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Research Paper

Lung cancer among the Elderly in Denmark – A comprehensive population-based cohort study

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A B S T R A C T

Objective: Lung cancer primarily occurs in the elderly with a median age at diagnosis in Denmark of 73 years. However, elderly patients are under-represented in clinical trials as well as in screening studies. In this study, we aim to characterize elderly patients with lung cancer and explore the diagnostic intensity, treatment patterns, and survival.

Method: Patients diagnosed with lung cancer between 2014 and 2017 according to the Danish Cancer Registry, and with clinical information in the Danish Lung Cancer Registry were included. Patient information was linked by the unique social identification number to information from Statistics Denmark.

Results: We included n = 17,835 patients in this study, of whom 2,871 (16.1 %) were 80 years or older. Fewer elderly patients had lung biopsies (47 % vs 53 %) or mediastinal procedures (34 % vs 26 %), compared to the younger patients ($p < 0.001$). Fewer elderly patients had treatment registration (60 % vs 85 %), and fewer received treatment with curative intent (23 % vs 42 %) compared to patients younger than 80 years ($p < 0.001$). The elderly patients had 2.1 (CI 95 % 1.9 – 2.2) times higher odds of dying within 12 months after diagnosis than younger patients.

Conclusion: The diagnostic intensity among lung cancer patients aged eighty years or above is lower compared to younger patients. Being elderly is associated with not undergoing surgical treatment or treatment with curative intent. Across all treatment groups, being older than eighty years of age was associated with an adverse prognosis.

1. Introduction

The prognosis for lung cancer patients remains dire, representing the predominant cause of cancer-related mortality worldwide [1]. In Denmark, fast-track cancer patient pathways (CPPs) have been implemented in order to ensure a swift diagnostic work-up and referral to treatment with minimal delay [2]. Furthermore, notable advancement in treatment have been achieved for both limited-stage and for advanced-stage disease [3–5]. These treatment advances have resulted in an improved prognosis for lung cancer patients in Denmark. However, the current one-year overall survival rate for Danish lung cancer patients is 57.3 % (year of diagnosis 2021), and the five-year survival rate is 22.3 % (year of diagnosis 2017) [6].

Lung cancer is a disease that primarily occurs in the elderly. In 2022, the median age at diagnosis was 73 years in Denmark [6]. In developed countries, lung cancer is primarily caused by long standing exposure to tobacco smoke, correlating with substantial comorbidities [7–9]. Nevertheless, advanced age itself stands as an established risk factor for a poor prognosis in lung cancer. This is likely due to a combination of unmodifiable factors, including age-related frailty, increased vulnerability, diminished treatment tolerability and the onset of age-related comorbidities [10,11]. Modifiable factors such as deconditioning, lack of awareness, depression and living alone can also contribute to this effect. The initiation of lung cancer treatment is less common in older compared to younger patients. This may be attributed to elderly patients displaying reduced motivation to opt for aggressive treatments, and/or clinicians perceiving them as less suitable candidates for major surgery or potentially toxic non-surgical treatment [12,13]. Moreover, elderly lung cancer patients are generally under-represented in clinical trials, encompassing both medical treatment and in screening studies [14,15].

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As a result, our knowledge on diagnostic and treatment patterns concerning the sizable proportion of older patients with lung cancer remains limited.

We aimed to characterize older patients with lung cancer (80 years and above) in terms of sociodemographic parameters, comorbidity, smoking history, lung function and performance status. Furthermore, we aimed to describe the diagnostic intensity, and evaluate treatment patterns among older patients with lung cancer, compared to patients younger than eighty at time of diagnosis, and to ascertain how these factors correlate with short-term prognosis.

2. Methods

Design: Population-based cohort study.

2.1. Data sources

The Danish Lung Cancer Registry (DLCR) was established in 2000 [16,17]. It is mandatory for all departments involved in the diagnostic work-up and treatment of lung cancer to report patient-related and clinical data to the registry. Only first-time diagnoses of lung cancer are registered. Data are linked with data on the histopathological profile of the lung cancer and data on admissions and outpatient visits in the Danish health care system from the Danish Pathology Registry and National Patient Registry, respectively. The Danish Cancer Registry (DCR) contains data on all incident cancers in Denmark, it is used for research and statistical purposes only [18]. It contains limited patient-related data and an array of data on relevant tumor characteristics. Statistics Denmark contains data on cohabitation status, length of education and income.

We identified lung cancer patients diagnosed from 2014 to 2017 in the DCR. These data were merged using the unique personal identification number with socioeconomic data from Statistics Denmark. This has been described in detail elsewhere [19]. In the present study, data from the Danckert et al. was merged with clinicopathological data from the DLCR. Considering that the patients in the study database were identified through the Danish Cancer Registry, we expected a concordance rate of approximately 90 % with the DLCR [20]. Only patients registered in both databases were incorporated into the primary study cohort.

2.2. Definition of variables of interest

From the DLCR, we retrieved the following patient-related factors: Lung function (expected forced expiratory volume in one second in liters, FEV1 and percentage of diffusion capacity for carbon monoxide, DLCO). From height in centimeters and weight in kilograms, we calculated the body mass index (BMI). Furthermore, smoking history, defined as accumulated pack year (20 cigarette equivalents pr. day for one year), Eastern Cooperative Oncology Group (ECOG) Performance Status, burden of comorbidity (Charlson Comorbidity index) [21] were retrieved.

Clinical parameters: Up to three procedures leading to diagnosis, can be registered in the DLCR based on ICD-10 procedure codes. From these codes, the diagnostic procedures were categorized into: lung biopsy (both transthoracic and transbronchial), mediastinal staging procedures including lymph node biopsies, endobronchial and endoscopic ultrasound (EBUS and EUS respectively) and mediastinoscopy, imaging procedures as computed tomography (CT), positron emission tomography (PET), cerebral imaging, both CT and magnetic resonance (MR), biopsies from metastatic sites, (including pleurocentesis) and "others" (including but not limited to extra cerebral MRI, and lung scintigraphy).

Treatment parameters: Initial treatment type, either surgery or non-surgical treatment. If a surgery registration was missing, we assumed that no surgery had been performed. We also registered whether the patient received treatment with curative intent, either surgical or non-surgical. Non-surgical included both stereotactic body radiotherapy and combined chemo- radiotherapy.

For the analyses concerning diagnostic work-up, treatment and prognosis patients diagnosed with lung cancer through death certificate only (DCO) were excluded.

2.3. Statistical analyses

Categorical variables were compared by Pearson chi squared distribution. Numeric variables were compared by Mann-Whitney *U* test.

Associations between age and study variables were analyzed using adjusted logistic regression analyses, incorporating both categorical and numeric variables as specified. Surgical treatment is primarily considered in patients diagnosed with NSCLC in stage I and II. However, surgery could still be a treatment option in patients with more advanced disease, thus in addition to established treatment defining variables, we included all stages in the adjusted logistic regression models. The results of the regression analyses are reported as odds ratios (OR) along with 95 % confidence intervals (CI 95 %). A p-value < 0.05 was considered as statistically significant. All analyses were performed by using Stata® 17.

2.4. Ethics

The study has been approved by the Danish Data Protection Agency.

3. Results

We identified 19,175 patients with lung cancer in the DLCR, and 19,014 patients in the Danish Cancer Registry; of the latter 19 were registered twice due to registration of a metachronous lung cancer. N = 17,864 patients were registered in both registries and thus eligible for inclusion. We excluded n = 29 as they were registered as DCO and ultimately included n = 17,835, with n = 2,871 (16 %) in the elderly group and n = 14,964 (84 %) in the younger group.

Baseline characteristics are provided in Table 1. As seen, elderly patients were more likely not to have a final TNM-classification 8.0 vs. 4.7 % (p < 0.001) and no cytopathological diagnosis 40.3 vs. 15.4 % (p < 0.001).). Furthermore, the elderly had a lower proportion of small cell lung cancers and adenocarcinomas, while the proportion of squamous cell carcinoma was higher among the elderly. The elderly generally had lower educational level, lower income and more often lived alone. In addition, the elderly patients had worse performance status. The mean FEV1 was approx. 400 ml lower among the elderly (p < 0.001), and there were significantly more elderly in the high-burden comorbidity group compared to the young: 42 % (n = 1202) vs. 31 % (n = 4668), respectively (p < 0.001).

3.1. Diagnostic work-up

We assessed the distribution of the main diagnostic procedures in the two age groups, and found 7,931 (53 %) in the younger vs 1,343 (47 %) in the elderly group had a lung biopsy performed (p < 0.001). Mediastinal procedures were performed in 5,156 (34 %) of the younger vs. 739 (26 %) in the elderly group (p < 0.001) and 1,410 (9.4 %) vs. 376 (13.1 %) had a biopsy from a metastatic site, respectively (p < 0.001).

When adjusted for stage, comorbidity, lung function and performance status, age group in itself was not significantly associated with the likelihood of having a lung biopsy performed, OR 0.92 (95 %CI 0.84–1.02). However, when not adjusted for either performance status or lung function, elderly patients were less likely to undergo a lung biopsy, OR 0.78 (95 %CI 0.72—0.85). In the fully adjusted model elderly patients were less likely to undergo mediastinal procedures OR 0.77 (95 %CI 0.70 – 0.86) (Table 2).

Concerning patients registered with stage IV lung cancer, we evaluated the diagnostic intensity between the two groups, elderly n = 1,393, younger n = 7,275. Among these, respectively 21.8 % (n = 303)

Table 1
Patient characteristics by age.

	<80 years	>=80 years	Total	P-value
n (%)	14,964 (83.9)	2871 (16.1)	17,835 (100.0)	
Age at diagnosis, mean (sd)	67 (8)	84 (3)	70 (10)	<0.001
Age at diagnosis, median (iqi)	69 (62; 73)	83 (81; 85)	70 (64; 77)	<0.001
Sex, n (%)				
Women	7449 (49.8)	1410 (49.1)	8859 (49.7)	
Men	7515 (50.2)	1461 (50.9)	8976 (50.3)	0.50
Marital status, n (%)				
Single	6065 (40.6)	1634 (57.0)	7699 (43.3)	
Married/co-habiting	8878 (59.4)	1235 (43.0)	10,113 (56.7)	<0.001
Educational level, n (%)				
Low	6368 (43.6)	1547 (55.5)	7915 (45.5)	
Intermediate	6104 (41.8)	899 (32.3)	7003 (40.3)	
High	2139 (14.6)	341 (12.2)	2480 (14.3)	<0.001
Income quartile, n (%)				
1	4471 (29.9)	939 (32.7)	5410 (30.3)	
2	4785 (32.0)	1153 (40.2)	5938 (33.3)	
3	3469 (23.2)	548 (19.1)	4017 (22.5)	
4	2235 (14.9)	231 (8.0)	2466 (13.8)	<0.001
BMI, mean (sd)	25.2 (9.4)	24.4 (5.8)	25.1 (8.9)	<0.001
ECOG PS, n (%)				
0	5974 (39.9)	536 (18.7)	6510 (36.5)	
1	4161 (27.8)	826 (28.8)	4987 (28.0)	
2	1816 (12.1)	520 (18.1)	2336 (13.1)	
3	993 (6.6)	406 (14.1)	1399 (7.8)	
4	399 (2.7)	198 (6.9)	597 (3.3)	
Missing	1621 (10.8)	385 (13.4)	2006 (11.2)	<0.001
CCI, n (%)				
0	6996 (46.8)	981 (34.2)	7977 (44.7)	
1	3305 (22.1)	691 (24.1)	3996 (22.4)	
2	4663 (31.2)	1199 (41.7)	5862 (32.9)	<0.001
FEV1, mean (sd)	1.87 (0.75)	1.52 (0.61)	1.82 (0.74)	<0.001
DLCO, mean (sd)	66 (21)	63 (22)	66 (22)	<0.001
Pack-year, mean (sd)	40.14 (22.37)	38.52 (23.91)	39.91 (22.61)	<0.001
TNM Stage, n (%)				
I	2550 (17.0)	441 (15.4)	2991 (16.8)	
II	1249 (8.3)	258 (9.0)	1507 (8.4)	
III	3188 (21.3)	548 (19.1)	3736 (20.9)	
IV	7275 (48.6)	1393 (48.5)	8668 (48.6)	
Missing	702 (4.7)	231 (8.0)	933 (5.2)	<0.001
Pathology, n (%)				
Small cell	1873 (12.5)	184 (6.4)	2057 (11.5)	
Large cell neuroendocrine	116 (0.8)	12 (0.4)	128 (0.7)	
Non-small cell	1425 (9.5)	212 (7.4)	1637 (9.2)	
Squamous	2411 (16.1)	485 (16.9)	2896 (16.2)	

Table 1 (*continued*)

	<80 years	>=80 years	Total	P-value
Adenocarcinoma	5927 (39.6)	704 (24.5)	6631 (37.1)	
Large cell carcinoma	29 (0.2)	3 (0.1)	32 (0.2)	
Adenosquamous	52 (0.3)	11 (0.4)	63 (0.4)	
Neuroendocrine	76 (0.5)	11 (0.4)	87 (0.5)	
Carcinoid	217 (1.5)	16 (0.6)	233 (1.3)	
NOS	308 (2.1)	40 (1.4)	348 (2.0)	
Mixed tumor	229 (1.5)	36 (1.3)	265 (1.5)	
Missing	2301 (15.4)	1157 (40.3)	3458 (19.5)	<0.001
ALK mutation				
Negative	6125 (40.9)	897 (31.2)		
Positive	116 (0.8)	9 (0.3)		
Not registered	8723 (58.3	1965 (68.4)		<0.001
EGFR				
Negative	6446 (43.1)	934 (32.5)		
Positive	565 (3.8)	117 (4.1)		
Not registered	7953 (53.2)	1820 (63.4)		< 0.001

ECOG PS = Eastern Cooperative Oncology Group Performance Status. CCI = Charlson Comorbidity index. FEV1 = forced expiratory value in one second. DLCO = diffusing capacity of the lungs for carbon monoxide. TNM = Tumor Node Metastasis 7th edition. NOS = not otherwise specified. ALK = anaplastic lymphoma kinase. EGFR = epidermal growth factor receptor.

Table 2
Multivariate logistic regression analyses of associations with key diagnostic procedures and clinicopathological parameters.

	Lung biopsies		Mediastinal procedures	
	Odds ratio	95 %CI	Odds ratio	95 %CI
TNM Stage				
I	Ref			
II	0.72	0.61–0.84	1.77	1.51–2.07
III	0.28	0.24–0.31	4.97	4.40–5.61
IV	0.20	0.18–0.22	3.27	2.94–3.69
Missing	0.29	0.24–0.36	3.33	2.74–4.04
Age group				
Young	Ref			
Elderly	0.92	0.84–1.02	0.77	0.70–0.85
CCI				
0	Ref			
1–2	1.03	0.96–1.11	1.06	0.98–1.15
≥ 3	1.13	1.02–1-25	1.00	0.90–1.11
FEV-1*	1.05	1.00–1.1	1.07	1.02–1.13
ECOG PS				
0	Ref			
1	0.96	0.88–1.05	1.00	0.92–1.09
2	0.92	0.82—1.03	1.00	0.89–1.12
3	0.61	0.53–0.70	0.74	0.64–0.87
4	0.47	0.37–0.61	0.50	0.38–0.65
Missing	0.72	0.62–0.84	1.09	0.93–1.27

TNM = Tumor Node Metastasis 7th edition. CCI = Charlson Comorbidity index ECOG PS = Eastern Cooperative Oncology Group Performance Status. *Numeric variable, for each one-liter increase in FEV-1.

vs. 16.3 % (1186) had biopsy performed from a metastatic site ($p < 0.001$). Concerning stage IV patients who did not have a biopsy from a metastatic site (elderly n = 1,090, younger, n = 6,089), 40.6 % (n = 442) in the elderly group had a lung biopsy performed vs. 46.1 % (n = 2,844) in the younger group ($p < 0.001$). Finally, among stage IV patients with no registered metastatic biopsy or lung biopsy (elderly n = 648, younger n = 3,245), we assessed the proportions undergoing a mediastinal procedure in the two groups. In the elderly group 43.5 % (n = 282) vs. 65.3 % (n = 2,120) in the younger group had a mediastinal procedure performed ($p < 0.001$). To further support our findings, we explored if stage

IV patients who did not have a registered lung biopsy, mediastinal procedure and a metastatic biopsy, had a registered histologic subtype (elderly n = 366 and younger, n = 1,125). We found that 81.5 % (n = 297) in elderly group vs. 40.7 % (n = 458) in the younger group did not have a histologic subtype registered in the DLCR ($p < 0.001$).

3.2. Treatment

In terms of treatment, n = 12,712 (85 %) in the younger group and n = 1,735 (60 %) in the elderly group had a treatment registration in the DLCR ($p < 0.001$). Furthermore, n = 6,248 (42 %) in the younger group vs. n = 667 (23 %) in the elderly group received treatment with curative intent ($p < 0.001$). Ultimately, n = 3552 (24 %) vs. n = 319 (11 %) had surgery performed ($p < 0.001$). Correspondingly, n = 2696 (18 %) and n = 348 (12 %), in the younger and elderly group, respectively, had non-surgical curatively intended treatment, thus either radiotherapy or combined radio-/chemo therapy ($p < 0.001$).

In the unadjusted logistic regression model, the OR for undergoing surgery was 0.40 (CI 95 % 0.35 – 0.45) among the elderly compared to the younger. As seen in Table 3, elderly patients were still less likely to undergo surgical treatment, even after adjusting for the effect of stage, comorbidity, lung function, cohabitation status and performance status.

3.3. Prognosis

The elderly patients had an unadjusted OR of 2.1 (CI 95 % 1.9 – 2.2) times higher odds for dying within 12 months after diagnosis than younger patients, in the multivariate analysis (Table 4) the OR was 1.59 (CI 95 % 1.43–1.77). Not undergoing resection, increasing stage and burden of comorbidity were all associated with increasing odds for dying within 12 months. In contrast being married or living with a partner was associated with lower odds of death within 12 months (OR = 0.9 (CI 95 %: 0.84 – 0.97)).

Table 3
Multivariate logistic regression analyses of associations between clinicopathological and sociodemographic parameters and undergoing curatively intended surgery.

	Odds ratio	95 %CI
TNM Stage		
I	Ref	
II	0.86	0.74–1.00
III	0.09	0.08–0.10
IV	0.01	0.01–0.014
Missing	0.11	0.09–0.15
Age group		
Young	Ref	
Elderly	0.47	0.40–0.56
CCI		
0	Ref	
1–2	0.89	0.79–1.00
≥ 3	0.72	0.63–0.84
FEV-1 *	2.04	1.89–2.20
ECOG PS		
0	Ref	
1	0.51	0.46–0.58
2	0.21	0.17–0.25
3	0.08	0.05–0.13
4	0.15	0.07–0.34
Missing	0.47	0.37–0.59
Cohabitation status		
Single	Ref	
Married/cohabitating	1.03	0.92–1.14

TNM = Tumor Node Metastasis 7th edition. CCI = Charlson Comorbidity index ECOG PS = Eastern Cooperative Oncology Group Performance Status. FEV-1 = forced expiratory volume in one second. *Numeric variable. For each one-liter increase in FEV-1.

Table 4
Multivariate logistic regression analyses of associations between clinicopathological and sociodemographic parameters and 12-month mortality.

	Odds ratio	95 %CI
TNM Stage		
I	Ref	
II	2.42	2.01–2.91
III	3.63	3.14–4.20
IV	11.17	9.70–12.86
Missing	5.22	4.31–6.34
Age group		
Young	Ref	
Elderly	1.59	1.43–1.77
CCI		
0	Ref	
1–2	1.11	1.02–1.20
≥ 3	1.32	1.19–1.47
Surgery	0.23	0.20–0.26
ECOG PS		
0	Ref	
1	1.66	1.52–1.81
2	2.88	2.56–3.23
3	7.32	6.15–8.73
4	19.56	13.19–28.99
Missing	3.22	2.84–3.66
Cohabitation status		
Single	Ref	
Married/cohabitating	0.90	0.84–0.97

TNM = Tumor Node Metastasis 7th edition. CCI = Charlson Comorbidity index ECOG PS = Eastern Cooperative Oncology Group Performance Status.

4. Discussion

Based on our comprehensive and population-based dataset, we have demonstrated that significant adverse prognostic factors, encompassing both patient-related and socioeconomic, are more prevalent within the elderly population of lung cancer patients. The diagnostic intensity appears to be reduced in the elderly group. The elderly patients less frequently undergo curative treatment and have a poorer prognosis.

There have been diverse definitions regarding the characterization of an elderly lung cancer patient, and notably, the age limit for treatment has generally increased over the last decades. This development seems reasonable in light of the improved treatment options, increasing lifespans, and improved health status among the elderly population [22]. We have chosen the cutoff of 80 years since it is in line with other recent studies [23–25].

Regarding the diagnostic process and stage designation, we have not encountered any studies specifically addressing these areas concerning elderly lung cancer patients. Several studies have evaluated the safety and feasibility of undertaking invasive procedures in elderly patients. However, these studies lack comparability due to different age categorizations and different procedures under evaluation. Hence Evison et al. defined elderly as age 70 or above in a single center study of safety and performance of EBUS TBNA. The study included 451, off whom 44 % were elderly and they found that elderly had worse performance status, but similar complication rates and both groups had a diagnostic accuracy above 90 % [26]. In another single center study Ulasli et al. included 317 patients, where older was defined as 65 or above (n = 109) assessing the utility of transbronchial needle aspiration in the two groups and found similar complication rates and diagnostic yield [27]. A single center study focusing exclusively on patients aged 75 or older, assessed the safety and diagnostic yield of transthoracic needle aspiration. In that study, Willey et al. defined elderly as individuals aged 85 or older and found similar diagnostic yield and complication rates [28]. These three references underscore the challenges associated with varying age classifications. In the present study, we are unable to assess safety aspects related to the individual diagnostic procedure. However, to our knowledge, this is the first nationwide study to provide register-based data concerning the diagnostic intensity and even though data presented here may be of lesser accuracy than single center studies, we are able to assess different patterns in clinical practice on a significantly larger scale. Thus, we found that fewer elderly patients receive a final stage designation (missing stage, Table 1) and histopathologic verification, the rates of lung biopsies are similar, but the rates of invasive mediastinal procedures, which is often a preparation for a treatment with curative intent, are lower in the elderly group compared to the younger. The diagnostic intensity appears to be lower in general among elderly stage IV patients, compared to the younger.

Our currently unique findings regarding the diagnostic work-up in elderly patients, should ideally be compared with similar datasets from other countries, if available. This would facilitate benchmarking of diagnostic intensity among these patients and enable monitoring changes in clinical practice over time. To which extent these results reflect hesitancy by the clinicians or refusal by the patients to undergo invasive procedures remain. We have found no studies concerning the later. A recent Danish qualitative study by Christensen et al. concerning patient perspectives in relation to the fast-track lung cancer patient pathway, found that undergoing the lung cancer patient pathway was associated with high levels of anxiety [29]. This aspect might discourage some patients from undergoing unpleasant and potentially risky invasive procedures.

We found that older age is independently associated with not undergoing surgery. Furthermore, we confirmed that other factors that contraindicate surgery such as a high burden of comorbidity and reduced lung function occur more frequently among elderly patients [23,30,31]. Refusal among the elderly to undergo major treatment arguably contribute to differences in treatment patterns, as concluded by a national Taiwanese study by Wang et al. This study also found, consistent with our findings, that comorbidity, advanced stage and low socioeconomic status were associated with treatment refusal, which in turn was associated with an adverse prognosis.

5. Strengths and limitations

This study is the first nationwide study where profound sociodemographic data are merged with clinical information on lung cancer patients. This allows us to obtain an understanding of which aspects are associated with a suboptimal course of disease. We have used highly valid national registries, thereby reducing selection bias to a minimum. There are, however, also limitations to the study. We excluded patients that were not in both databases. The level of disagreement was limited and within the range of what we expected; thus, we do not believe that this has affected the results. We have not been able to verify the register-based data from other data sources, such as medical records or patient interviews, and registration errors could have occurred. However, such errors would need to be of a high magnitude to be able to bias the results, which is unlikely. We have not been able to assess the extent of patient refusal from invasive diagnostic procedures and/or surgical treatment modalities. We were not able to sub-classify non-surgical curative treatment into SBRT vs. chemo-radiotherapy, which could have identified further differences in treatment patterns.

We have encountered varying degrees of missing data, which may have weakened some of the associations that we assessed. Nonetheless, we do not suspect that this has led to information bias, nor has it influenced the direction of the observed associations.

6. Conclusion

Overall, the diagnostic intensity among patients aged eighty years or older and registered with lung cancer is lower than for younger patient. Being elderly is associated with a decreased likelihood of undergoing surgical treatment or receiving treatment with curative intent. Furthermore, older patients were more comorbid, had lower lung functions, lower income, lower level of education and were more frequently living alone. These factors, combined with age exceeding eighty years, consistently contributed to a more unfavorable disease c course and prognosis across all treatment groups.

CRediT authorship contribution statement

Niels Lyhne Christensen: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anja Gouliaev:** Writing – review & editing, Project administration. **Sean McPhail:** Writing – original draft, Supervision, Conceptualization. **Georgios Lyratzopoulos:** Writing – review & editing, Supervision, Conceptualization. **Torben Riis Rasmussen:** Writing – review & editing, Supervision, Data curation. **Henry Jensen:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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