Lung cancer survival in never-smokers and exposure to residential radon: results of the LCRINS study.

Authors

Ana Casal Mouriño,[a,b] Alberto Ruano-Ravina,[b,c] María Torres-Durán,[d] Isaura Parente-Lamelas,[e] Mariano Provencio-Pulla,[f] Olalla Castro-Añón,[g] Iria Vidal-García,[h] Carolina Pena-Álvarez,[i] José Abal-Arca,[e] María Piñeiro-Lamas,[c] Ismael Fuente Merino,[j] Alberto Fernández-Villar,[d] Ihab Abdulkader,[k] Luis Valdés Cuadrado,[a,l] Juan Miguel Barros-Dios,[b,c,m] Mónica Pérez-Ríos.[b,c]

Author affiliations

[a]Department of Pneumology, Santiago de Compostela University Clinical Teaching Hospital, Santiago de Compostela, Spain

[b]Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain

[c]Consortium for Biomedical Research in Epidemiology & Public Health (*CIBER en Epidemiología and Salud Pública - CIBERESP*), Spain

[d]Department of Pneumology, Vigo University Teaching Hospital Complex, Vigo, Spain

[e]Department of Pneumology, Ourense University Teaching Hospital Complex, Ourense, Spain

[f]Department of Oncology, Puerta de Hierro University Teaching Hospital, Madrid, Spain

[g] Department of Pneumology, Lucus Augusti Hospital, Lugo, Spain

[h] Department of Pneumology, A Coruña University Teaching Hospital Complex, Spain

[i] Galician Oncology Centre, A Coruña (Corunna), Spain.

[j] Environmental Radioactivity Laboratory (*Laboratorio de Radiactividad Ambiental - LARUC*), University of Cantabria
[k]Department of Pathology, Clinic University Hospital of Santiago de Compostela, Spain.
[l]Interdisciplinary Neumology Research Group, Health Research Institute of Santiago de Compostela **(**Instituto Investigación Sanitaria de Santiago de Compostela/IDIS), Spain.
[m]Department of Preventive Medicine, Santiago de Compostela University Teaching Hospital Complex, Santiago de Compostela, Spain.

Address for correspondence: Alberto Ruano-Ravina, Departamento de Medicina Preventiva and Salud Pública, Universidad de Medicina, C/San Francisco s/n, University of Santiago de Compostela, 15782. Santiago de Compostela, Spain. E-mail: alberto.ruano@usc.es

This paper forms part of the work leading to Ana Casal-Mouriño's PhD degree.

Declarations of interest: none.

Abbreviations: WHO: World Health Organization, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, BRAF: proto-oncogene B-raf, SEER: Surveillance Epidemiology and End Results.

ABSTRACT

We aimed to evaluate lung cancer survival in never-smokers, both overall and specifically by sex, exposure to residential-radon, age, histological type, and diagnostic stage.

We included lung cancer cases diagnosed in a multicentre, hospital-based, case-control-study of never-smoker patients, diagnosed from January-2011 to March-2015 (Lung Cancer Research In Never Smokers study).

369 never-smokers (79% women; median age 71 years; 80% adenocarcinoma; 66% stage IV) were included.

Median overall survival, and at one, 3 and 5 years of diagnosis was 18.3 months, 61%, 32% and 22%, respectively. Higher median survival rates were obtained for: younger age, adenocarcinoma, actionable mutations, and earlier-stage at diagnosis. Higher indoor radon showed a higher risk of death in multivariate analysis.

Median lung cancer survival in never-smokers seems higher than that in ever-smokers. Patients with actionable mutations have a significantly higher survival. Higher indoor-radon exposure has a negative effect on survival.

***Keywords*:** lung neoplasms; never-smokers; indoor radon; survival.

1. Introduction

Lung cancer is a major public health problem, in that it ranks as the leading cause of cancer-related death and causes approximately 388,000 and 1.4 million deaths per annum in Europe and worldwide respectively.[1,2] In the last decade, the number of deaths due to lung cancer has decreased in both sexes, albeit more markedly so in men, owing to women's late incorporation into the smoking habit.[3] While the main risk factor for lung cancer is smoking habit,[4] exposure to residential radon is the second leading cause of this disease in smokers and the leading cause in never-smokers.[5] Up to 15% of lung cancers in men and 53% of lung cancers in women are not attributable to smoking habit, with lung cancer in never-smokers being considered a different clinical entity.[6-7]

Consequently, approximately 10% to 30% of all lung cancers occur in never-smokers,[8,9] a phenomenon that tends to be more common in women having a median age at diagnosis of around 69 years, with adenocarcinoma being the predominant histological type.[10,11] Similarly, the presence of mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) rearrangements are both more frequent among never-smokers.

Overall lung cancer survival is low and has hardly improved in recent years, ranging from 10% to 20% at 5 years of diagnosis.[7] In terms of never-smoker-specific lung cancer survival, the few studies published point to a better survival rate among this group than among ever-smokers. The studies covered in a recent review report median survival figures of 5 to 23.9 months in smokers versus 7.7 to 44.6 months in never-smokers.[12] Similarly, the survival rate at 5 years of diagnosis among never-smokers with localised cancer stage was 55.6%.[13] Furthermore, sex and age at diagnosis are known to influence survival, with older-aged men presenting with more comorbidities and higher treatment-related mortality rates than do younger patients.[14] However, the single most influential factor in survival is stage at diagnosis: it is the most important

prognostic variable and, as such, accounts for survival rate among never-smokers being low, since most are diagnosed in advanced stages.[15]

As mentioned above, among never-smokers exposure to residential radon assumes vital importance. While recent studies show that there is an association between exposure to radon and presence of lung cancer in never-smokers (particularly, if concentrations are higher than 200 Bq/m^3), it is not known how such exposure might affect the survival of such never-smoker cases,[16] since there are no studies in print.

Accordingly, the aim of this study was to evaluate lung cancer survival in never-smokers, both overall and specifically by sex, exposure to residential radon, age at diagnosis, histological type, and stage at diagnosis. To this end, we analysed data drawn from a series of never-smoker cases recruited in a multicentre hospital-based study in Galicia (Lung Cancer Research In Never Smokers/LCRINS study),[17-19] a Spanish region which is also a high radon-risk area.

2. Methods

2.1 Study design and setting

A multicentre, hospital-based, case-control study was conducted on patients from 7 hospitals in north-west Spain (Galicia): patient recruitment took place from January 2011 to March 2015. This present study only included cases drawn from the above case-control study. All the cases included were patients with histologically confirmed lung cancer, and were never-smokers according to the WHO definition, namely, anyone who has smoked: 1) fewer than 100 cigarettes in his/her lifetime; or 2) less than 1 cigarette per day during a period of no more than 6 months. At the time of their inclusion, all the cases were aged over 18 years, without any upper age limit. The study protocol was approved by the

relevant clinical research ethics committee (reference 2010/295). Informed consent was obtained from all patients included in the study.

2.2 Data-collection

All patients were interviewed by trained researchers, who used a questionnaire to collect information on multiple lung cancer risk factors, including exposure to ambient tobacco smoke, leisure time activities, occupation, etc. Exposure to residential radon was likewise measured with the aid of track detectors (CR-39 Radosys Inc., Budapest, Hungary), with patients being instructed on how to place the detectors correctly in the home (main bedroom). These detectors had to remain in patients' homes for a minimum of 3 months. A telephone follow-up was conducted to clarify any possible doubts. On conclusion of the measurement period, patients were required to send the detectors to the Galician Radon Laboratory (Faculty of Medicine, Santiago de Compostela University, Spain), a facility officially certified by the National Accreditation Body (*Entidad de Acreditación Nacional*) for measurement of airborne radon.

2.3. Patient follow-up

All patients were followed up until date of death or last observation. This follow-up was performed by consulting patients' electronic medical records (EMR), which were reviewed from June to August 2019. Follow-up time was calculated as the period between date of death or last observation, defined as an EMR activity (appointment for analysis, appointment for oncology, etc), and date of diagnosis. This follow-up time was then used to calculate survival at one, three and five years of diagnosis. Data pertaining to living patients were truncated at five years of diagnosis.

2.4 Statistical analysis

Firstly, we performed a descriptive univariate analysis of the study population,

and then analysed subjects' survival using the Kaplan-Meier method. Secondly, we obtained median survival at one, three and five years of diagnosis. Survival was calculated specifically by sex, histological type, stage at diagnosis, age at diagnosis, and level of residential radon concentration (600 or more, 300 to 599, 100 to 299, and under 100 Bq/m3). The log-rank test was used for all comparisons of survival functions by reference to the respective categories, with results deemed significant at $p<0.05$. All statistical analyses were performed using the IBM SPSS v22 computer software programme (IBM, Armonk, NY, USA).

3. Results

The study covered a total of 369 never-smoker patients (Table 1), 79% of whom were women. Median age at diagnosis was 67 years for men and 72 years for women. The most frequent histological type was adenocarcinoma (294 cases – 80%) and the most frequent stage at diagnosis was stage IV (66%). The median residential radon concentration (available for 306 patients) was 186 Bq/m^3.
Passive smoking exposure was observed in 155 patients (41,9%), and there were no significant differences on survival at 3 or 5 years due to environmental tobacco smoke exposure (data not shown). 41 cases had comorbid conditions, only 4 patients showed COPD, 18 ischaemic heart disease and 14 diabetes. Presence of mutations was analysed in 263 patients, 152 (41.2%) of whom presented with some type of specific mutation: of these, 130 (85.5%) presented with EGFR mutations, 21 (13.8%) presented with ALK mutations, and 1 (0.7%) had the BRAF mutation.

Among the patients with mutant EGFR, 48 (36.9%) presented with mutation in exon 21, 48 (36.9%) presented with mutation in exon 19, and 6 (4.6%) presented with mutation in exon 20. Treatment options of these patients were distributed as expected: 21,7% had undergone surgery, 53.4% chemotherapy and 39.6% radiotherapy. The presence of comorbidities was low, as expected since these patients are all neversmokers.

The data on median overall survival at one, 3 and 5 years of diagnosis can be seen in Table 2, along with the characteristics of the patients. Median overall survival was 18.3 months (95% CI: 14.6 – 22.0). There were no statistically significant differences by sex (Figure 1a). Survival rate at one, 3 and 5 years of diagnosis was 61% (in both sexes), 32% (32% in women and 30% in men), and 22% (25% in women and 13% in men) respectively.

Figure 1b shows survival by age at diagnosis. Cases diagnosed at age ≤71 years had a longer median survival than did diagnosed older patients, with the relevant figures being 26.7 months (95% CI 20.1 – 33.3) and 11.1 months (95% CI: 8.3 – 13.8) respectively (p<0.001).

Figure 1c depicts survival by reference to residential radon concentrations. No statistically significant differences were observed for survival by residential radon concentration (p=0.075). Cases with highest concentrations (>600 Bq/m3) had a median survival of 21.6 months, whereas cases with lower concentrations had a shorter survival.

Median survival by histological type can be seen in Figure 1d. The best survival was observed for patients with large cell lung cancer and adenocarcinoma (20.2 months), and the worst survival was observed for small-cell and squamous cancer, with a median survival of around 8 months. Median survival of patients who presented with some type of mutation (EGFR, ALK or BRAF) was higher than median overall survival, with figures of 20.7 months (95% CI: 16.2 – 25.2) versus 13.3 months (95% CI: 9.2 – 17.5) respectively (p=0.027). Median survival of patients with EGFR mutation was 20 months versus 48 months for patients with ALK translocation. Figure 1e shows the results for median survival by reference to the presence or absence of mutations, though only for patients with stage IV at diagnosis.

Median survival by stage at diagnosis can be seen in Fig. 1f. Lowest survival was for stage IV, with a median survival of 11.8 months (95%CI: 10.1–13.6). Median survival at stage I was 52 months (95% CI: 49.3–55.4).

Finally, Fig. 2a, b and 2c show survival at 5 years regarding having received surgery, chemotherapy or radiotherapy. Surgery is clearly the treatment most associated with higher survival, while chemotherapy and radiotherapy have a positive effect during the first years of followup.

Multivariate results of survival at 3 and 5 years of follow-up can be observed in Table 3. At 5-years of follow-up the variable most associated with worse survival was stage IV at diagnosis followed by not having received surgery. Age at diagnosis and higher radon exposure were also associated with a higher risk of death at 5 years. Of note, those participants exposed to indoor radon higher than 300 Bq/m3 had a HR of 1.42 (95%CI 1.06–1.90).

4. Discussion

Median lung cancer survival in never-smokers was 18.3 months. Some variables were associated with a higher 5-year survival apart from that already known (chemotherapy, radiotherapy, surgery or stage at diagnosis). These variables were a younger age, with younger patients, histological type, and presence of EGFR or ALK mutations. Of note, we found a better survival at 3 and 5-years of follow-up for those patients having lower residential radon concentrations (i.e.<300 Bq/m3), and this is the first study in reporting such association. In terms of sample size, ours is one of the largest studies on never-smoker survival to be conducted in Europe, and is the only one that has assessed the impact of residential radon on lung cancer survival.

When compared to results previously reported for ever-smokers in the literature, median survival of never-smokers appears to be higher. Overall, the CONCORD study [7] data describe survival at 5 years of diagnosis in ever-smokers as ranging

from 10% to 20% in the greater part of the countries included (13.5% in Spain). While the 1231 eversmokers evaluated by Viñolas et al.'s study [20] registered a median survival of 13.1 months. A possible explanation for this longer survival among never-smokers, is the high rate of mutations compared with that observed for ever-smokers (42% of mutations in never-smokers in our sample versus 12%–15% reported for ever-smokers). Survival at 5 years of diagnosis in never-smokers observed by our study appears to be higher (5-year survival rate of 23%). US data sourced from Surveillance and Epidemiology End Results (SEER) show survival rate for eversmokers at 5 years of diagnosis of 20%, with this rate being lower for cases in advanced stages (5.2%) [21]. When we compare 5-year survival with other studies, it seems that the present one is shorter compared to that observed for studies including oriental patients. Our results are more similar when we compare them with available evidence in Caucasics. Parente-Lamelas et al. [22] evaluated a total of 396 neversmokers (61% in stage IV), with a survival rate at 5 years of diagnosis of 12.4%. Viñolas et al. [20] likewise obtained a 15% median survival rate at 5 years of diagnosis in women never-smokers in stage IV. Since our study is more recent, many of the included patients were able to benefit from treatment with targeted therapies.

As mentioned above, recent studies [14] indicate a higher risk of suffering from lung cancer where there are high concentrations of residential radon (> 200Bq/m3). Our study observed a worse 3 and 5-year survival in multivariate analysis for patients exposed to indoor radon higher than 300 Bq/m3. The specific mechanisms of development of lung cancer due to residential radon exposure among never-smokers have not yet been completely elucidated, and we do not know what could influence this higher survival among those presenting lower radon concentrations.

Insofar as survival results by sex were concerned, our study yielded no statistically significant differences. In the literature, published studies report diverse results. Cho et al. [23] evaluated a total of 592 women never-smokers, who had a higher survival rate than that of men. Similarly, the paper by Johnson

et al. [24] describes better survival results for women. On the other hand, in their sample of 382 neversmoker patients, Hsu et al. [25] obtained the same median survival for men and women with pulmonary adenocarcinoma (22.8 months).

In terms of histological lineage, median survival was higher for never-smoker patients with pulmonary adenocarcinoma, and squamous cell carcinoma had the highest 5-year risk of death in multivariate analysis (compared with adenocarcinoma as a reference). These findings are in line with the available evidence. It should be noted that our study obtained a negligible number of patients with histology other than pulmonary adenocarcinoma, which means that the survival results for other histological lineages may not be altogether accurate. In their paper, Han et al. [26] included 309 never-smoker patients with pulmonary adenocarcinoma, obtaining a median survival similar to that observed by our study (22.3–22.9 months).

Median survival at diagnosis was higher in those patients who presented with some type of specific mutation. The study by Viñolas et al. [20] observed a longer median survival for patients with EGFR mutation than for patients without any mutations (25.6 and 16.2 months respectively). In their meta-analysis, Liu et al. [27] describe median survival in never-smoker patients with mutations, ranging from 29.3 to 36 months. These results are very important, since observation in a real clinical situation shows that the presence of actionable mutations in some patients and not in others implies a median survival of some 7 months longer for such patients, and almost twofold survival at five years of diagnosis in patients with stage IV (11% versus 6%). We have not included the presence of mutations in the full multivariate survival analysis because these mutations are usually only searched in stage IV patients and therefore we should have restricted our analysis to those patients.

This study has a number of advantages. It is a multicentre hospitalbased study, something that enhances its external validity, and it is also one of the first studies to evaluate radon as a possible factor that influences survival. To this end, we managed to put together what we consider to be a major-sized sample (369

patients), particularly in view of the few papers available to date on survival in never-smokers.

Lastly, this study has some limitations. First, the number of men included in the study was low as compared to the number of women enrolled, which is due to the fact that the majority of men had smoked at some time. A further limitation is that we have measured overall survival instead of specific lung cancer survival. Nevertheless, since approximately 90% of lung cancer cases die from this disease, we do not expect that this fact may have change the results. In a recent review on lung cancer survival in never-smokers, none of the included studies measured lung cancer specific survival [12].

In conclusion, never-smoker patients with lung cancer appear to have a longer median survival than do ever-smokers. Median lung cancer survival among never-smokers was higher with lower age at diagnosis, adenocarcinoma, presence of mutations, and earlier stage at diagnosis. A very interesting result, that has to be confirmed by other studies is that those patients with higher indoor radon concentrations (i.e. higher than 300 Bq/m3) have worse survival at 3 and 5 years from diagnosis.

Funding

This paper was funded by the following competitive research grants awarded to the individual case-control studies, which are part of this pooled study:

- Galician Regional Authority (*Xunta de Galicia*): 10CSA208057PR "Risk factors of lung cancer in never smokers: a multicentre case-control study in the Northwest of Spain." 2010.
- Carlos III Institute of Health (*Instituto de Salud Carlos III*), Ministry of Science and Innovation of Spain, grant number PI03/1248. 2003.
- Carlos III Institute of Health (grant FIS 92/0176) and the Galician Regional

Health Authority (grant XUGA 91010). 1992.
- Galician Regional Authority: grant number XUGA 208001B93. 1993.
- Carlos III Institute of Health, Ministry of Science and Innovation of Spain, grant number PI13/01765. 2013.
- ISCIII - PI15/01211 - Cofinanciado FEDER.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

[1] J. Ferlay, M. Colombet, I. Soerjomataram, T. Dyba, G. Randi, M. Bettio, A. Gavin, O. Visser, F. Bray, Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018, Eur. J. Canc. (2018) 1–32.

[2] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-tieulent, A. Jemal, Global cancer statistics, 2012, Ca - Cancer J. Clin. 65 (2015) 87–108.

[3] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, Ca - Cancer J. Clin. 68 (2018) 7–30.

[4] S.A. Khuder, Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis, Lung Canc. 31 (2001) 139–148.

[5] WHO, H. Zeeb, F. Shannoun, et al., Handbook on Indoor Radon: a Public Health Perspective, WHO Library Cataloguing- in-Publication Data, Geneva, Switzarland, 2009.

[6] S. Jenks, Is lung cancer incidence increasing in never-smokers? J. Natl. Cancer Inst. 108 (2016) 3–4.

[7] C. Allemani, T. Matsuda, V. Di Carlo, et al., Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries, Lancet 391 (2018) 1023–1075.

[8] J. Ferlay, H.R. Shin, F. Bray, D. Forman, D. Mathers, D.M. Parkin, Estimates of worldwide burden of cancer in 2008: globocan 2008, Int. J. Canc. 127 (2010) 2893–2917.

[9] S. Sun, J.H. Schiller, A.H. Gazdar, Lung cancer in never smokers – a different disease, Nat. Rev. Canc. 778–90 (2007).

[10] D. Salmerón, M.D. Chirlaque, M. Isabel Izarzugaza, M.J. Sánchez, R. Marcos-Gragera, E. Ardanaz, et al., Lung cancer prognosis in Spain: the role of histology, age and sex, Respir. Med. 106 (2012) 1301–1308.

[11] D. Pham, M.G. Kris, G.J. Riely, et al., Use of cigarette-smoking history to estimate the likelihood of mutations in epidermal growth factor receptor gene exons 19 and 21 in lung adenocarcinomas, J. Clin. Oncol. 24 (2006) 1700–1704.

[12] A. Casal-Mouriño, L. Valdés, J.M. Barros-Dios, A. Ruano-Ravina, Lung cancer survival among never smokers, Canc. Lett. 451 (2019) 142–149.
[13] Cancer stat facts: Lung and bronchus cancer [Internet], National cancer Institute surveillance, Epidemiology, and End Results, Cancer Epidemiol. Biomarkers Prev 26 (4) (2017 Apr) 632–641, https://doi.org/10.1158/1055-9965.EPI-16-0520 Epub 2016 Dec 12.
[14] O. Pérez-Martínez, I. Vidal-García, C. Montero-Martínez, M. Provencio, A. Ruano-Ravina, Description and survival of stage I and II lung cancer patients, Arch. Bronconeumol. 54 (8) (2018) 420–426.
[15] A.J. Alberg, M.V. Brock, J.G. Ford, J.M. Samet, S.D. Spivack, Epidemiology of lung cancer: diagnosis and management of lung cancer, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, third ed., vol. 143, 2013, pp. 1–29 Chest, 5.
[16] M. Torres-Durán, J.M. Barros-Dios, A. Fernández-Villar, A. Ruano-Ravina, Residential radon and lung cancer in never smokers. A systematic review, Canc. Lett.345 (2014) 21–26.
[17] M. Torres-Durán, A. Ruano-Ravina, I. Parente-Lamelas, et al., Lung cancer in neversmokers: a case–control study in a radon-prone area (Galicia, Spain), Eur. Respir. J. 44 (2014) 994–1001.
[18] M. Lorenzo-González, A. Ruano-Ravina, M. Torres-Durán, et al., Lung cancer and residential radon in never-smokers: a pooling study in the Northwest of Spain, Environ. Res. 172 (2019) 713–718.
[19] M. Lorenzo-González, A. Ruano-Ravina, J. Peón, M. Pineiro, J.M. Barros-Dios, Residential radon in Galicia: A cross-sectional study in a radon-prone area, J Radiol Prot. 37 (2017) 728–741.
[20] N. Viñolas, P. Garrido, D. Isla, et al., Lung cancer in never-smoking women: a subanalysis of the Spanish female-specific database WORLD07, Canc. Invest. 35 (5) (2017) 358–365, https://doi.org/10.1080/07357907.2017.1295461.
[21] N. Howlader, A.M. Noone, M. Krapcho, D. Miller, A. Brest, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D.R. Lewis, H.S. Chen, E.J. Feuer, K.A. Cronin, SEER Cancer Statistics Review, National Cancer Institute, 1975-2016.

[22] I. Parente-Lamelas, J. Abal-Arca, N. Blanco-Cid, et al., Clinical characteristics and survival in never smokers with lung cancer, Arch. Bronconeumol. 50 (2) (2014) 62–66.
[23] J. Cho, S.M. Choi, J. Lee, et al., Proportion and clinical features of never-smokers with non-small cell lung cancer, Chin. J. Canc. 36 (2017) 20.
[24] M.L. Johnson, C.S. Sima, J. Chaft, et al., Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinomas, Cancer 119 (2) (2013) 356–362.
[25] L.H. Hsu, N.M. Chu, C.C. Liu, et al., Sex-associated differences in non-small cell lung cancer in the new era: Is gender an independent prognostic factor? Lung Canc. 66 (2009) 262–267.
[26] Han JY, Park K, Kim Sw, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J. Clin. Oncol. 30:1122-1128.
[27] X. Liu, P. Wang, C. Zhang, Z. Ma, Epidermal growth factor receptor (EGFR): a rising star in the era of precision medicine of lung cancer, Oncotarget 30 (2017) 50209–50220.

Table 1. Description of the sample

Variable		N (%)
Sex	Women	292 (79.1%)
	Men	77 (20.9%)
Age at diagnosis (median, mean, P_{25}, P_{75})	Global	71.0; 69.1; 60.8-79.0 years
	Women	71.8; 69.5; 61.3-79.0 years
	Men	67.4; 67.3; 58.7-79.2 years
Histological type	Adenocarcinoma	294 (79.7%)
	Squamous	32 (8.7%)
	Small cell	22 (5.9%)
	Large cell	6 (1.6%)
	Other	15 (4.1%)
Residential radon concentration (mean, median, P_{25}-P_{75})		
	Total	267.3; 186.5; 109.8-332.5 Bq/m^3
Presence of mutations	No specific mutation	106 (28.7%)
	Not mutated	111 (30.1%)
	Mutated	152 (41.2%)
Specific mutations	EGFR	130 (85.5%)
	ALK	21 (13.8%)
	BRAF	1 (0.7%)
Diagnostic stage	I	45 (12.2%)
	II	23 (6.2%)
	IIIA	35 (9.5%)
	IIIB	22 (6.0%)
	IV	244 (66.1%)

Treatment received	Surgery	80 (21,7%)
	Chemotherapy	197 (53,4%)
	Radiotherapy	146 (39,6%)
Passive smoking exposure (yes)		155 (41,9%)
Comorbid conditions	COPD	4 (1,1%)
	Diabetes mellitus	14 (3,8%)
	Ischaemic heart disease	18 (4,9%)

Table 2. Survival in months by participants' characteristics

Variable		Median survival at 5 years (months)	1 year (%)	*p*-value (log rank)	3 years (%)	*p*-value (log rank)	5 years (%)	*p*-value (log rank)
Global		18.3	61%	--	32%	--	22%	--
Sex	Women	18.8	61%		32%		25%	
	Men	15.7	61%	0.877	30%	0.783	13%	0.258
Age	≤ 71 years	26.7	75%		40%		30%	
	> 71 years	11.1	47%	<0.001	23%	<0.001	15%	<0.001
Histological type	Adenocarcinoma	20.2	63%		33%		24%	
	Squamous	8.1	41%		19%		6%	
	Small cell	8.7	41%	0.006	18%	0.008	12%	0.003
	Large cell	19.9	67%		33%		33%	
	Other	37.2	87%		53%		44%	
Mutation in stage IV	Non-mutated	8	43%		14%		7%	
	Mutated	15.7	63%	0.01	25%	0.05	11%	0.027
Stage	I	52.3	87%		75%		72%	
	II	31.3	74%		45%		39%	
	IIIA	50.2	89%	<0.001	56%	<0.001	44%	<0.001
	IIIB	20.2	73%		36%		29%	
	IV	11.8	49%		19%		9%	
Residential radon	< 100 Bq/m^3	20.7	66%		30%		22%	
	100 – 299 Bq/m^3	18.8	60%		34%		23%	
	300 – 599 Bq/m^3	14.6	55%	0.629	23%	0.427	14%	0.206
	≥ 600 Bq/m^3	21.6	66%		41%		38%	

Table 3. Multivariate results of survival at 3 and 5 years of follow-up.

	Survival at 3 years of follow-up				Survival at 5 years of follow-up			
Variable	**Bivariate Cox Analysis**		**Multivariate Cox Analysis**		**Bivariate Cox Analysis**		**Multivariate Cox Analysis**	
	HR (IC 95%)	**p-value**	**HR (IC 95%)**	**p-value**	**HR (IC 95%)**	**p-value**	**HR (IC 95%)**	**p-value**
Sex								
Women	1				1			
Men	1.04 (0.77–1.41)	0.784			1.18 (0.89–1.56)	0.259		
Age at diagnosis	1.03 (1.02–1.04)	< 0.001	1.02 (1.01–1.04)	< 0.001	1.03 (1.02–1.04)	< 0.001	1.03 (1.02–1.04)	< 0.001
Histological type								
Adenocarcinoma	1		1		1		1	
Squamous	1.76 (1.16–2.65)	0.007	1.91 (1.20–3.04)	0.006	1.83 (1.24–2.70)	0.002	1.87 (1.22–2.88)	0.004
Small cell	1.69 (1.04–2.74)	0.034	1.61 (0.92–2.82)	0.097	1.66 (1.04–2.65)	0.035	1.23 (0.73–2.08)	0.440
Large cell	1.03 (0.38–2.76)	0.958	2.20 (0.80–6.05)	0.125	0.89 (0.33–2.39)	0.816	2.07 (0.76–5.69)	0.156
Other	0.58 (0.27–1.23)	0.158	0.45 (0.18–1.14)	0.091	0.60 (0.29–1.21)	0.149	0.53 (0.23–1.22)	0.135
Stage at diagnosis								
I	1		1		1		1	
II	2.59 (1.14–5.87)	0.023	3.47 (1.35–8.91)	0.010	2.81 (1.28–6.17)	0.010	3.67 (1.51–8.94)	0.004
III	2.39 (1.19–4.78)	0.014	1.94 (0.90–4.18)	0.092	2.69 (1.39–5.20)	0.003	2.29 (1.11–4.74)	0.026
IV	5.98 (3.25–11.00)	< 0.001	3.59 (1.76–7.30)	< 0.001	7.00 (3.90–12.56)	< 0.001	4.91 (2.49–9.72)	< 0.001
Residential radon								
< 300Bq/m2	1		1		1		1	
≥300Bq/m2	1.11 (0.82–1.49)	0.508	1.41 (1.04–1.92)	0.030	1.07 (0.81–1.43)	0.624	1.42 (1.06–1.90)	0.020
Surgery								
Yes	1		1		1		1	
No	5.42 (3.46–8.50)	< 0.001	3.80 (2.06–7.01)	< 0.001	5.20 (3.48–7.77)	< 0.001	3.16 (1.84–5.41)	< 0.001
Chemotherapy								
Yes	1		1		1		1	
No	1.33 (1.04–1.71)	0.023	1.70 (1.24–2.32)	< 0.001	1.23 (0.97–1.56)	0.090	1.70 (1.28–2.27)	< 0.001
Radiotherapy								
Yes	1		1		1			
No	1.24 (0.96–1.60)	0.098	1.32 (0.96–1.80)	0.086	1.15 (0.91–1.47)	0.246		

Figure 1. Survival functions for: A) sex; B) age (over or under 71 years at diagnosis); C) median residential radon concentration; D) histological type; E) presence of stage IV mutations; and F) stage at diagnosis.

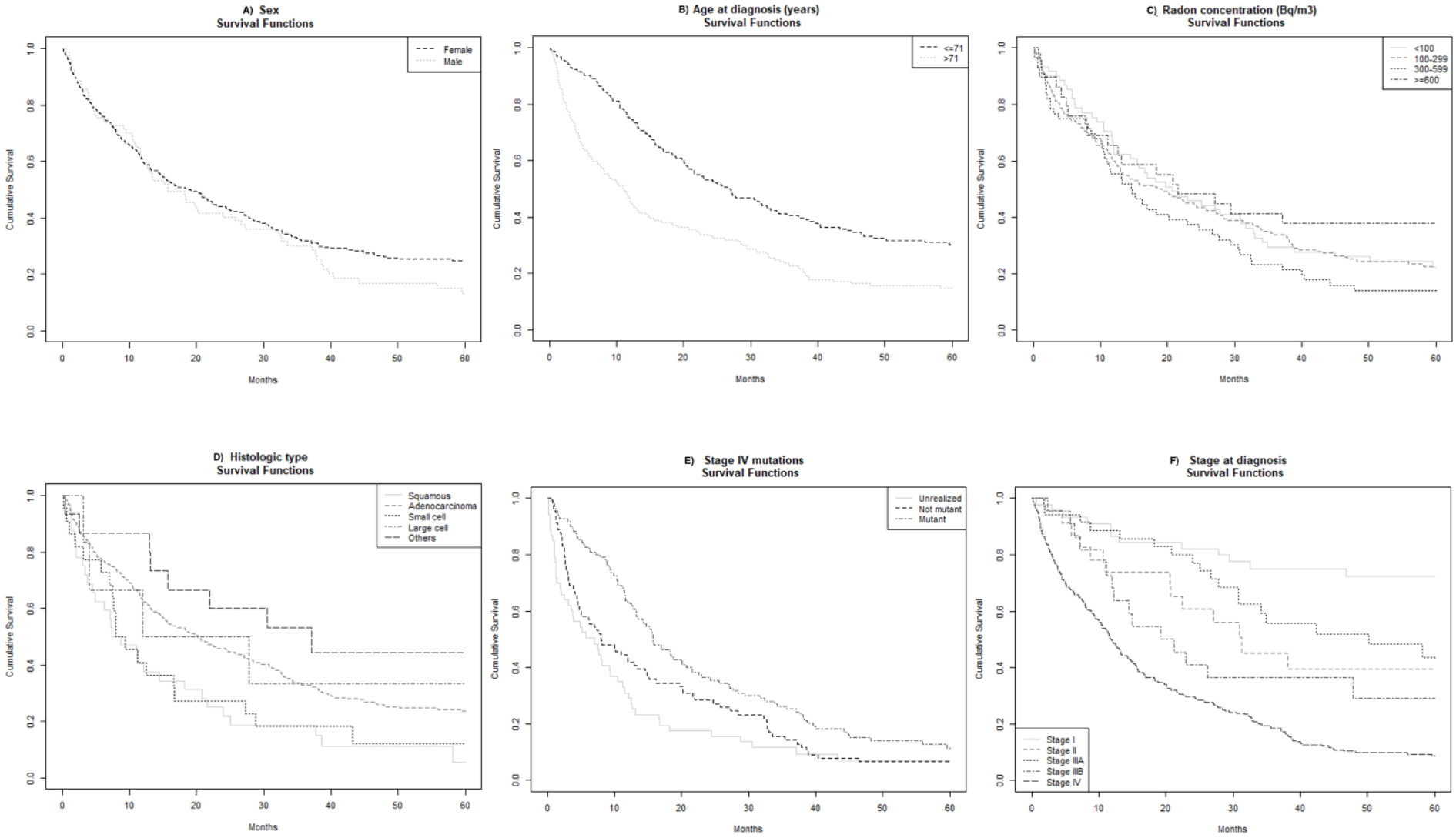

Figure 2. Survival plots comparing survival at 3 and 5 years regarding type of treatment: A) surgery (A1: 3 years vs A2: 5 years); B) chemotherapy (B1: 3 years vs B2: 5 years); and C) radiotherapy (C1: 3 years vs C2: 5 years).