	0%
IV	35% (n=12)	67% (n=4)	0%
Tumor localisation			
upper lobes	60% (36%/24%)	50% (17%/33%)	50% (50%/0%)
middle lobe	7%	0%	25%
lower lobes	31% (17%/14%)	50% (33%/17%)	25% (0%/25%)
multifocal/diffuse	2%	17%	25%
centrally	21%	67%	25%
peripheral	67%	17%	50%

IPF = idiopathic pulmonary fibrosis, NSIP = non-specific interstitial pneumonia, COP = cryptic organizing pneumonia, IIP = idiopathic interstitial pneumonia, LC = lung cancer, FVC = forced vital capacity, FEV = forced expiratory volume, DLCO = diffusion capacity for Carbon monoxide, SCLC = small cell lung cancer, NSCLC = non-small cell lung cancer, SQCC = squamous cell carcinoma, ADC = adenocarcinoma, ADSQ = adeno-squamous carcinoma, LCNEC = large cell neuroendocrine carcinoma, SC = sarcomatoid carcinoma

in 36% which was comparable to NSIP; 59% of NSIP cases were diagnosed before LC with an interval of 49 months and 17% were diagnosed synchronously. 25% of the COP/LC diagnoses were synchronous whereas LC diagnosis was made prior to COP in 50% (mean interval 8.5 years). 93% (IPF), 67% (NSIP), and 50% (COP) were male. The overall age at IIP diagnosis was comparable among all three groups with 67 years in IPF (range: 44-84), 68 in NSIP (62-76) and 70 in COP (66-76). Active or former smokers were higher in IPF patients (93%) compared to NSIP (83%) and COP patients (75%).

Overall, relevant comorbidities at the time of first diagnosis of the respective IIP were led by cardiovascular disorders (64% without coronary artery disease (CAD), 45% with CAD only) followed by emphysema as detected on HRCT (38%), pulmonary hypertension verified by right heart catheter (17%), diabetes (17%), malignancies other than LC (17%) -mainly bladder cancer (9%)-, GERD (14%), and sleep apnea syndrome (12%). In 5% a family history of IPF was recorded.

Pulmonary function parameters

Pulmonary function testing at the time of LC diagnosis revealed a median forced vital capacity (FVC) of 3.3 l [1.5-4.9], 82% [44-118] predicted, a total lung capacity (TLC) of 5.3 l [2.4-7.9], 84% [38-105] and a median diffusion capacity for Carbon monoxide (DLCO) of 41% [18-98] for IPF patients, a median FVC of 2.6 [1,3-5,3] l, 72 [52-107] % predicted, a median TLC of 4,9 [3,5-6,6] l, 80 [57-90] % and a median DLCO of 43 [27-53]% predicted for NSIP patients and a median FVC of 3 [2,1-4,9] l, 93 [69-141]% predicted, a median TLC of 6,7 [4.2-9.2] l, 114 [89-138]% predicted with a median DLCO 77 [77]% predicted in COP patients (Table 1).

Distribution and stage of lung cancer among IIP patients

Overall, 18 patients were affected by squamous cell carcinoma (SQCC; 34.6%), 18 by adenocarcinoma (ADC; 34.6%), 10 by small cell lung cancer (SCLC; 19.2%), 3 by adeno-squamous carcinoma (ASC; 5.8%), 2 by large cell neuroendocrine carcinoma (LCNEC; 3.8%), and 1 by sarcomatoid carcinoma (SC; 1.9%). For details concerning tumor stages we refer to Table 1. In IPF 67% of the tumors were located in the periphery while this was only the case in 17% and 50% of the NSIP and COP patients, respectively (Table 1). Anatomical LC localization in IPF, NSIP and COP respectively was 60%, 50% and 50% in the upper lobes, in 7%, 0%, 50% in the middle lobe, and in 31%, 50% and 25% in the lower lobes. Furthermore, one IPF patient had multifocal manifestations of lepidic predominant ADC.

Among the IPF patients 15 patients were affected by SQCC (35.7%), 13 by ADC (31%), 8 by SCLC (19%), 3 by ASC (7.1%), 2 by LCNEC (4.8%), and 1 by SC (2.4%). A typical case is exemplarily depicted in Figure 1. In the NSIP group 2 patients were affected by SQCC (33.3%), 2 by ADC (33.3%), and 2 by SCLC (33.3%). In the COP group one patient was affected by SQCC (25%) and 3 patients by ADC (75%; Table 1).

Therapy, treatment -related complications, and outcome

Treatment of the underlying IIP was as follows: IPF was treated either with best supportive care (50%), N-Acetylcysteine (NAC) (19%), prednisone (14%), prednisone/NAC (7%), prednisone/Azathioprine/NAC (5%) or other regimens (5%). NSIP was treated either with best supportive care (33%), NAC (33%), or with prednisone/NAC (33%), while all patients with COP were treated with steroids (100%).

Regarding LC treatment in the IIPs, for IPF patients with either NSCLC or SCLC surgery was performed in 32% and 12.5% respectively, radiotherapy in 32% and 0%, radio-chemotherapy in 15% and 12.5% respectively, chemotherapy in 10.5% and 75% respectively, best supportive care in 10.5% and 0% respectively and chemotherapy for relapse in 12% and 38% respectively. The indication for surgery in the SCLC case was a pulmonary nodule (T1N0M0) which turned out to be SCLC after surgery.

In NSIP with either NSCLC or SCLC, surgery was performed in 50% and 0% respectively, in both NSIP with NSCLC patients followed by radiotherapy, radio-chemotherapy in 25% and 0%, chemotherapy in 25% and 100%, respectively, best supportive care in none and chemotherapy for relapse in 0% and 50%, respectively. For COP patients (only NSCLC cases) therapy consisted in 75% of surgical treatment and in 25% of radiochemotherapy.

Therapy associated toxicities were observed in 55%, 17%, and 0% of the IPF, NSIP, and COP patients, respectively. Of note, the incidence of surgery related complications was high with 67%, mainly pneumonia and acute myocardial infarction. Moreover, 30 day mortality among the operated patients was 25% in the IPF group (myocardial infarction, n=3 and pneumonia, n=2) and 0% among the NSIP and COP patients. Regarding patients receiving irradiation the complication rate was 45% in IPF pa-

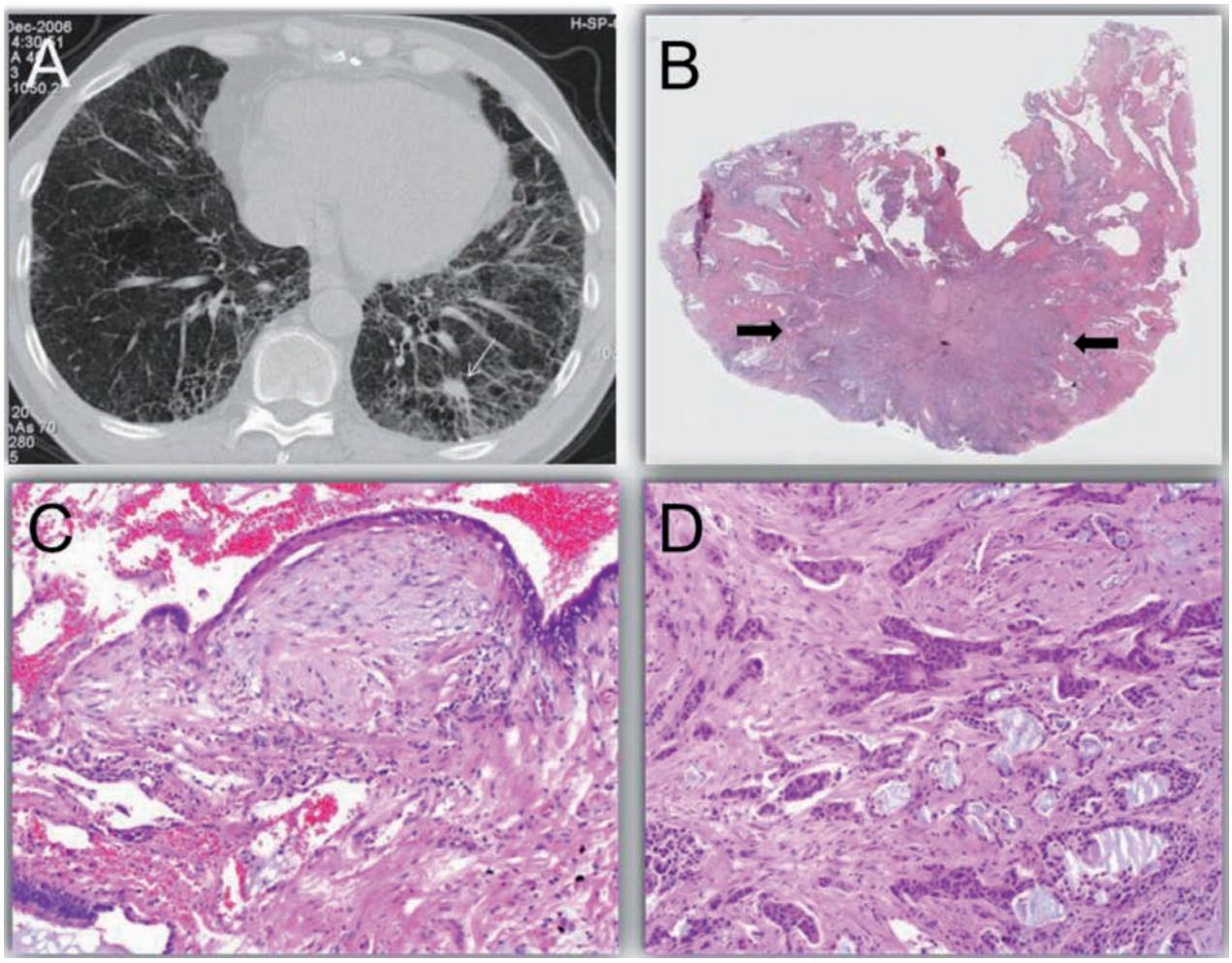

Fig. 1. Exemplary case of idiopathic pulmonary fibrosis with synchronous adeno-squamous cell carcinoma**.** A: Computed tomography with basal honeycombing and a small lesion suspect for malignancy (arrow). B: Overview of the resection specimen showing interstitial fibrosis with honeycombing and fibroblast foci (C) and a central lesion (depicted by arrows). Histopathology revealed a adeno-squamous cell carcinoma (D).

tients with a high incidence of radiation induced pneumonitis in 4 out of 17 irradiated IPF patients (24%); also pulmonary infections and one acute myocardial infarction occurred in this group. For NSIP patients radiation induced pneumonitis occurred in 1 out of 3 NSIP patients (33%; Table 2). Chemotherapy related toxicity was also high in IPF patients with 63% consisting of pulmonary infections, respiratory insufficiency, cardiovascular complications and neutropenia. Of note, acute exacerbations after surgery were not observed in neither of the IIPs undergoing surgery for LC.

Despite the high incidence of lung cancer therapy-related complications in IPF patients, a significant survival impact was not detected (p=0.470). The analysis of the influence of distinct comorbidities in the IIP with lung cancer cohort revealed that coronary artery disease (CAD) in the IPF and LC cohort had a significant negative survival impact (with CAD 4 months, without CAD 15 months, p=0.008)

Mean survival for IPF, NSIP, and COP patients with LC was 20, 35, and 88 months, respectively (Figure 2). Although the small groups of IIP subtypes with different tumor entities and different tumor stages clearly hamper survival analysis, Kaplan-Meier curves point out to a worse outcome of IPF patients compared to NSIP and COP patients (Figure 2; p=0.126).

Table 2. Therapy-related complications in IPF, NSIP, and COP patients affected by lung cancer

	Therapy-related complications		
	IPF (n=42 total)	NSIP (n=6 total)	COP (n=4 total)
Surgery-related AE (of (n) in IPF(12), NSIP(2), COP(4))	67%	0%	0%
pneumonia	50%	0%	0%
myocardial infarction	33%	0%	0%
respiratory failure	8.5%	0%	0%
pneumothorax	25%	0%	0%
others	16.5%	0%	0%
Radiotherapy-related AE (of (n) in IPF(11), NSIP(2), COP(1))	45%	0%	0%
radiation pneumonitis	27%	0%	0%
pulmonary infections	36%	0%	0%
myocardial infarction	9%	0%	0%
respiratory failure	9%	0%	0%
Radiochemotherapy-related AE (of (n) in IPF(6), NSIP(1), COP(1))	17%	100%	0%
radiation pneumonitis	17%	100%	0%
Chemotherapy-related AE (of (n) in IPF(8), NSIP(3), COP(0))	63%	0%	0%
pneumonia	37.5%	0%	0%
respiratory failure	12.5%	0%	0%
cardiovascular failure	12.5%	0%	0%
cytopenia	12.5%	0%	0%

IPF = idiopathic pulmonary fibrosis, NSIP = non-specific interstitial pneumonia, COP = cryptic organizing pneumonia, AE = adverse event (=therapy-related complications)

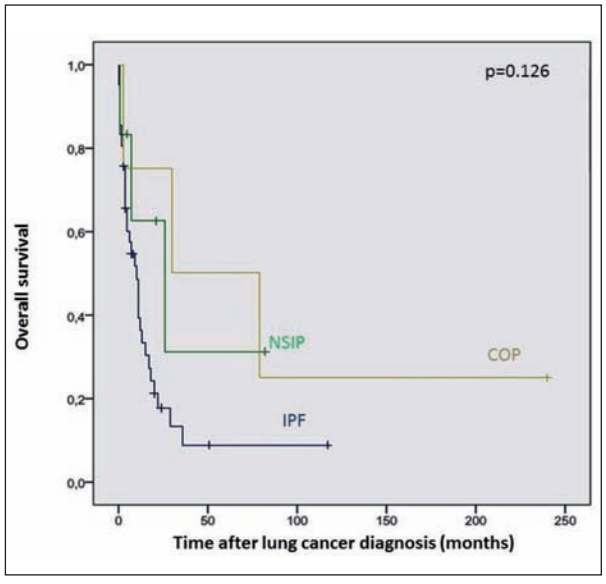

Fig. 2. Overall survival of IPF, NSIP, and COP patients affected by lung cancer after surgical resection. Although statistically not significant Kaplan Meier analyses indicate a worse outcome for IPF patients compared to NSIP and COP patients

Discussion

In patients with IIPs, especially those with IPF, syn- or metachronous LC is a frequently observed, severe comorbidity. However, reports on larger cohorts are sparse and treatment guidelines for patients with this "liaison dangereuse" are lacking so far. Also early detection is harder, since a small LC is difficult to detect in a lung suffering from a fibrotic lung disease. This is the first report which comparatively analyses treatment, outcome and therapy related complications of syn- or metachronous LC in different IIP entities treated by surgery, chemotherapy, and radiotherapy. We demonstrate that LC has a high incidence especially in IPF patients. We report for the first time that therapy-related toxicities occur especially in IPF after various treatment modalities but less in NSIP and COP patients and are associated with high mortality in IPF.

Respiratory failure is considered the most frequent cause of death in IPF but heart failure, ischemic heart disease, infections, and pulmonary emboli are other common causes of death in these patients (15, 16). Indeed, cardiovascular and respiratory disorders were the most frequent comorbidities of

IIP patients in this study and also major causes for therapy-related complications and death.

Another interesting finding of the present report is a relevant rate of other malignancies, especially a high rate of bladder cancer. To our knowledge this has not been reported before and deserves further investigation. A potential explanation might be the shared risk factor smoking for LC, bladder cancer and IPF.

There is evidence that LC in IPF occurs more frequently in elderly male smokers and most tumors arise in peripheral areas involving fibrosis. In our cohort smokers were more prevalent in IPF compared to NSIP or COP subgroups. The incidence rates of SQCC as well as multiple LC were reported to be significantly higher in IPF compared to non-IPF patients (17). Similar findings were also reported by Park and colleagues (18). Indeed, we also found SQCC the most prevalent NSCLC subtype in IPF with the majority of tumours located in the periphery and more frequently in the upper than the lower lobes. However, in general there is no significant difference in the subtype of IPF-associated LC compared to the total LC population, which indicates that the features of the IPF-associated LC are also similar to those in the total LC population (18). This is also supported by our data. However, others found that SCLC was predominant in multiple LC in IPF patients (19). Conversely, ADC were reported as the most frequent subtype by others and suggested to occur in relation to fibrotic scars (20-22). We only noticed a slightly higher prevalence of SCLC patients in the NSIP group compared to the total LC population which is most likely explained by the small number of respective cases.

If applicable, the current treatment of LC in IPF patients is similar to that of LC in general and includes chemotherapy and radiation in addition to surgical resection or combinations of these. Surgical resection of LC in patients with IPF is a potentially curative option in early cancer stages but associated with significant postoperative morbidity and mortality (23-29), which is also confirmed by our data. Among others, postoperative complications include pneumonia, bronchopleural fistulas, and persistent air leaks (24, 30). Although not seen in our cohort, the most serious postoperative complication is an acute exacerbation of the interstitial lung disease (31, 32) with a reported incidence of about 20% and a mortality rate >50% (33). Concerning the procedure-specific mortality, pneumonectomy (33% vs. 5%) and lobectomy (12% vs. 3%) had a much higher risk compared to a control group (25). There is also first evidence that lung transplantations are also associated with an unfavourable outcome if LC is diagnosed coincidentally in the explanted lung (34). All patients with complicated wedge resections were reported to have low preoperative percentages for forced vital capacity of 69+/-6% whereas surgical approaches were suggested to be only carefully indicated for these patients (30). In contrast, others found that preoperative pulmonary function data are no relevant predictors of postoperative mortality (25). In general and beyond postoperative complications, the poor survival after surgery is also attributed to a high incidence of a second primary LC as well as the poor natural history of IPF in general (35). In view of the risks associated with surgery, careful patient selection and close postoperative care is essential in IPF patients in order to achieve an optimal surgical outcome (24-26, 30, 35). Furthermore, novel strategies to reduce the rate of postoperative complications are warranted (36).

There are only sparse data concerning chemotherapy in IIP with LC (37, 38). The reported incidence of acute IIP exacerbation related to chemotherapy is 23% (38) however; we did not observe a single case with chemotherapy-related exacerbations in our cohort. Pulmonary infections were the most frequent complication following chemotherapy but still with lower rates compared to surgery. As a possible alternative to conventional chemotherapy, the effective administration of gefitinib to a patient with IPF- associated LC was described (39), yet this agent also is known to induce diffuse alveolar damage. However, further studies will be necessary to substantiate this strategy and to establish new, promising treatment options. Most likely or at least most wanted are those aiming both against IPF and LC at the same time.

To the best of our knowledge no data were published yet concerning radiation of LC in IIP patients. Whereas radiation was safe without significant complications in NSIP and COP patients we observed high rates of radiation pneumonitis and pulmonary infections in the IPF group. The overall high rates of complications rather argue against radiation therapy in the context of LC in IPF.

Local tumour ablation might be another option in some of these severely pulmonary compromised patients, while it has been used safely in patients suffering from severe emphysema (40).

There are some limitations to our study, mostly based on the retrospective nature of its design. In this context, the diagnostic accuracy of the idiopathic interstitial pneumonias has to be mentioned. While only patients with a definitive diagnosis of IPF had been included and secondary causes of NSIP and COP were excluded, it should be noted that the clinical characteristics of the patients presented here, especially those of the NSIP patients, do not represent typical IIP cohorts. The reported IIP cohorts represent patients with IIP and lung cancer, the prevalence of smokers was also higher in this series than in typical IIP cohorts. Furthermore, there might also be some risk factors for IIP patients developing LC, e.g. higher age and male sex in NSIP and especially smoking in all IIPs. Thus, direct comparison to typical IIP patient cohorts is difficult. However, all cases had been discussed at the time of their first diagnoses in a multidisciplinary board and had been re-evaluated in the context of this analysis, which significantly increases the confidence of the diagnosis (41). A second critical observation is the high percentage of synchronously diagnosed LC and IPF which is not entirely supported by the literature (8). Yet, this observation might reflect the delayed diagnosis of IPF due to misinterpretation of symptoms as related to smoking habits or aging (42) and the neglect of interstitial lung diseases by some. Based on informal surveys and the authors own clinical experiences, the synchronous diagnosis of these diseases is an often observed phenomena. Finally, the low rate of acute exacerbation IPF reported here after surgery is not in line with the rates reported in the recent literature (27). While one explanation might be that e.g. acute exacerbation of IPF has been misdiagnosed as pulmonary infection or other causes in our center, potential reasons could also be the use of different anaesthetic and/or surgical procedures. Yet, this has to be evaluated in prospective studies.

Conclusion

In conclusion, IPF patients have a high risk for the development of syn- and metachronous LC while the incidence is much lower in other IIPs. Moreover, all lung cancer treatment modalities are associated with a high rate of morbidity and perhaps mortality in IPF but not in other IIPs as demonstrated by our data. Therefore, the optimal treatment strategy in patients with this "liaison dangereuse" needs to be determined and closely monitored care of IPF patients in specialized ILD ambulances seems to be mandatory in order to detect LC as early as possible and both for the achievement of an optimal outcome.

Competing interests

This report was in part supported by an unrestricted scientific grant by InterMune. We (the authors) declare that we have no further competing interests.

Authors' contributions

Study design: AW, FJFH, MK
Clinical data acquisition: AE, SET, MS, UO, KP, FJFH, MK
Pathological data acquisition: AW, PAS
Radiological data acquisition: MP, CPH
Data analysis and interpretation: all authors
Writing of the manuscript: AW, MK
Final approval of the manuscript: all authors

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. CA Cancer J Clin 2011, 61(2):69-90.
2. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK: Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. American journal of respiratory and critical care medicine 2007, 176(3):277-284.
3. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A et al.: The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax 2011, 66(6):462-467.
4. Liebow AA: Definition and classification of interstitial pneumonias in human pathology. Resp Res 1975, 8:1.
5. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG et al.: An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine 2013, 188(6):733-748.
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK et al.: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine 2011, 183(6):788-824.

7. Le Jeune I, Gribbin J, West J, Smith C, Cullinan P, Hubbard R: The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. Respiratory medicine 2007, 101(12):2534-2540.
8. Ozawa Y, Suda T, Naito T, Enomoto N, Hashimoto D, Fujisawa T et al.: Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology 2009, 14(5):723-728.
9. Panos RJ, Mortenson RL, Niccoli SA, King TE, Jr.: Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 1990, 88(4):396-404.
10. Araki T, Katsura H, Sawabe M, Kida K: A clinical study of idiopathic pulmonary fibrosis based on autopsy studies in elderly patients. Intern Med 2003, 42(6):483-489.
11. Hironaka M, Fukayama M: Pulmonary fibrosis and lung carcinoma: a comparative study of metaplastic epithelia in honeycombed areas of usual interstitial pneumonia with or without lung carcinoma. Pathol Int 1999, 49(12):1060-1066.
12. Matsushita H, Tanaka S, Saiki Y, Hara M, Nakata K, Tanimura S et al.: Lung cancer associated with usual interstitial pneumonia. Pathol Int 1995, 45(12):925-932.
13. Sato T, Yamadori I, Fujita J, Hamada N, Yonei T, Bandoh S et al.: Three cases of non-specific interstitial pneumonia associated with primary lung cancer. Intern Med 2004, 43(8):721-726.
14. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. American journal of respiratory and critical care medicine 2002, 165(2):277-304.
15. Travis WD, Colby TV, Koss MN, Rosado-de-Christenson ML, Müller NL, King TE: Non-neoplastic disorders of the lower respiratory tract, vol. 1. Washington: The American Registry of Pathology; 2002.
16. Ley B, Collard HR, King TE, Jr.: Clinical course and prediction of survival in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine 2011, 183(4):431-440.
17. Kawasaki H, Ogura T, Yokose T, Nagai K, Nishiwaki Y, Esumi H: p53 gene alteration in atypical epithelial lesions and carcinoma in patients with idiopathic pulmonary fibrosis. Human pathology 2001, 32(10):1043-1049.
18. Park J, Kim DS, Shim TS, Lim CM, Koh Y, Lee SD et al.: Lung cancer in patients with idiopathic pulmonary fibrosis. The European respiratory journal 2001, 17(6):1216-1219.
19. Mizushima Y, Kobayashi M: Clinical characteristics of synchronous multiple lung cancer associated with idiopathic pulmonary fibrosis. A review of Japanese cases. Chest 1995, 108(5):1272-1277.
20. Meyer EC, Liebow AA: Relationship of Interstitial Pneumonia Honeycombing and Atypical Epithelial Proliferation to Cancer of the Lung. Cancer 1965, 18:322-351.
21. Kawai T, Yakumaru K, Suzukiet M, Kageyama K: Diffuse interstitial pulmonary fibrosis and lung cancer. Acta Pathol Jpn 1987, 37:11-19.
22. Yanling M, Seneviratne CK, Koss M: Idiopathic pulmonary fibrosis and malignancy. Current opinion in Pulmonary Medicine 2001, 7:278-282.
23. Aubry MC, Myers JL, Douglas WW, Tazelaar HD, Washington Stephens TL, Hartman TE et al.: Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. Mayo Clin Proc 2002, 77(8):763-770.
24. Kawasaki H, Nagai K, Yoshida J, Nishimura M, Nishiwaki Y: Postoperative morbidity, mortality, and survival in lung cancer associated with idiopathic pulmonary fibrosis. J Surg Oncol 2002, 81(1):33-37.
25. Kumar P, Goldstraw P, Yamada K, Nicholson AG, Wells AU, Hansell DM et al.: Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. J Thorac Cardiovasc Surg 2003, 125(6):1321-1327.
26. Artinian V, Kvale PA: Cancer and interstitial lung disease. Curr Opin Pulm Med 2004, 10(5):425-434.
27. Watanabe A, Miyajima M, Mishina T, Nakazawa J, Harada R, Kawaharada N, Higami T: Surgical treatment for primary lung cancer combined with idiopathic pulmonary fibrosis. General thoracic and cardiovascular surgery 2013, 61(5):254-261.
28. Yano M, Sasaki H, Moriyama S, Hikosaka Y, Yokota K, Kobayashi S et al: Post-operative acute exacerbation of pulmonary fibrosis in lung cancer patients undergoing lung resection. Interactive cardiovascular and thoracic surgery 2012, 14(2):146-150.
29. Sakamoto S, Homma S, Mun M, Fujii T, Kurosaki A, Yoshimura K: Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients: a retrospective study. Intern Med 2011, 50(2):77-85.
30. Kushibe K, Kawaguchi T, Takahama M, Kimura M, Tojo T, Taniguchi S: Operative indications for lung cancer with idiopathic pulmonary fibrosis. Thorac Cardiovasc Surg 2007, 55(8):505-508.
31. Sakamoto S, Homma S, Kawabata M, Kono T, Seki K, Nakata K et al.: [Fatal acute exacerbation of idiopathic pulmonary fibrosis/usual interstitial pneumonia initially in the right lung after surgery lobectomy for left lung cancer]. Nihon Kokyuki Gakkai Zasshi 2004, 42(8):760-766.
32. Yuksel M, Ozyurtkan MO, Bostanci K, Ahiskali R, Kodalli N: Acute exacerbation of interstitial fibrosis after pulmonary resection. The Annals of thoracic surgery 2006, 82(1):336-338.
33. Hoshikawa Y, Kondo T: [Perioperative lung injury: acute exacerbation of idiopathic pulmonary fibrosis and acute interstitial pneumonia after pulmonary resection]. Nippon Geka Gakkai Zasshi 2004, 105(12):757-762.
34. Penalver Cuesta JC, Jorda Aragon C, Escriva Peiro J, Ceron Navarro J, Calvo Medina V, Padilla Alarcon J: [Lung transplantation: bronchogenic carcinoma in the native lung]. Arch Bronconeumol 2007, 43(2):126-128.
35. Fujimoto T, Okazaki T, Matsukura T, Hanawa T, Yamashita N, Nishimura K et al: Operation for lung cancer in patients with idiopathic pulmonary fibrosis: surgical contraindication? The Annals of thoracic surgery 2003, 76(5):1674-1678.
36. Yamauchi Y, Izumi Y, Inoue M, Sugiura H, Goto T, Anraku M et al.: Safety of postoperative administration of human urinary trypsin inhibitor in lung cancer patients with idiopathic pulmonary fibrosis. PloS one 2011, 6(12):e29053.
37. Minegishi Y, Sudoh J, Kuribayasi H, Mizutani H, Seike M, Azuma A et al: The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias. Lung Cancer 2011, 71(1):70-74.
38. Minegishi Y, Takenaka K, Mizutani H, Sudoh J, Noro R, Okano T et al.: Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. Intern Med 2009, 48(9):665-672.
39. Kishi K, Nakata K, Yoshimura K: Efficacy of gefitinib in a patient with lung cancer associated with idiopathic pulmonary fibrosis. J Thorac Oncol 2006, 1(7):733-734.
40. Schneider T, Puderbach M, Kunz J, Bischof A, Giesel FL, Dienemann H et al.: Simultaneous computed tomography-guided biopsy and radiofrequency ablation of solitary pulmonary malignancy in high-risk patients. Respiration; international review of thoracic diseases 2012, 84(6):501-508.
41. Flaherty KR, King TE, Jr., Raghu G, Lynch JP, 3rd, Colby TV, Travis WD et al.: Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? American journal of respiratory and critical care medicine 2004, 170(8):904-910.
42. Valeyre D: Towards a better diagnosis of idiopathic pulmonary fibrosis. European respiratory review : an official journal of the European Respiratory Society 2011, 20(120):108-113.