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Original article

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The DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey. International survey and call for consensus.

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Abstract:

Background: Currently there is major lack of agreement on the diagnostic and therapeutic management of patients with Idiopathic Pulmonary Fibrosis (IPF) and lung cancer (LC). Our

aim was to identify variations in diagnostic and management strategies across different institutions and provide rationale for a consensus statement on this issue.

Methods: This was a joint-survey by ERS Assemblies 8, 11 and 12. The survey consisted of 25 questions.

Results: Four hundred ninety four (n=494) physicians from 68 different countries and 5 continents responded to the survey. 94% of participants were pulmonologists and 1.8% thoracic surgeons and 1.9% oncologists. 97.7% involved MDT approaches on diagnosis and management. Regular low-dose HRCT scan was used by 49.5% of the respondents to screen for LC in IPF. PET scan and EBUS bronchoscopy is performed by 60% and 88%, to diagnose nodular lesions with mediastinal lymphadenopathy in patients with advanced and mild IPF, respectively. 83% of respondents continue anti-fibrotics following LC diagnosis; safety precautions during surgical interventions including low-tidal volume are applied by 67%. Stereotactic radiotherapy is used to treat patients with advanced IPF (DL_{CO}<35%) and otherwise operable NSCLC by 54% of respondents and doublet platinum regimens and immunotherapy for metastatic disease by 25% and 31.9%, respectively. Almost all participants (93%) replied that a consensus statement for the management of these patients is highly warranted.

Conclusion: The diagnosis and management of IPF-LC is heterogeneous with most respondents calling for a consensus statement.

Key words: idiopathic pulmonary fibrosis, lung cancer, survey, management, consensus

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a debilitating fibrotic lung disease of unknown origin and pathogenesis with a steady increase in both incidence and mortality (40.000 patients die from IPF each year in USA, the same as breast cancer). Until recently, there was no effective therapy for IPF, except lung transplantation[1]. Although there are two compounds licensed for the treatment of IPF shown to reduce disease progression with encouraging safety and efficacy data [2, 3], neither compound has been tested prospectively in IPF patients with major comorbidities such as lung cancer[4]. Recent epidemiologic evidence suggests that 3 to 22% of patients with IPF develop lung cancer with an increasing risk during disease course up

to 50% and a nearly 5-fold increased risk compared to the general population[5-8].This has a negative impact on patients' survival and quality of life[9-12] and most treatments for lung cancer are associated with a high morbidity and mortality in patients with IPF. Additionally, IPF and lung cancer have striking pathogenetic commonalities including microsatellite instability, epigenetic alterations, telomere attrition and impaired cellular bioenergetics [4, 13-16]. Unfortunately, there is considerable lack of agreement on the diagnostic and therapeutic management of these patients[17]. Current ATS/ERS/JRS/ALAT guidelines (2018)[1] do not address this crucial issue and there are no large randomized controlled trial data on IPF-LC available[13].

We hypothesized that clinical approaches to the diagnosis and management of IPF-LC might vary substantially across different institutions internationally, with documentation of this allowing research questions to be prioritized. Thus, we conducted an international survey, called the DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey, to identify variations in diagnostic and management strategies across different institutions, raise awareness on the co-existence of these two diseases, provide rationale for a consensus statement on this issue and fuel future research and clinical study design. Some of the results have been previously published in the form of an abstract.

Materials and Methods

Questionnaire and participating physicians

To identify all items to be included in the survey, we performed literature research on diagnosis, treatment and management of IPF-LC www.ncbi.nlm.nih.gov/pubmed and https://scholar.google.com by setting specific key words as indicated in supplementary file 1. Following this, an expert panel was formulated, encompassing respiratory physicians and oncologists from European Respiratory Society (ERS) Assemblies 8, 11, and 12 (Thoracic Surgery and Lung Transplantation, Thoracic Oncology and Interstitial Lung Diseases, respectively). Members of the expert panel were required to have experience in the diagnosis and management of IPF and LC and work in reference centers of excellence for

Interstitial Lung Diseases ILDs) and Thoracic Oncology, to participate in an email-based discussion to structure the survey. The final version of the questionnaire comprised an overall of 25 questions divided to five categories: 1) Participants, 2) General knowledge, 2) Diagnosis, 3) Management, 5) Future perspectives (supplementary file 2). Questionnaire was distributed through two different platforms, Google and SurveyMonkey. Google platform was used from ERS to disseminate the questionnaire through members of the ERS Assemblies 8, 11 and 12. Survey Monkey platform was used to disseminate the survey to other participants identified (through an Internet Search) to have a particular interest on ILDs and Thoracic Oncology. Results were homogenized into an excel spreadsheet and duplicate participants were excluded from the analysis. In both cases, participants were invited to participate through an e-mail link. The questionnaire was available from March 2019 – September 2019. Details on the questionnaire can be found in supplementary file 3.

Statistical analysis

All questions of the survey involved categorical answers and absolute and relative frequencies were calculated. Due to the exploratory nature of this survey and the small number of participants in country subgroups, no comparisons between participants from different countries or continents were performed and thus no p-values were calculated. All frequencies were treated descriptively.

Results

Participants

Overall, 494 physicians from 68 different countries and 5 continents responded to the survey with a response rate of 28% (494/1758) **(Figure 1)**. 94% of participants were pulmonologists and 1.8% thoracic surgeons and 1.9% thoracic oncologists. 67% and 21.6% were from University and non-University hospitals, respectively and 51.5% were treating > 20 patients with IPF per year. The majority of the participants (63.2%) stated a clinical experience of > 10 years as specialists **(Figure 2)**.

General Knowledge

LC incidence was between 5-10% of total IPF cases according to 45.3% of participants, while a big discrepancy between participants stating an incidence of 1-5% (30.8%) and those

stating an incidence >20% (21.8%), was noted. Both the incidence and the type of non-lung cancer cases were unknown to a large proportion of the participants (38.8% and 45.6%, respectively). Prostate, colon and breast cancer were reported as the most common types of non-lung cancer cases in patients with IPF by 19.3%, 14.2% and 3.9%, respectively (data not shown). The majority of the participants (54%) declared that lower lobes are the most frequent anatomic location of the lung cancer lesions in their cohort of patients while upper lobes were the most frequent location in 18.3%. According to the majority of participants (85.2%) non-small cell lung cancer (NSCLC) was the most common histologic type of lung cancer in patients with IPF, with adenocarcinoma being the most frequent (58.6%) , followed by squamous (26.6%) and small-cell lung cancer (SCLC) (12.3%) **(Figure 3)**.

Diagnostic approaches

Annual low dose HRCT represented the most frequent screening modality for lung cancer in patients with IPF in 78.7% of participants, followed by no screening at all in 17.6% of participants. Positron Emission Tomography (PET) CT scan followed by endobronchial ultrasound bronchoscopy (EBUS), in case of PET positivity, was applied as diagnostic approach in the majority of participants in patients with 20 mm central nodular lesions and IPF of either mild-to-moderate (FVC>50%, DL_{CO}>35%) or severe (FVC<50%, DL_{CO}<35%) functional impairment (87.9% and 59.7%, respectively); yet, this approach was performed more often in mild-to-moderate disease than in severe disease. Median latency time between diagnosis of IPF and LC was above 12 months, as stated by 57% of respondents, while it was unknown by 27.7% **(Figure 4)**.

Management procedures

Multidisciplinary approaches for the management of patients with IPF-LC were applied by 78.2% of respondents. The majority of participants (83.8%) continued treatment with anti-fibrotics when a patient with IPF was diagnosed with LC. Major disagreement was noted in whether moderate or severe IPF is an absolute contraindication for radiotherapy of chemotherapy in patients with locally advanced NSCLC, with 40.2% of participants disagreeing, 37.2% agreeing and 20.2 % stating uncertainty. **(Figure 5)**. In a patient with IPF

of mild-to-moderate functional impairment (FVC>50%, DL_{CO}>35%) diagnosed with otherwise operable NSCLC (TNM stage I-II) surgery, stereotactic radiotherapy (depending on the cancer stage) and continuation of anti-fibrotics were the three most frequent management approaches in 78.2%, 40.5% and 40% of the participants, respectively. On the other hand in a patient with advanced IPF (FVC<50%, DL_{CO}<35%) and otherwise operable NSCLC (TNM stage I-II) the three most frequent management strategies were stereotactic radiotherapy, continuation of anti-fibrotics and palliative care in 54.1%, 37.6% and 30.6%, respectively, while 1/5 (21.4%) participants performed surgical interventions. In the case of both advanced IPF and LC (TNM stage IV) the majority of participants (69%) applied palliative care, followed by anti-fibrotics (37%), immune-check point inhibitors (31.9%) and targeted therapy (35.4%). Doublet platinum regimens and immunotherapy for metastatic disease were chosen by 25% and 31.9%, respectively **(Figure 6)**.

Regarding pre- and peri-operative safety precautions, continuation of anti-fibrotics, low tidal volume, avoidance of high fraction of inspired oxygen and minimal surgical interventions represented the most frequently applied approaches in 67.1%, 55.1%, 45.5% and 30.6% of participants, respectively **(Figure 5)**.

Future perspectives

Based on the vast majority of participants (92.9%) a consensus statement for the diagnosis and management of patients with IPF-LC is mandatory for improved, homogeneous and standardized approaches. Further comments of particular interest provided by individual participants in the context of an open question were: the need for a global registry, the role of immune-check point inhibitors and targeted treatments, future research studies and clinical trials.

Discussion

Currently there is a major need for a consensus view of diagnostic and management strategies in patients with concomitant IPF and LC. Our findings highlighted the variability in management approaches of patients with concomitant IPF and LC, as participants reached consensus in only 5 items of the questionnaire. Our study demonstrated that there is a pressing need for increased awareness as well, given that in our survey only 28% of

physicians responded to the invitation. To this end, areas of uncertainty and disagreement between physicians across the world need to be identified and addressed. It is a common misconception that consensus statements need a level of data not present in this field. Our survey included a significant number of participants (n=494) from 6 continents and identified key areas of uncertainty, as indicated by major heterogeneity in diagnostic and management practices. It also highlighted a general agreement among all participants to generate a consensus statement for harmonized approaches that will fuel clinical trials and further research.

Results of our survey could be summarized in two categories based on whether agreement between participants reached consensus, defined as percent agreement between respondents above 75%. Interestingly, our survey revealed that participants reached consensus in only 5 items of the questionnaire, including: 1) use of MDD approaches (78.2%), 2) continuation of anti-fibrotic treatment in patients with IPF diagnosed with LC (83.8%), 3) application of PET-CT scan and EBUS for the diagnosis of a central nodular lesion of 20 mm in patients with mild-to-moderate IPF and mediastinal lymphadenopathy (87.9%), 4) surgical lung interventions in mild-to-moderate IPF cases(78.2%) , 5) need for a consensus statement (92.9%). This observation confirms our initial hypothesis regarding major variability in management approaches, reflecting areas of major uncertainty and highlighting the need for a consensus statement. Regarding areas of major variability and uncertainty in management strategies these could be summarized as follows: 1) Screening for lung cancer using low dose HRCT on a regular (annual) basis, 2) Optimal selection of patients for surgical lung interventions, chemotherapy and radiotherapy. 3) The role of anti-fibrotics on prevention of lung cancer, treatment of lung cancer and reduction of acute exacerbations of IPF post-operatively.

Based on the latest US Preventive Services Task Force Recommendation Statement all patients with IPF should be considered as high-risk for developing lung cancer, given a much higher incidence compared to patients currently screened for lung cancer[7]. Thus close monitoring by means of annual HRCT should be considered as mandatory as it happens with other chronic lung diseases, including COPD [18]. This has become a more important issue with the implementation of novel anti-fibrotics leading to better disease outcomes and survival prolongation, given a potential accumulative incidence of LC. Surprisingly, a

substantial minority of participants suggested either an HRCT scan in case of additional symptoms (29.1%) or no screening at all (17.6%). Though it is evident in our clinical practice, yet the benefit of screening patients with IPF by means of HRCT on a regular basis has not been proven in the context of a prospective study, as it has been shown in asymptomatic middle-aged smokers.

Optimal selection of patients with IPF-LC for diagnostic and therapeutic interventions represents an ongoing debate. In our survey, participants agreed that patients with mild-to-moderate IPF and otherwise operable LC lesions should be subjected either to bronchoscopic (87.9%) or lung resection procedures (78.2%) for diagnostic and therapeutic purposes, respectively, because the benefits outweigh the risks. On the contrary, agreement rates were substantially decreased in severe IPF cases with operable LC lesions, where interventional procedures were suggested by 59.6% and 21.4% of respondents, for diagnosis and treatment, respectively, due to potential severe post-operative complications. Retrospective series have shown that patients with IPF exhibit higher risk for postoperative acute respiratory events than non-IPF patients[19], especially acute exacerbation[20]. Experts suggest that reduction of the duration of one-lung ventilation, videothoracoscopic surgery under spontaneous ventilation in selected patients, minimal tissue manipulation, low-tidal volume ventilation strategies and avoidance of high fraction of inspired oxygen (FiO_2) perioperatively may exert prophylactic effects[21], [22]. In a large retrospective Japanese cohort of 1763 patients with different forms of ILDs and lung resection for LC, duration and extent of surgical procedures, as well as peri-operative fraction of inspired oxygen and fluid intake were independent risk factors of acute exacerbations [23]. To this end, a preoperative multi-disciplinary evaluation should also include thoracic surgeons and anesthesiologists in order to increase their awareness on peri- and post-operative complications of aggressive ventilation and excessive tissue manipulation, especially in patients with severely impaired lung compliance, as those with IPF. We believe that surgical lung interventions should be performed in highly selected cases based on reliable prognosticators such as functional and general performance status or composite physiologic index (CPI), a multidimensional scoring system that quantifies functional and radiological impairment[14]. The deceptive nature of functional parameters in the presence of emphysema needs to consider in this context.

Currently there are scarce data on the optimal chemotherapeutic regimen in patients with IPF-LC. In our survey only 1/4 participants would implement doublet platinum regimens in patients with IPF and metastatic LC. Studies have shown increased pulmonary toxicity in patients with interstitial lung disease who were treated with either docetaxel or pemetrexed as well as etoposide-based regimens[24, 25]. So far, only carboplatin has shown moderate therapeutic effects with minimal toxicity[26]. A randomized controlled study (J-SONIC) investigating the efficacy of carboplatin plus nab-paclitaxel with or without nintedanib in patients with NSCLC associated with IPF is currently ongoing in Japan and results are greatly anticipated. In the context of similar disease pathophysiology between lung cancer and IPF[15], studies investigating the effects of new immunomodulatory agents including programmed death-ligand (PD-L) 1 inhibitors, would be of significant interest for a selective number of cases, i.e. those with upregulated PD1/PD-L1 axis[27]; yet caution should be applied considering cases of interstitial pneumonia potentially associated with nivolumab treatment[28, 29]. Molecular testing for epidermal growth factor-receptor (EGFR), KRAS and EML4-ALK mutations could also be performed for targeted treatments, as indicated by some of the participants.

With regards to radiotherapy scarce data has shown deleterious effects on patients with established lung fibrosis[9] suggesting that radiotherapy involving the lung, including stereotactic radiotherapy, should be generally avoided, unless life-threatening situations arise. Besides radiation pneumonitis, mortality radiofrequency ablation was mainly due to pneumothoraces [30]. This is important considering that 40% of patients with IPF present with concomitant emphysema [31]. Despite these data, stereotactic radiotherapy was the predominant therapeutic intervention for severe IPF cases with operable LC lesions IPF-LC, as indicated by 54.1% of participants. Proton beam therapy has recently shown promising results in terms of safety in a small series of patients with IPF and lung cancer; yet, the study was underpowered and retrospective[32]. Further studies are needed on the safety and efficacy of chemotherapeutic and immunomodulatory regimens as well as modern irradiation techniques including proton beam therapy.

Another challenge of the real-world clinical practice is whether anti-fibrotic agents can be combined or even synergize with chemotherapy or radiotherapy. Nintedanib has been developed as antiangiogenic molecule and has been approved for treatment of non-

squamous non-small-cell lung cancer[33] in combination with docetaxel-based second line therapy. Retrospective data suggested a beneficial effect of preoperative pirfenidone on the incidence of postoperative acute exacerbations in patients with adenocarcinoma and IPF[34]. In agreement with the majority of respondents, we suggest that anti-fibrotic agents should not be discontinued during diagnostic or therapeutic work-up of lung cancer, as benefits seem to outweigh the risk for unfavorable outcomes. Whether nintedanib monotherapy as cancer treatment represents a plausible strategy needs to be addressed in the context of clinical trials. Final decision should be based on multi-disciplinary discussion including oncologists and on a case-by-case basis considering severity of IPF, TNM stage of LC, performance status of the patient and patient's preferences.

Early implementation of palliative care may be appropriate and possibly improve patients' quality of life despite no effect on survival[35]. In agreement with current literature showing encouraging efficacy data in both the field of oncology [36] and lung fibrosis[37-39], the majority of participants (69.1%) suggested palliative care as a therapeutic option, particularly in advanced cases of IPF-LC. This statement also supports the latest views that palliative care should be offered early to all patients with IPF. Larger studies using validated outcome measures are sorely needed to assess the effects of palliative care interventions on symptoms, quality of life and survival of patients with IPF-LC irrespective of disease severity.

Despite its important attributes our survey exhibits several limitations that should addressed cautiously. Although the study was powered by the participation of almost 500 respondents across the world, results may reflect personal opinions of physicians and may not represent objective assessment of every day clinical practices. Additionally, there was an overrepresentation of pulmonologists (94%) while thoracic oncologists, radio--oncologists and surgeons were underrepresented. Heterogeneity in answers may also mirror differences in access to treatments (targeted therapies, immune-checkpoint inhibitors) and diagnostic modalities (i.e. PET CT scan, EBUS) which may be limited in some countries for regulatory issues. Moreover, our main aim was to survey international practices on diagnosis and treatment of patients with IPF-LC and thus our study is unable to provide accurate epidemiological data. This needs to be addressed in the context of global registries, either retrospectively or prospectively. Such registries are more timely than ever, given that patients with IPF live longer and incidence of lung cancer might increase. Finally,

our survey was impossible to cover all areas of uncertainty in the field of IPF-LC. In particular, data on the impact of CPFE and ILAs on management decisions is sorely needed. Another major limitation that needs to be addressed is the lack of information on patient preferences regarding diagnostic and therapeutic interventions considering the fact that we are dealing with a very vulnerable population of patients. On the other hand, our questionnaire was anonymous and therefore answers provided are expected to be less biased.

Conclusion

In conclusion, our survey revealed major heterogeneity in diagnostic and management strategies in patients with IPF-LC, mainly arising from lack of knowledge and uncertainty in key areas of this field. ILD practitioners and oncologists almost unanimously agreed that in this poorly defined area a consensus statement for harmonized and standardized approaches is eagerly anticipated. This will fuel future trials and research studies with major impact on patients' survival and quality of life.

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References

1. Raghu, G., et al., *Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline.* Am J Respir Crit Care Med, 2018. **198**(5): p. e44-e68.
2. Richeldi, L., et al., *Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis.* N Engl J Med, 2014. **370**(22): p. 2071-82.
3. Noble, P.W., et al., *Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials.* Eur Respir J, 2016. **47**(1): p. 243-53.
4. Karampitsakos, T., et al., *Lung cancer in patients with idiopathic pulmonary fibrosis.* Pulm Pharmacol Ther, 2017. **45**: p. 1-10.
5. Park, J., et al., *Lung cancer in patients with idiopathic pulmonary fibrosis.* Eur Respir J, 2001. **17**(6): p. 1216-9.
6. Le Jeune, I., et al., *The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK.* Respir Med, 2007. **101**(12): p. 2534-40.
7. Ozawa, Y., et al., *Cumulative incidence of and predictive factors for lung cancer in IPF.* Respirology, 2009. **14**(5): p. 723-8.
8. Tzouvelekis, A., et al., *Lung cancer in patients with Idiopathic Pulmonary Fibrosis. A retrospective multicenter study in Greece.* Pulm Pharmacol Ther, 2020. **60**: p. 101880.
9. Kreuter, M., et al., *Treatment and outcome of lung cancer in idiopathic interstitial pneumonias.* Sarcoidosis Vasc Diffuse Lung Dis, 2015. **31**(4): p. 266-74.
10. Kreuter, M., et al., *Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis.* PLoS One, 2016. **11**(3): p. e0151425.
11. Kanaji, N., et al., *Impact of idiopathic pulmonary fibrosis on advanced non-small cell lung cancer survival.* J Cancer Res Clin Oncol, 2016. **142**(8): p. 1855-65.
12. Tomassetti, S., et al., *The impact of lung cancer on survival of idiopathic pulmonary fibrosis.* Chest, 2015. **147**(1): p. 157-164.
13. Tzouvelekis, A., et al., *Patients with IPF and lung cancer: diagnosis and management.* Lancet Respir Med, 2018. **6**(2): p. 86-88.
14. Tzilas, V., et al., *Taking a giant step in the diagnosis of idiopathic pulmonary fibrosis.* Lancet Respir Med, 2017.
15. Vancheri, C., et al., *Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology.* Eur Respir J, 2010. **35**(3): p. 496-504.

16. Vassilakis, D.A., et al., *Frequent genetic alterations at the microsatellite level in cytologic sputum samples of patients with idiopathic pulmonary fibrosis.* Am J Respir Crit Care Med, 2000. **162**(3 Pt 1): p. 1115-9.
17. Naccache, J.-M., et al., *Lung cancer and interstitial lung disease: a literature review.* Journal of Thoracic Disease, 2018. **10**(6): p. 3829-3844.
18. Moyer, V.A. and U.S.P.S.T. Force, *Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement.* Ann Intern Med, 2014. **160**(5): p. 330-8.
19. Sakata, R., Y. Fujii, and H. Kuwano, *Thoracic and cardiovascular surgery in Japan during 2008: annual report by The Japanese Association for Thoracic Surgery.* Gen Thorac Cardiovasc Surg, 2010. **58**(7): p. 356-83.
20. Kreuter, M., et al., *A global perspective on acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF): results from an international survey.* European Respiratory Journal, 2018. **52**(suppl 62): p. OA542.
21. Choi, S.M., et al., *Postoperative pulmonary complications after surgery in patients with interstitial lung disease.* Respiration, 2014. **87**(4): p. 287-93.
22. Acute Respiratory Distress Syndrome, N., et al., *Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.* N Engl J Med, 2000. **342**(18): p. 1301-8.
23. Sato, T., et al., *Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer.* J Thorac Cardiovasc Surg, 2014. **147**(5): p. 1604-1611 e3.
24. Watanabe, N., et al., *Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia.* Cancer Chemother Pharmacol, 2015. **76**(1): p. 69-74.
25. Minegishi, Y., et al., *The feasibility study of Carboplatin plus Etoposide for advanced small cell lung cancer with idiopathic interstitial pneumonias.* J Thorac Oncol, 2011. **6**(4): p. 801-7.
26. Watanabe, N., et al., *Efficacy of chemotherapy for advanced non-small cell lung cancer with idiopathic pulmonary fibrosis.* Respiration, 2013. **85**(4): p. 326-31.
27. Celada, L.J., et al., *PD-1 up-regulation on CD4(+) T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-beta1 production.* Sci Transl Med, 2018. **10**(460).
28. Kanai, O., et al., *Concurrence of nivolumab-induced interstitial lung disease and cancer invasion.* Respirol Case Rep, 2017. **5**(6): p. e00257.
29. Kato, T., et al., *Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer.* Lung Cancer, 2017. **104**: p. 111-118.
30. Chen, H., et al., *Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review.* Int J Radiat Oncol Biol Phys, 2017. **98**(3): p. 622-631.
31. Cottin, V., et al., *Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity.* European Respiratory Journal, 2005. **26**(4): p. 586-593.
32. Ono, T., et al., *The clinical results of proton beam therapy in patients with idiopathic pulmonary fibrosis: a single center experience.* Radiat Oncol, 2016. **11**: p. 56.
33. Reck, M., et al., *Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial.* Lancet Oncol, 2014. **15**(2): p. 143-55.
34. Iwata, T., et al., *Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis.* Ann Thorac Surg, 2016. **102**(6): p. 1905-1910.
35. Kreuter, M., et al., *Palliative care in interstitial lung disease: living well.* Lancet Respir Med, 2017.
36. Harding, R. and F.E. Murtagh, *Palliative care for management of small-cell lung cancer.* Lancet, 2006. **367**(9509): p. 474.

37. Bajwah, S., et al., *Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention.* Thorax, 2015. **70**(9): p. 830-9.
38. Bajwah, S., et al., *The palliative care needs for fibrotic interstitial lung disease: a qualitative study of patients, informal caregivers and health professionals.* Palliat Med, 2013. **27**(9): p. 869-76.
39. Higginson, I.J., et al., *An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.* Lancet Respir Med, 2014. **2**(12): p. 979-87.

Figure 1. Participants - Origin

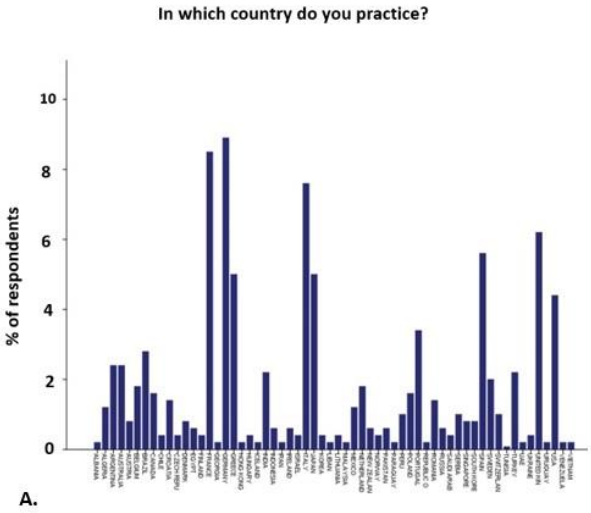
Figure 2. Participants - Characteristics

Figure 3. General knowledge

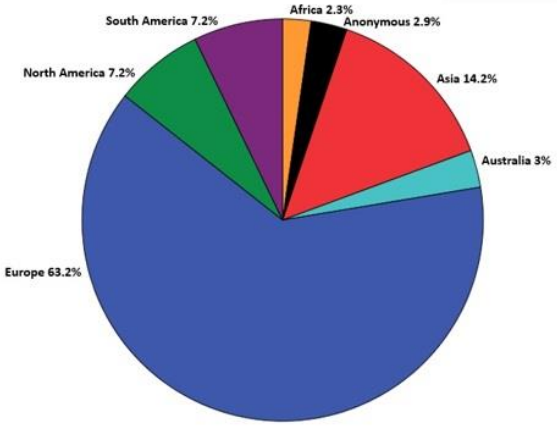
Figure 4. Diagnostics

Figure 5. Management procedures

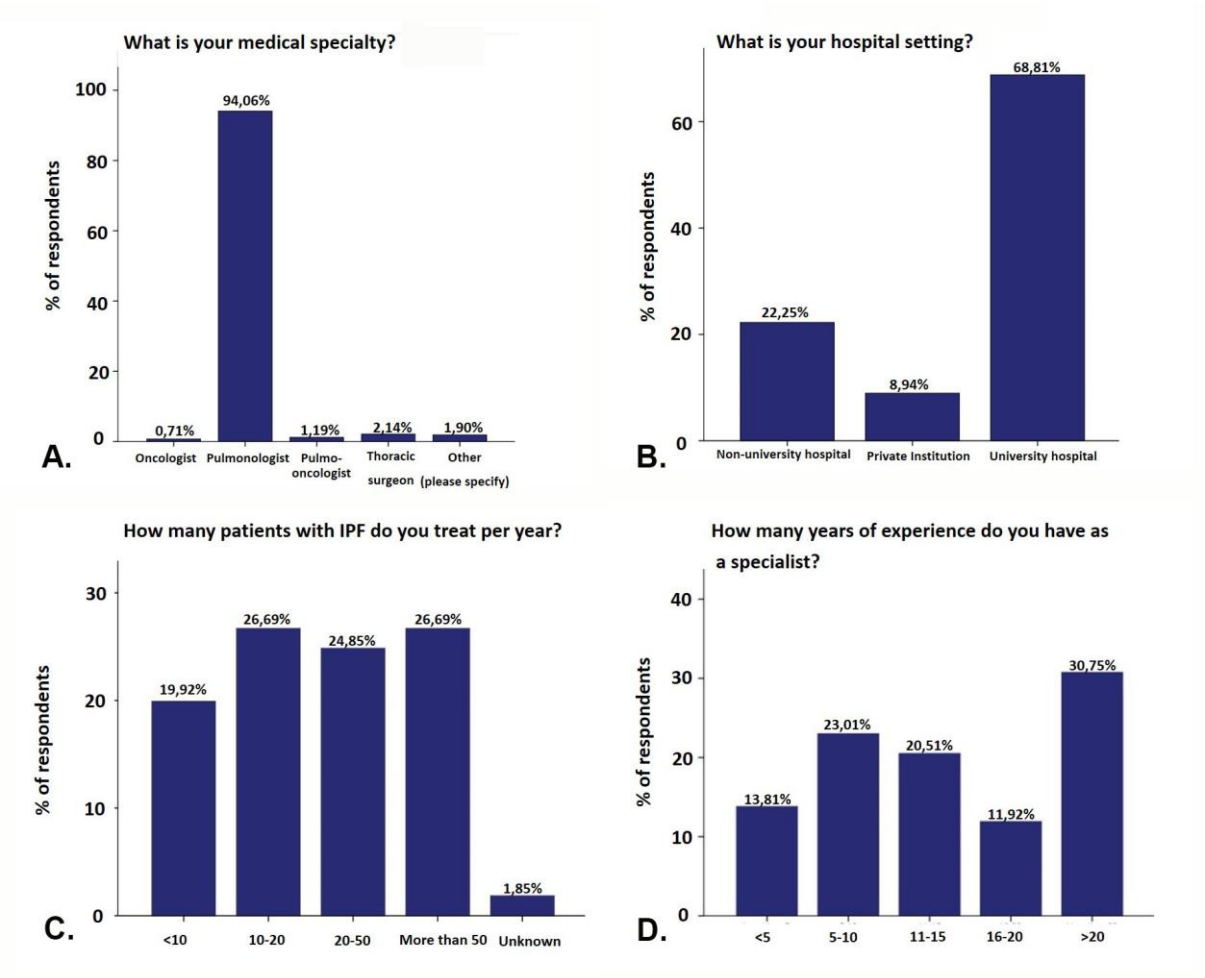
Figure 6. Management Procedures – II

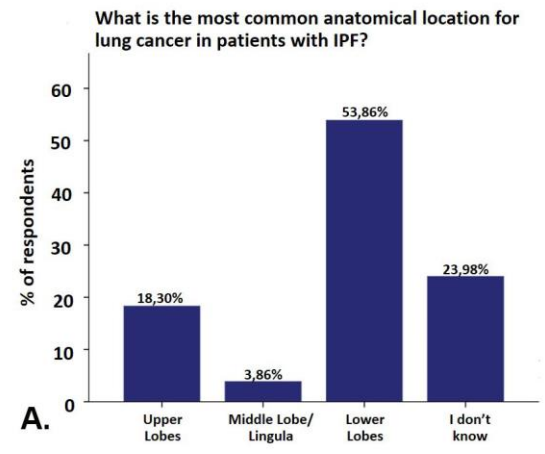

In which country do you practice?
% of respondents
10
8
6
4
2
0

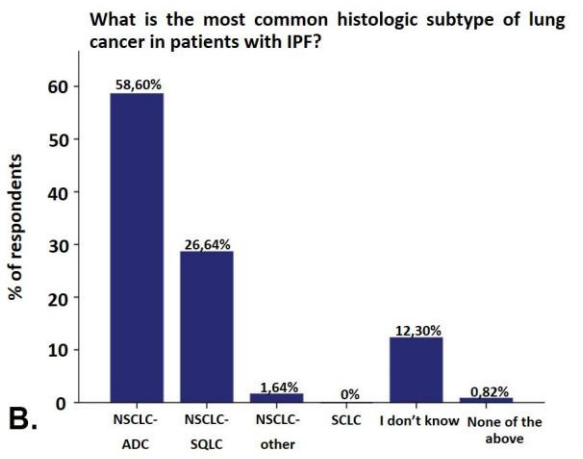
A.

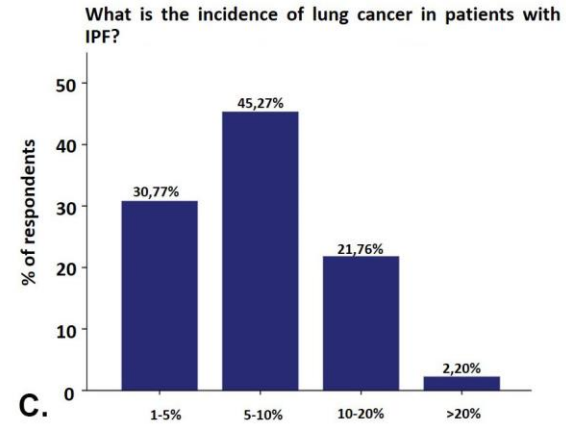

Africa 2.3%
Anonymous 2.9%
South America 7.2%
North America 7.2%
Asia 14.2%
Australia 3%
Europe 63.2%

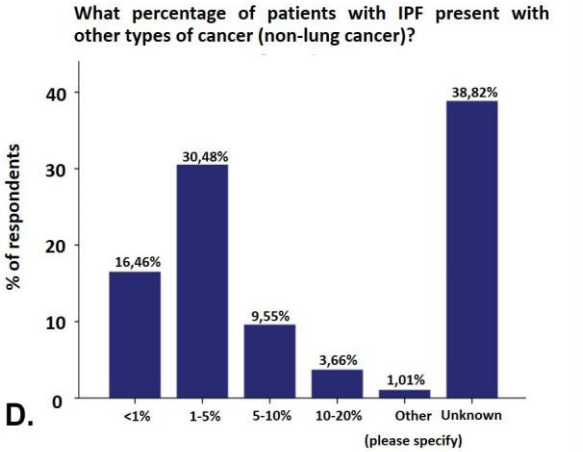
B.

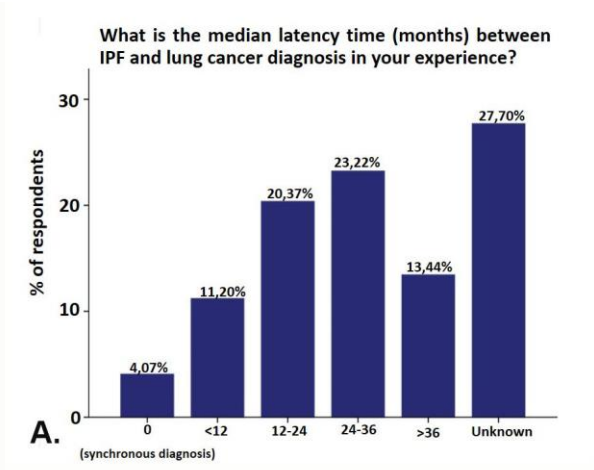

What is your medical specialty?
% of respondents
100
80
60
40
20
0
94,06%
0,71%
1,19%
2,14%
1,90%
Oncologist
Pulmonologist
Pulmo-oncologist
Thoracic surgeon
Other (please specify)
A.
What is your hospital setting?
% of respondents
60
40
20
0
68,81%
22,25%
8,94%
Non-university hospital
Private Institution
University hospital
B.
How many patients with IPF do you treat per year?
% of respondents
30
20
10
0
19,92%
26,69%
24,85%
26,69%
1,85%
<10
10-20
20-50
More than 50
Unknown
C.
How many years of experience do you have as a specialist?
% of respondents
40
30
20
10
0
13,81%
23,01%
20,51%
11,92%
30,75%
<5
5-10
11-15
16-20
>20
D.

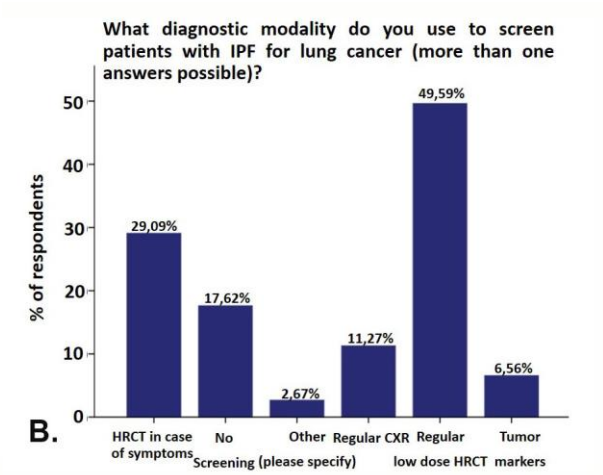

What is the most common anatomical location for lung cancer in patients with IPF?
% of respondents
60
50
40
30
20
10
0
18,30%
3,86%
53,86%
23,98%
Upper Lobes
Middle Lobe/ Lingula
Lower Lobes
I don't know
A.

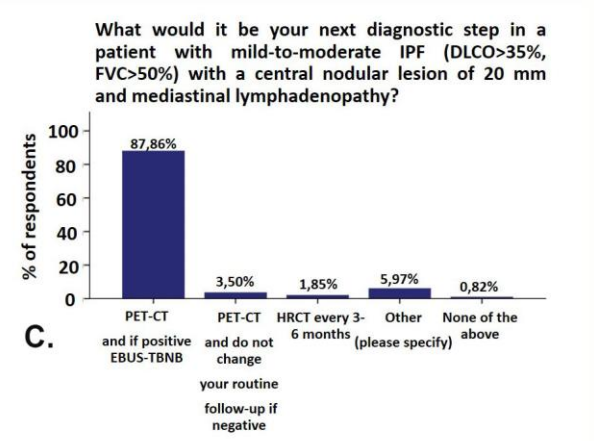

What is the most common histologic subtype of lung cancer in patients with IPF?
% of respondents
60
50
40
30
20
10
0
58,60%
26,64%
1,64%
0%
12,30%
0,82%
NSCLC-ADC
NSCLC-SQLC
NSCLC-other
SCLC
I don't know
None of the above
B.

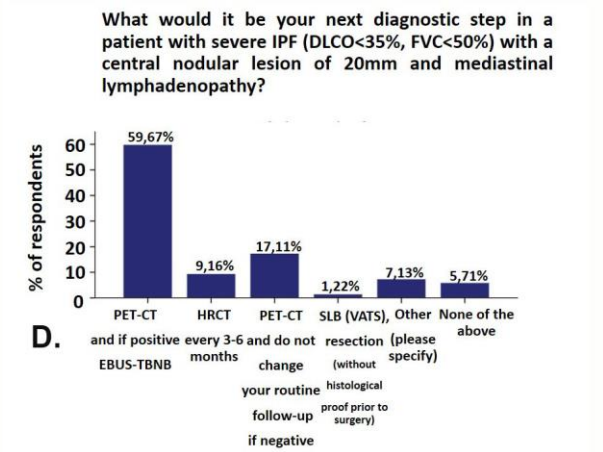

What is the incidence of lung cancer in patients with IPF?
% of respondents
50
40
30
20
10
0
30,77%
45,27%
21,76%
2,20%
1-5%
5-10%
10-20%
>20%
C.

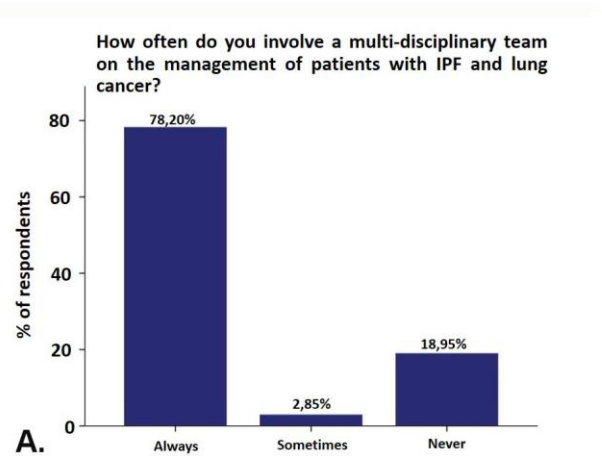

What percentage of patients with IPF present with other types of cancer (non-lung cancer)?
% of respondents
40
30
20
10
0
16,46%
30,48%
9,55%
3,66%
1,01%
38,82%
<1%
1-5%
5-10%
10-20%
Other (please specify)
Unknown
D.

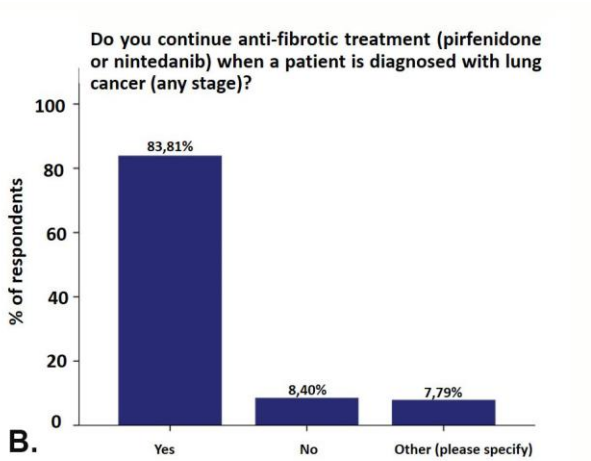

What is the median latency time (months) between IPF and lung cancer diagnosis in your experience?
% of respondents
30
20
10
0
4,07%
11,20%
20,37%
23,22%
13,44%
27,70%
A.
0 (synchronous diagnosis)
<12
12-24
24-36
>36
Unknown

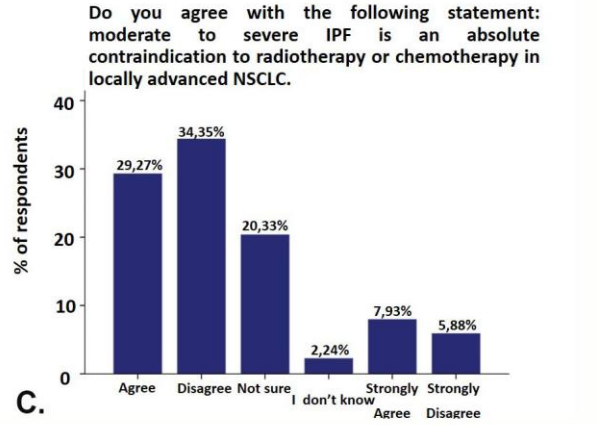

What diagnostic modality do you use to screen patients with IPF for lung cancer (more than one answers possible)?
% of respondents
50
40
30
20
10
0
29,09%
17,62%
2,67%
11,27%
49,59%
6,56%
B.
HRCT in case of symptoms
No Screening
Other (please specify)
Regular CXR
Regular low dose HRCT
Tumor markers

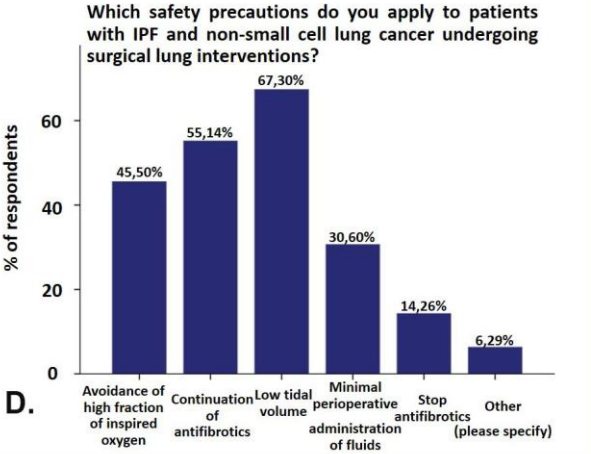

What would it be your next diagnostic step in a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%) with a central nodular lesion of 20 mm and mediastinal lymphadenopathy?
% of respondents
100
80
60
40
20
0
87,86%
3,50%
1,85%
5,97%
0,82%
C.
PET-CT and if positive EBUS-TBNB
PET-CT and do not change your routine follow-up if negative
HRCT every 3-6 months
Other (please specify)
None of the above

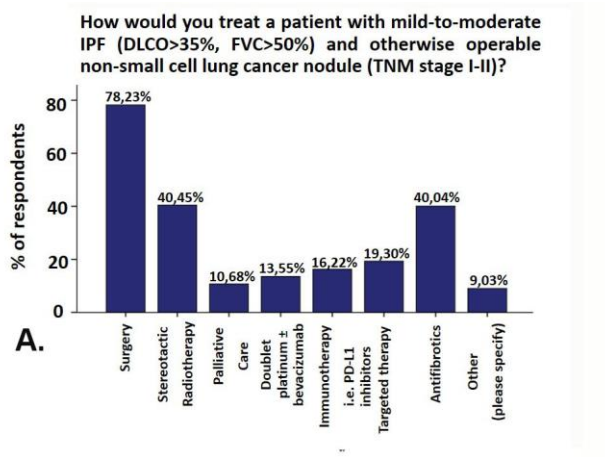

What would it be your next diagnostic step in a patient with severe IPF (DLCO<35%, FVC<50%) with a central nodular lesion of 20mm and mediastinal lymphadenopathy?
% of respondents
60
50
40
30
20
10
0
59,67%
9,16%
17,11%
1,22%
7,13%
5,71%
D.
PET-CT and if positive EBUS-TBNB
HRCT every 3-6 months
PET-CT and do not change your routine follow-up if negative
SLB (VATS), resection (without histological proof prior to surgery)
Other (please specify)
None of the above

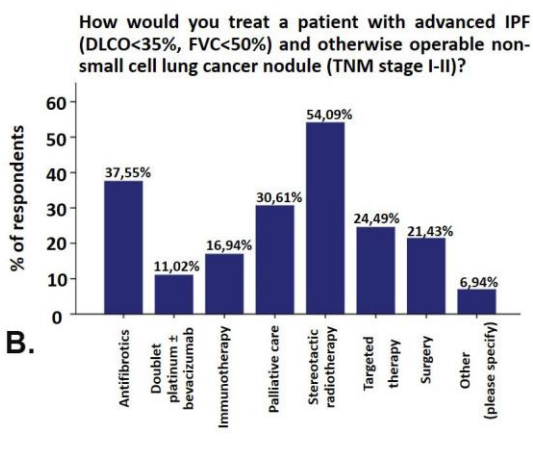

How often do you involve a multi-disciplinary team on the management of patients with IPF and lung cancer?
% of respondents
0
20
40
60
80
78,20%
2,85%
18,95%
Always
Sometimes
Never
A.

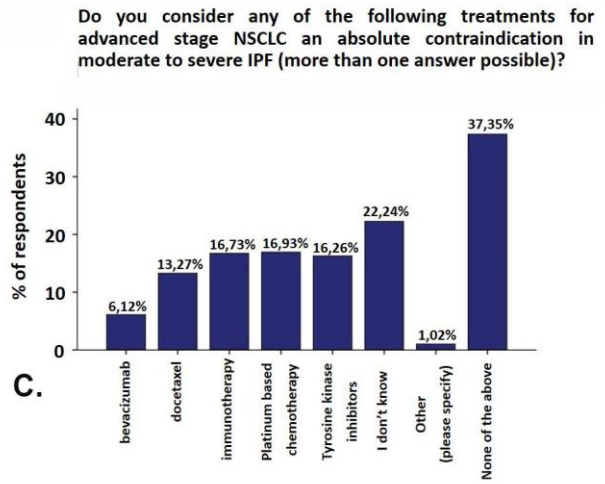

Do you continue anti-fibrotic treatment (pirfenidone or nintedanib) when a patient is diagnosed with lung cancer (any stage)?
% of respondents
0
20
40
60
80
100
83,81%
8,40%
7,79%
Yes
No
Other (please specify)
B.

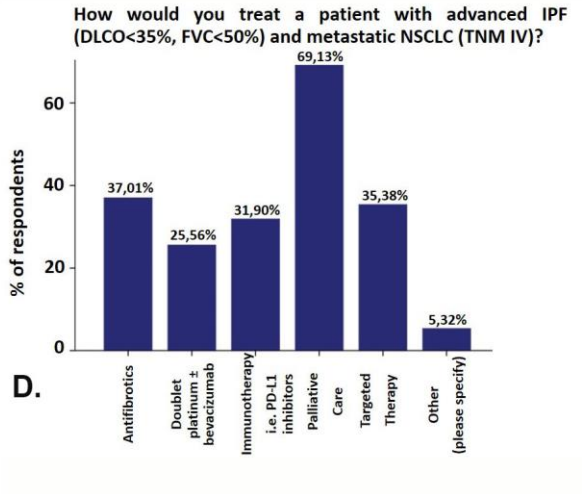

Do you agree with the following statement: moderate to severe IPF is an absolute contraindication to radiotherapy or chemotherapy in locally advanced NSCLC.
% of respondents
0
10
20
30
40
29,27%
34,35%
20,33%
2,24%
7,93%
5,88%
Agree
Disagree
Not sure
I don't know
Strongly Agree
Strongly Disagree
C.


Which safety precautions do you apply to patients with IPF and non-small cell lung cancer undergoing surgical lung interventions?
% of respondents
0
20
40
60
45,50%
55,14%
67,30%
30,60%
14,26%
6,29%
Avoidance of high fraction of inspired oxygen
Continuation of antifibrotics
Low tidal volume
Minimal perioperative administration of fluids
Stop antifibrotics
Other (please specify)
D.


How would you treat a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%) and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?
% of respondents
78,23%
40,45%
10,68%
13,55%
16,22%
19,30%
40,04%
9,03%
Surgery
Stereotactic Radiotherapy
Palliative Care
Doublet platinum ± bevacizumab
Immunotherapy
i.e. PD-L1 inhibitors
Targeted therapy
Antifibrotics
Other (please specify)
A.


How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%) and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?
% of respondents
37,55%
11,02%
16,94%
30,61%
54,09%
24,49%
21,43%
6,94%
Antifibrotics
Doublet platinum ± bevacizumab
Immunotherapy
Palliative care
Stereotactic radiotherapy
Targeted therapy
Surgery
Other (please specify)
B.


Do you consider any of the following treatments for advanced stage NSCLC an absolute contraindication in moderate to severe IPF (more than one answer possible)?
% of respondents
6,12%
13,27%
16,73%
16,93%
16,26%
22,24%
1,02%
37,35%
bevacizumab
docetaxel
immunotherapy
Platinum based chemotherapy
Tyrosine kinase inhibitors
I don't know
Other (please specify)
None of the above
C.


How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%) and metastatic NSCLC (TNM IV)?
% of respondents
37,01%
25,56%
31,90%
69,13%
35,38%
5,32%
Antifibrotics
Doublet platinum ± bevacizumab
Immunotherapy
i.e. PD-L1 inhibitors
Palliative Care
Targeted Therapy
Other (please specify)
D.

Supplementary data

The DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey. International survey and call for consensus.

Argyris Tzouvelekis[1], Katerina Antoniou[2], Michael Kreuter[3,4], Matthew Evison[5], Torsten G Blum[6], Venerino Poletti[7], Bogdan Grigoriu[8], Carlo Vancheri[9], Paolo Spagnolo[10], Theodoros Karampitsakos[1], Francesco Bonella[11], Athol Wells[12], Ganesh Raghu[13], Maria Molina-Molina[14], Daniel Culver[15], Elisabeth Bendstrup[16],Nesrin Mogulkoc[17], Stefano Elia[18],Jacques Cadranel[19], Demosthenes Bouros[20]

[1] Department of Internal and Respiratory Medicine, Medical School University of Patras, Greece; [2]Department of Respiratory Medicine, University of Crete, Greece; [3]Center for Interstitial and Rare Lung Diseases, Pneumology, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [4]German Center for Lung Research, Heidelberg, Germany, [5]Manchester Thoracic Oncology Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK; [6]Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Berlin, Germany; [7] Department of Thoracic Diseases, "GB. Morgagni" Hospital, Forlì, Italy; [8] Service des Soins Intensifs et Urgences Oncologiques & Oncologie thoracique Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles (ULB), Belgium; [9]Regional Referral Centre for Rare Lung Diseases, A. O. U. "Policlinico-Vittorio Emanuele" Dept. Of Clinical and Experimental Medicine, University of Catania, Italy; [10] Respiratory Disease Unit, Department of Cardiac Thoracic, Vascular Sciences and Public Health, University of Padova, Italy; [11] Dept of Pneumology and Allergy, Ruhrlandklinik Medical Faculty, University of Duisburg-Essen, Essen, Germany; [12] Interstitial Lung Disease Unit, Department of Respiratory Medicine, Royal Brompton and Harefield NHS Foundation Trust, London, UK; [13] Center for Interstitial Lung Disease, University of Washington, Seattle, WA, USA, [14] Hospital Universitari de Bellvitge, L'Hospitalet de LLobregat, Barcelona, Spain; [15]Cleveland Clinic, Respiratory Institute, Cleveland, OH, USA; [16]Center for Rare Lung Diseases, Department of Respiratory Diseases and Allergy, Aarhus University Hospital,Denmark.[17]Department of Pulmonology, Faculty of Medicine, Ege University; İzmir-Turkey; [18] Thoracic Surgery Unit, Tor Vergata University, Rome, Italy; [19]Service de Pneumologie, APHP, Hôpital Tenon and Sorbonne Université, Paris, France; [20]First Academic Department of Respiratory Medicine, National and Kapodistrian University of Athens, Greece

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Search terminology:

Idiopathic pulmonary fibrosis and lung cancer

idiopathic pulmonary fibrosis and lung cancer medical specialty,

idiopathic pulmonary fibrosis and lung cancer experience,

idiopathic pulmonary fibrosis and lung cancer hospital,

idiopathic pulmonary fibrosis and lung cancer patients,

idiopathic pulmonary fibrosis and lung cancer incidence,

idiopathic pulmonary fibrosis and lung cancer multidisciplinary team,

idiopathic pulmonary fibrosis and lung cancer management,

idiopathic pulmonary fibrosis and lung cancer diagnostic modality,

idiopathic pulmonary fibrosis and lung cancer histologic subtype,

idiopathic pulmonary fibrosis and lung cancer anatomic location,

idiopathic pulmonary fibrosis and lung cancer median latency time of diagnosis,

idiopathic pulmonary fibrosis and lung cancer percentage,

idiopathic pulmonary fibrosis and lung cancer percentage of other cancer,

idiopathic pulmonary fibrosis and lung cancer common type of other malignancy,

idiopathic pulmonary fibrosis and lung cancer contraindication,

idiopathic pulmonary fibrosis and lung cancer radiotherapy,

idiopathic pulmonary fibrosis and lung cancer chemotherapy,

idiopathic pulmonary fibrosis and lung cancer advanced stage,

idiopathic pulmonary fibrosis and lung cancer antifibrotics,

idiopathic pulmonary fibrosis and lung cancer safety precautions,

idiopathic pulmonary fibrosis and lung cancer surgical lung interventions,

idiopathic pulmonary fibrosis and lung cancer surgery,

idiopathic pulmonary fibrosis and lung cancer operable nodule,

idiopathic pulmonary fibrosis and lung cancer metastatic disease,

idiopathic pulmonary fibrosis and lung cancer treatment,

idiopathic pulmonary fibrosis mild to moderate disease,

idiopathic pulmonary fibrosis moderate to severe disease,

lung cancer stage,

idiopathic pulmonary fibrosis and lung cancer mediastinal lymphadenopathy,

idiopathic pulmonary fibrosis and lung cancer diagnostic step,

idiopathic pulmonary fibrosis and lung cancer diagnosis,

idiopathic pulmonary fibrosis and lung cancer management,

idiopathic pulmonary fibrosis and lung cancer consensus statement

Supplementary data

The DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey. International survey and call for consensus.

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[1] Department of Internal and Respiratory Medicine, Medical School University of Patras, Greece; [2]Department of Respiratory Medicine, University of Crete, Greece; [3]Center for Interstitial and Rare Lung Diseases, Pneumology, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [4]German Center for Lung Research, Heidelberg, Germany, [5]Manchester Thoracic Oncology Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK; [6]Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Berlin, Germany; [7] Department of Thoracic Diseases, "GB. Morgagni" Hospital, Forlì, Italy; [8] Service des Soins Intensifs et Urgences Oncologiques & Oncologie thoracique Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles (ULB), Belgium; [9]Regional Referral Centre for Rare Lung Diseases, A. O. U. "Policlinico-Vittorio Emanuele" Dept. Of Clinical and Experimental Medicine, University of Catania, Italy; [10] Respiratory Disease Unit, Department of Cardiac Thoracic, Vascular Sciences and Public Health, University of Padova, Italy; [11] Dept of Pneumology and Allergy, Ruhrlandklinik Medical Faculty, University of Duisburg-Essen, Essen, Germany; [12] Interstitial Lung Disease Unit, Department of Respiratory Medicine, Royal Brompton and Harefield NHS Foundation Trust, London, UK; [13] Center for Interstitial Lung Disease, University of Washington, Seattle, WA, USA, [14] Hospital Universitari de Bellvitge, L'Hospitalet de LLobregat, Barcelona, Spain; [15]Cleveland Clinic, Respiratory Institute, Cleveland, OH, USA; [16]Center for Rare Lung Diseases, Department of Respiratory Diseases and Allergy, Aarhus University Hospital,Denmark.[17]Department of Pulmonology, Faculty of Medicine, Ege University; İzmir-Turkey; [18] Thoracic Surgery Unit, Tor Vergata University, Rome, Italy; [19]Service de Pneumologie, APHP, Hôpital Tenon and Sorbonne Université, Paris, France; [20]First Academic Department of Respiratory Medicine, National and Kapodistrian University of Athens, Greece

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Idiopathic Pulmonary Fibrosis (IPF) is a debilitating fibrotic lung disease with a steady increase in both incidence and mortality. In addition, the clinical course of patients with IPF is often complicated by major comorbidities including lung cancer. Despite abundant epidemiologic and mechanistic links between IPF and lung cancer there is considerable lack of knowledge on the diagnostic and therapeutic management of these patients.

To this end, the ERS Assembly 12 (Interstitial Lung Diseases), took the initiative to collaborate with Assembly 11 (Thoracic Oncology) and Assembly 8 (Thoracic Surgery and Lung Transplantation) to create and launch a joint-survey, namely DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS), in which we invite you to participate by clicking in the following link and answering the questions included.

The main objectives of this survey are:

- To identify variations in diagnostic and management strategies across different hospitals and institutions
- To raise awareness on the association between the two conditions
- To provide rationale for a consensus statement for an improved, homogeneous and standardized approach

The estimated time of completion is less than 10 minutes. We greatly appreciate your time and we anticipate your valuable feedback. Results of the survey will be exploited as a publication in an ERS-journal and/or abstract in upcoming ERS and ATS international conferences. Names of the respondents will be included as collaborators in the acknowledgement section of the manuscript.

1. **In which country do you practice?**

…….

2. **What is your medical specialty?**

Pulmonologist ☐

Oncologist ☐

Thoracic surgeon ☐

Anesthesiologist ☐

Pulmo-oncologist ☐

Radio-oncologist ☐

Other (please specify) ☐

3. **How many years of experience do you have as a specialist?**

Less than 5 ☐

5-10 ☐

11-15 ☐

16-20 ☐

More than 20 ☐

4. **What is your hospital setting?**

University Hospital ☐

Non-university hospital ☐

Private institution/practice ☐

5. **How many patients with IPF do you treat per year?**

<10 ☐

10-20 ☐

20-50 ☐

More than 50 ☐

Unknown ☐

6. **What is the incidence of lung cancer in patients with IPF?**

1-5% ☐

5-10% ☐

10-20% ☐

>20% ☐

7. How often do you involve a multi-disciplinary team on the management of patients with IPF and lung cancer?

Always ☐

Sometimes ☐

Never ☐

8. **What diagnostic modality do you use to screen patients with IPF for lung cancer (more than one answers possible)?**

Regular low dose HRCT scan ☐

Regular CXR ☐

HRCT scan in case of symptoms ☐

Tumor markers (Ca19/9, CA125, CEA) ☐

No screening ☐

Other (please specify) ☐

9. **What is the most common histologic subtype of lung cancer in patients with IPF?**

NSCLC-Adenocarcinoma ☐

NSCLC-Squamous cell ☐

NSCLC- other ☐

Small cell ☐

I don't know ☐

None of the above ☐

10. **What is the most common anatomical location for lung cancer in patients with IPF?**

Upper lobes ☐

Middle lobe or lingula ☐

Lower lobes ☐

I don't know ☐

11. What is the median latency time (months) between IPF and lung cancer diagnosis in your experience?

0 (synchronous diagnosis) ☐

<12 ☐

12-24 ☐

24-36 ☐

>36 ☐

Unknown ☐

12. What percentage of patients with IPF present with other types of cancer (non-lung cancer)?

<1% ☐

1-5% ☐

5-10% ☐

10-20% ☐

Unknown ☐

Other (please specify) ☐

13. Which is the most common type of malignancy other than lung cancer occurring in patients with IPF?

Breast cancer ☐

Colon cancer ☐

Prostate cancer ☐

Hematologic malignancies (excluding MDS) ☐

Liver cancer ☐

Renal cancer ☐

Urinary bladder cancer ☐

Unknown ☐

Other (please specify) ☐

14. Do you agree with the following statement: moderate to severe IPF is an absolute contraindication to radiotherapy or chemoradiotherapy in locally advanced NSCLC.

Strongly agree ☐

Agree ☐

I am not sure ☐

Disagree ☐

Strongly disagree ☐

I don't know ☐

15. Do you consider any of the following treatments for advanced stage NSCLC an absolute contraindication in moderate to severe IPF (more than one answer possible)

Platinum based chemotherapy ☐

Docetaxel ☐

Immunotherapy ☐

Tyrosine kinase inhibitors ☐

Bevacizumab ☐

None of the above ☐

I don't know ☐

Other (please specify) ☐

16. Do you continue anti-fibrotic treatment (pirfenidone or nintedanib) when a patient is diagnosed with lung cancer (any stage)?

Yes ☐

No ☐

Other (please specify) ☐

17. Which safety precautions do you apply to patients with IPF and non-small cell lung cancer undergoing surgical lung interventions?

Low tidal volume ☐

Avoidance of high fraction of inspired oxygen ☐

Minimal perioperative administration of fluids ☐

Stop antifibrotic drugs ☐

Continuation of antifibrotic drugs ☐

Other (please specify) ☐

18. How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%, and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?

surgery ☐

stereotactic radiotherapy ☐

palliative care ☐

doublet platinum ± bevacizumab ☐

Immunotherapy ☐

Targeted therapy ☐

Antifibrotics ☐

Other (please specify) ☐

19. How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%) and metastatic NSCLC (TNM IV) ?

Palliative care ☐

doublet platinum ± bevacizumab ☐

Immunotherapy i.e. PDL1 inhibitors ☐

Targeted therapy ☐

Anti-fibrotics ☐

Other (please specify) ☐

20. How would you treat a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%), and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?

surgery ☐

stereotactic radiotherapy ☐

palliative care ☐

doublet platinum ± bevacizumab ☐

Immunotherapy i.e. PDL1 inhibitors ☐

Targeted therapy ☐

Antifibrotics ☐

Other (please specify) ☐

21. What would it be your next diagnostic step in a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%) with a central nodular lesion of 20 mm and mediastinal lymphadenopathy?

Monitor the patient with HRCT scan every 3-6 months ☐

Perform PET CT scan and do not change your routine follow-up work if negative ☐

Perform PET CT scan and if positive then apply endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) ☐

None of the above ☐

Other (please specify) ☐

22. What would it be your next diagnostic step in a patient with severe IPF (DLCO<35%, FVC<50%) with a central nodular lesion of 20mm and mediastinal lymphadenopathy?

Monitor the patient with HRCT scan every 3-6 months ☐

Perform PET CT scan and do not change your routine follow-up work if negative ☐

Perform PET CT scan and if positive then apply endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) ☐

Perform surgical lung biopsy (VATS) and resection without histological proof prior to surgery ☐

None of the above ☐

Other (please specify) ☐

23. Do you think a consensus statement for the diagnosis and management of patients with IPF and lung cancer is necessary?

Yes ☐

No ☐

24. Other points that are missing and considered to be necessary……..

25. Please provide your personal contact details (non-mandatory)……..

Supplementary data

The DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey. International survey and call for consensus.

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Table 1. In which country do you practice?

Answer	% of respondents	N (respondents)
ALBANIA	0,20%	1
ALGERIA	1,20%	6
ARGENTINA	2,40%	12
AUSTRALIA	2,40%	12
AUSTRIA	0,80%	4
BELGIUM	1,80%	9
BRAZIL	2,80%	14
CANADA	1,60%	8
CHILE	0,40%	2
CROATIA	1,40%	7
CZECH REPUBLIC	0,40%	2
DENMARK	0,80%	4
EGYPT	0,60%	3
FINLAND	0,40%	2
FRANCE	8,50%	42
GEORGIA	0,20%	1
GERMANY	8,90%	44
GREECE	5,00%	25
HONG KONG	0,20%	1
HUNGARY	0,40%	2
ICELAND	0,20%	1
INDIA	2,20%	11
INDONESIA	0,60%	3
IRELAND	0,60%	3
IRAN	0,20%	1
ISRAEL	0,40%	2
ITALY	7,60%	38
JAPAN	5,00%	25
KOREA	0,40%	2
LIBAN	0,20%	1
LITHUANIA	0,40%	2
MALAYSIA	0,20%	1
MEXICO	1,20%	6
NETHERLANDS	1,80%	9
NEW ZEALAND	0,60%	3
NORWAY	0,40%	2
PAKISTAN	0,60%	3
PARAGUAY	0,20%	1
PERU	1,00%	5
POLAND	1,60%	8

PORTUGAL	3,40%	17
REPUBLIC OF MOLDOVA	0,20%	1
ROMANIA	1,40%	7
RUSSIA	0,60%	3
SAUDI ARABIA	0,40%	2
SERBIA	1,00%	5
SINGAPORE	0,80%	4
SOUTH KOREA	0,80%	4
SPAIN	5,60%	28
SWEDEN	2,00%	10
SWITZERLAND	1,00%	5
TUNISIA	0,08%	4
TURKEY	2,20%	11
UAE	0,20%	1
UKRAINE	0,40%	2
UNITED KINGDOM	6,20%	31
USA	4,40%	22
URUGUAY	0,20%	1
VENEZUELA	0,20%	1
VIETNAM	0,20%	1

Table 2. What is your medical specialty?

Answer	% of respondents	N (respondents)
Pulmonologist	94,06%	396
Oncologist	0,71%	3
Thoracic surgeon	2,14%	9
Anesthesiologist	0,00%	0
Pulmo-oncologist	1,19%	5
Radio-oncologist	0,00%	0
Other (please specify)	1,90%	8

Table 3. How many years of experience do you have as a specialist?

Answer	% of respondents	N (respondents)
Less than 5	13,81%	66
5-10	23,01%	110
11-15	20,51%	98
16-20	11,92%	57
More than 20	30,75%	147

Table 4. What is your hospital setting?

Answer	% of respondents	N (respondents)
University Hospital	68,81%	331
Non-university hospital	22,25%	107
Private institution/practice	8,94%	43

Table 5. How many patients with IPF do you treat per year?

Answer	% of respondents	N (respondents)
<10	19,92%	97
10-20	26,69%	130
20-50	24,85%	121
More than 50	26,69%	130
Unknown	1,85%	9

Table 6. What is the incidence of lung cancer in patients with IPF?

Answer	% of respondents	N (respondents)
1-5%	30,77%	140
5-10%	45,27%	206
10-20%	21,76%	99
>20%	2,20%	10

Table 7. How often do you involve a multi-disciplinary team on the management of patients with IPF and lung cancer?

Answer	% of respondents	N (respondents)
Always	78,20%	384
Sometimes	18,95%	93
Never	2,85%	14

Table 8. What diagnostic modality do you use to screen patients with IPF for lung cancer (more than one answers possible)?

Answer	% of respondents	N (respondents)
Regular low dose HRCT scan	49,59%	242
Regular CXR	11,27%	55
HRCT scan in case of symptoms	29,09%	142
Tumor markers (Ca19/9, CA125, CEA)	6,56%	32
No screening	17,62%	86
Other (please specify)	2,67%	13

Table 9. What is the most common histologic subtype of lung cancer in patients with IPF?

Answer	% of respondents	N (respondents)
NSCLC-Adenocarcinoma	58,60%	286
NSCLC-Squamous cell	26,64%	130
NSCLC- other	1,64%	8
Small cell	0,00%	0
I don't know	12,30%	60
None of the above	0,82%	4

Table 10. What is the most common anatomical location for lung cancer in patients with IPF?

Answer	% of respondents	N (respondents)
Upper lobes	18,30%	90
Middle lobe or lingula	3,86%	19
Lower lobes	53,86%	265
I don't know	23,98%	118

Table 11. What is the median latency time (months) between IPF and lung cancer diagnosis in your experience?

Answer	% of respondents	N (respondents)
0 (synchronous diagnosis)	4,07%	20
<12	11,20%	55
12-24	20,37%	100
24-36	23,22%	114
>36	13,44%	66
Unknown	27,70%	136

Table 12. What percentage of patients with IPF present with other types of cancer (non-lung cancer)?

Answer	% of respondents	N (respondents)
<1%	16,46%	81
1-5%	30,48%	150
5-10%	9,55%	47
10-20%	3,66%	18
Unknown	38,82%	191
Other (please specify)	1,01%	5

Table 13. Which is the most common type of malignancy other than lung cancer occurring in patients with IPF?

Answer	% of respondents	N (respondents)
Breast cancer	3,85%	19
Colon cancer	14,20%	70
Prostate cancer	19,27%	95
Hematologic malignancies (excluding MDS)	9,14%	45
Liver cancer	0,60%	3
Renal cancer	1,01%	5
Urinary bladder cancer	4,67%	23
Unknown	45,64%	225
Other (please specify)	1,62%	8

Table 14. Do you agree with the following statement: moderate to severe IPF is an absolute contraindication to radiotherapy or chemoradiotherapy in locally advanced NSCLC.

Answer	% of respondents	N (respondents)
Strongly agree	7,93%	39
Agree	29,27%	144
I am not sure	20,33%	100
Disagree	34,35%	169
Strongly disagree	5,88%	29
I don't know	2,24%	11

Table 15. Do you consider any of the following treatments for advanced stage NSCLC an absolute contraindication in moderate to severe IPF (more than one answer possible)?

Answer	% of respondents	N (respondents)
Platinum based chemotherapy	16,93%	83
Docetaxel	13,27%	65
Immunotherapy	16,73%	82
Tyrosine kinase inhibitors	16,26%	92
Bevacizumab	6,12%	30
None of the above	37,35%	183
I don't know	22,24%	109
Other (please specify)	1,02%	5

Table 16. Do you continue anti-fibrotic treatment (pirfenidone or nintedanib) when a patient is diagnosed with lung cancer (any stage)?

Answer	% of respondents	N (respondents)
Yes	83,81%	409
No	8,40%	41
Other (please specify)	7,79%	38

Table 17. Which safety precautions do you apply to patients with IPF and non-small cell lung cancer undergoing surgical lung interventions?

Answer	% of respondents	N (respondents)
Low tidal volume	67,30%	321
Avoidance of high fraction of inspired oxygen	45,50%	217
Minimal perioperative administration of fluids	30,60%	146
Stop antifibrotic drugs	14,26%	68
Continuation of antifibrotic drugs	55,14%	263
Other (please specify)	6,29%	30

Table 18. How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%), and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?

Answer	% of respondents	N (respondents)
Surgery	21,43%	105
stereotactic radiotherapy	54,09%	265
palliative care	30,61%	150
doublet platinum ± bevacizumab	11,02%	54
Immunotherapy	16,94%	83
Targeted therapy	24,49%	120
Antifibrotics	37,55%	184
Other (please specify)	6,94%	34

Table 19. How would you treat a patient with advanced IPF (DLCO<35%, FVC<50%) and metastatic NSCLC (TNM IV)?

Answer	% of respondents	N (respondents)
Palliative care	69,13%	338
doublet platinum ± bevacizumab	25,56%	125
Immunotherapy i.e. PDL1 inhibitors	31,90%	156
Targeted therapy	35,38%	173
Anti-fibrotics	37,01%	181
Other (please specify)	5,32%	26

Table 20. How would you treat a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%) and otherwise operable non-small cell lung cancer nodule (TNM stage I-II)?

Answer	% of respondents	N (respondents)
Surgery	78,23%	381
stereotactic radiotherapy	40,45%	197
palliative care	10,68%	52
doublet platinum ± bevacizumab	13,55%	66
Immunotherapy i.e. PDL1 inhibitors	16,22%	79
Targeted therapy	19,30%	94
Antifibrotics	40,04%	195
Other (please specify)	9,03%	44

Table 21. What would it be your next diagnostic step in a patient with mild-to-moderate IPF (DLCO>35%, FVC>50%) with a central nodular lesion of 20 mm and mediastinal lymphadenopathy?

Answer	% of respondents	N (respondents)
Monitor the patient with HRCT scan every 3-6 months	1,85%	9
Perform PET CT scan and do not change your routine follow-up work if negative	3,50%	17
Perform PET CT scan and if positive then apply endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB)	87,86%	427
None of the above	0,82%	4
Other (please specify)	5,97%	29

Table 22. What would it be your next diagnostic step in a patient with severe IPF (DLCO<35%, FVC<50%) with a central nodular lesion of 20mm and mediastinal lymphadenopathy?

Answer	% of respondents	N (respondents)
Monitor the patient with HRCT scan every 3-6 months	9,16%	45
Perform PET CT scan and do not change your routine follow-up work if negative	17,11%	84
Perform PET CT scan and if positive then apply endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB)	59,67%	293
Perform surgical lung biopsy (VATS) and resection without histological proof prior to surgery	1,22%	6
None of the above	5,71%	28
Other (please specify)	7,13%	35

Table 23. Do you think a consensus statement for the diagnosis and management of patients with IPF and lung cancer is necessary?

Answer	% of respondents	N (respondents)
Yes	92,90%	458
No	7,10%	35

Table 24. Other points that are missing and considered to be necessary.

Answer	% of respondents	N (respondents)
N/A		

Table 25. Please provide your personal contact details (non-mandatory).

Answer	% of respondents	N (respondents)
N/A		