



Early View

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Excess mortality and undertreatment in elderly lung cancer patients: treatment nihilism in the modern era?

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Take home message: Treatment strongly determines lung cancer survival, yet nihilism may threaten treatment provision and survival outcomes. Older patients in this cohort had reduced multidisciplinary presentation, less treatment (OR 0.24) and 28% increased mortality risk.

Abstract

Background: Treatment of elderly patients with lung cancer is significantly hindered by concerns about treatment tolerability, toxicity and limited clinical trial data in the elderly – potentially giving rise to treatment nihilism amongst clinicians. This study aims to describe survival in elderly patients with lung cancer and explore potential causes for excess mortality. **Methods:** Patients diagnosed with lung cancer in the Victorian Lung Cancer Registry between 2011-2018 were analysed (n=3,481). Patients were age-categorised and compared using Cox-regression modelling to determine mortality risk, after adjusting for confounding. Probability of being offered cancer treatments was also determined, further stratified by disease stage. **Results:** The eldest patients (≥ 80 years old) had significantly shorter median survival compared to younger age groups (<60: 2.0 yrs; 60-69: 1.5 yrs; 70-79: 1.6 yrs; ≥ 80 : 1.0 yrs; $p < 0.001$). Amongst those diagnosed with stage 1 or 2 lung cancer, there was no significant difference in adjusted-mortality between age groups. However, in those diagnosed with stage 3 or 4 disease, the eldest patients had an increased adjusted-mortality risk of 28% compared to patients younger than 60 years ($p = 0.005$), associated with markedly reduced probability of cancer treatment, after controlling for sex, performance status, comorbidities and histology type (OR 0.24, compared to <60yo strata, $p < 0.001$). **Conclusion:** Compared to younger patients, older patients with advanced-stage lung cancer have a disproportionately higher risk of mortality and lower likelihood of receiving cancer treatments, even when performance status and comorbidity are equivalent. These healthcare inequities could be indicative of widespread treatment nihilism towards elderly patients.

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1. Introduction

Lung cancer is the most common and lethal cancer worldwide with an estimated 1.76 million deaths in 2018 (1, 2). Age is a significant risk factor for lung cancer mortality, with peak mortality occurring in patients aged 80 years or older (3). Furthermore, the prevalence of cancer in the elderly is increasing, likely as a result of population growth, increased longevity and advances in medical care (4).

Survival following diagnosis may be impacted by patient, disease and treatment related factors. Many patient-related factors, including age, remain implacable - and with increasing age, there is likely to be increasing burden of comorbidity and frailty. Advancing age is strongly associated with poorer performance status, an important predictor of poor prognosis (5, 6). Therefore, careful elicitation of such patient-related factors is an important precedent in identifying treatment suitability.

Access to treatment for the elderly has the potential to be significantly limited by concerns regarding treatment tolerability, potential toxicity, uncertainty about treatment efficacy and nihilism. Estimation of treatment tolerability and toxicity in the elderly is challenging (7). Both renal and liver function are age dependent (8, 9) and pharmacokinetics and pharmacodynamics differ in the elderly compared to their younger counterparts (10). Age related renal impairment may therefore be associated with significant risk of toxicity from traditional chemotherapy (11), and indeed in the over 70 population, rates of severe treatment toxicity in advanced NSCLC have been observed to be doubled following radiotherapy and trebled following chemotherapy or combination chemotherapy and radiotherapy (12).

Concerns around the efficacy of treatment in the elderly may relate to an absence of evidence of efficacy of such treatments in the elderly. Underrepresentation of older patient groups in conventional chemotherapy trials has been long recognised (13) and similar underrepresentation is observed for novel therapeutics including immunotherapies (14). Such concerns are likely to lead to significant diagnostic and therapeutic nihilism causing clinicians to fail to investigate and potentially withhold required treatments due to anticipated regret (15).

A consideration of age is therefore a critical factor in the confirmation of appropriateness in the selection of established, novel and emerging treatments in managing elderly patients with lung cancer. Our study aims to describe treatment patterns in elderly patients, determine differences in mortality and identify risk factors for excess mortality.

2. Methods

Patients

We analysed all patients diagnosed with lung cancer in the Victorian Lung Cancer Registry (VLCR) between 2011 and 2017. The VLCR is a clinical quality registry, collecting information about diagnosis, management and outcomes of individuals newly diagnosed with lung cancer in Victoria (Australia) and providing risk-adjusted benchmarking of quality indicators to participating institutions (16). The VLCR currently captures over 80% of newly diagnosed lung cancers from the state of Victoria from 43 participating hospitals, representative of the majority of public and private hospitals. This study was approved by the Human Research Ethics Committee at Monash University (MUHREC - 22368).

Variables

Variables analysed included: age, sex, ethnicity, comorbidities, comorbid malignancy (excluding skin), performance status, histology, date of diagnosis, presentation at multi-disciplinary meeting, cancer treatment, palliative care referral, survival, and date of death. Ethnicity was coded based on the Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), 2016 (17). Histology was derived from tumour morphology using the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (18). Cancer treatment was defined as surgery, chemotherapy, radiotherapy, immunotherapy or targeted therapy (eg tyrosine kinase inhibitors). Comorbidities assessed by the VLCR are: diabetes, renal insufficiency, myocardial infarction, respiratory disease and neoplastic comorbidity. These illnesses are defined by specific criteria (see Supplemental table 1). Patients with missing data in any of these fields were excluded from analysis.

Statistical analysis

Age at diagnosis was categorised into four groups: <60 years; 60 to 69 years; 70 to 79 years, ≥ 80 years. Relationships between age group and baseline characteristics were assessed using chi-square tests. All-cause mortality was compared between age groups using Kaplan-Meier estimates. We used cox-regression modelling to estimate and compare mortality risk between age groups, after adjusting for confounders (sex, ethnicity, performance status, number of comorbidities, comorbid malignancy, disease stage, histology, cancer treatment).

We also assessed outcomes stratified by disease stage (early versus advanced stage) and compared the probability of receipt of cancer treatment for each age group using logistic regression, adjusting for confounders (sex, number of comorbidities, comorbid malignancy, performance status and histology). We

compared the frequency of patients in each age group who were discussed at multidisciplinary meetings. A sensitivity analysis of the primary outcomes was performed amongst patient excluded from analysis due to incomplete data and compared to the analytical sample. Analyses were performed using STATA version 13.

3. Results

A total of 3,481 patients were analysed. The distribution of age in the study population was: <60y: 679 (19.5%); 60-69y: 1,082 (31.1%); 70-79y: 1,191 (34.2%), ≥ 80 y: 529 (15.2%). The patient, disease and treatment characteristics of each age group is shown in Table 1. Of note, the eldest patient group (≥ 80 yo) tended to have more males, Europeans (and fewer South-East Asians), patients with poorer performance status ($p < 0.001$ for each). Not unexpectedly, older age strata tended to have more comorbidities than younger strata ($p < 0.001$) and the eldest patient group had more patients in early compared to advanced stage disease compared to the youngest patient group ($p = 0.012$). Considerably fewer patients in the eldest patient group received cancer treatment for lung cancer (<60y: 93.2%; 60-69y: 89.0%; 70-79y: 86.6%; ≥ 80 y: 71.8%; $p < 0.001$). A small minority of patients declined any cancer treatment, which increased with age strata (<60y: 16 (2.4%); 60-69y: 39 (3.6%); 70-79y: 44 (3.7%), ≥ 80 y: 40 (7.6%). The eldest patient group also had the highest rate of referral to palliative care (44%) compared to younger age groups (<60y: 27.9%; 60-69y: 26.1%; 70-79y: 29.8%; $p < 0.001$).

The probability of survival after being diagnosed with lung cancer, stratified by age group, is shown in the Kaplan-Meier curve (Figure 1). Median overall survival was progressively shorter with increasing age, (<60y: 2.0y; 60-69y: 1.5y; 70-79y: 1.6y; ≥ 80 y: 1.0y; $p < 0.001$).

Univariate and multivariate analyses were performed to estimate the mortality risk of various patient characteristics, see Table 2. Concordant with Kaplan-Meier estimates, the mortality risk tended to increase with advancing age. After adjusting for other risk factors, multivariate analysis demonstrated that only the eldest age group had an increased risk of all-cause mortality (HR death ≥ 80 yo: 1.31 compared to <60yo age group; $p = 0.001$). As expected, performance status and disease stage were the strongest predictors of mortality. Males, compared to females, also had a 16% increase risk of all-cause mortality, after adjusting for other risk factors. North/Western European, North/Eastern Asian and South/Eastern Asian ethnicity was associated with a significant protective effect on mortality compared to other ethnicities (Table 2), possibly related to treatment-responsive genetic mutations. The number of comorbidities did not significantly predict mortality. Small cell lung cancer and not-otherwise-specified (NOS) lung cancer histology were associated with higher mortality risk compared to other histological subtypes.

In advanced disease, only 63.8% of patients aged ≥ 80 y, were presented for discussion at a multi-disciplinary meeting (Table 3). This was markedly fewer compared to those in other age groups (<60y: 77.0%; 60-69y: 69.5%; 70-79y: 71.6%; $p < 0.001$). There was no statistical difference between age groups presented as a multi-disciplinary meeting in early stage disease.

Crude data demonstrated increased mortality in elderly patients, however for patients with stage 1 or 2 disease at diagnosis there was no significant difference in adjusted-mortality between age groups (see Table

4). In those diagnosed with stage 3 or 4 disease however, the eldest patients had an increased adjusted-mortality risk of 28% compared to patients aged less than 60yo ($p=0.005$). In early stage disease, there was no difference between age groups in the probability of being provided cancer treatments, after controlling for confounders. However, in late stage disease, the adjusted-probability of being provided cancer treatment significantly and progressively fell with increasing age; the eldest age group having an odds ratio of a quarter of those aged less than 60y (OR: 0.24; $p<0.001$).

Sensitivity analysis was performed to evaluate potential bias by patients excluded from primary analysis due to incomplete data ($n=4,199$; 54.7%), finding a poorer median overall survival in the excluded group (sample: 11.9 months vs excluded: 7.4 months, $p=0.011$) and a lower rate of cancer treatment compared to elderly patients in the analysed sample (sample: 71.8% vs excluded: 50.3%, $p<0.001$). We also found a disproportionately higher number of elderly patients that did not have histo-cytological confirmation compared to other age strata (<60y: 1.6%; 60-69y: 3.2%; 70-79y: 4.7%; ≥ 80 y: 14.6%; $p<0.001$).

4. Discussion

The central finding from our study is that elderly patients diagnosed with advanced lung cancer have a 28% excess mortality risk, driven by under-treatment of patients who may have otherwise had a favourable response. This association persists even after controlling for known factors that influence treatment tolerability and response: sex, comorbidities, performance status and histology (5, 19-21). Studies from lung cancer registries in other Western countries, including the United States and Germany, have also demonstrated under-treatment of elderly patients with lung cancer (22) (23). In addition to replicating these findings in an Australian setting, our study identifies high-risk groups within the elderly population who can be targeted for future intervention: those with advanced-stage lung cancer and those not discussed at multidisciplinary meetings.

One potential explanation for less cancer treatment being prescribed for elderly patients is treatment nihilism. Clinicians, family members or patients themselves may perceive treatment at advanced age as futile, especially in the context of incurable disease and significant risk of treatment toxicity. A survey of clinicians involved in care of elderly patients with lung cancer showed that stage was a major factor in determining management (24).

However, treatment of lung cancer in the elderly is not futile, even despite late-stage disease. There are emerging data that modified treatment regimens designed specifically for the elderly can offer better tolerated side-effect profiles whilst still maintaining a survival benefit. *Sigel et al* demonstrated, in a non-randomised study, that radiotherapy alone, compared to best supportive care, improved survival in elderly patients with stage III non-small cell lung cancer (25). However, benefits in mortality were offset by considerable toxicity leading to pneumonitis and oesophagitis requiring hospitalisation. Conversely, *Khor et al* reported a study on tolerability of curative intent radiotherapy in a population aged >85 years, finding 79% of patients completed the prescribed treatment without poor treatment tolerability, and 95% of patients completed all treatment, with poor performance status and age predicting tolerability and survival (26).

Careful patient selection for surgical resection of early stage disease in the elderly suggests that resection can also be performed with short and long-term outcomes consistent with younger cohorts, where sub-lobar resection appears to provide better short term survival and lobectomy better long-term survival (27, 28).

Tyrosine kinase inhibitors (TKI) may also provide a useful adjunct or alternative to chemotherapy. Compared head-to-head with single-agent chemotherapy, Gefitinib had equivalent survival benefit with good tolerability in the elderly (29). Taken together, these findings appear to provide an evolving body of clinical research supporting the delivery of evidence-based treatment of elderly patients with lung cancer. However, our sensitivity analysis shows that there were a disproportionate number of elderly patients who did not have histo-pathological confirmation – far greater than any other age strata. This could potentially limit therapeutic options in this population, particularly with regard to targeted therapies such TKIs, and adversely

affect survival. This is not an uncommon issue in real-life clinical practice; a study of non-small cell lung cancer patients in the National Lung Cancer Audit in England (NLCA) also found disproportionately lower odds of histo-cytological confirmation and anticancer treatment in elderly patients (30). In the modern era of expanded and well-tolerated therapies for lung cancer, histopathological confirmation should be encouraged for all patients, especially those of advanced age.

Despite this, there remains gross under-representation of elderly patients in cancer research (13). An analysis of phase III lung cancer trials in systemic therapy showed that a third of all trials excluded elderly patients and that the mean age of trial participants was nearly a decade younger than the median age of all newly diagnosed lung cancer patients in population-based cancer studies (13, 31). These findings are confirmed in meta-analysis of novel treatments including immunotherapy trials (14).

Self-reported questionnaire data suggests that the vast majority of clinicians view comorbidities and treatment toxicity as the most challenging issues encountered when providing care for elderly patients with lung cancer (24). Unfortunately, there are few decision aids available to help clinicians predict treatment success or failure in elderly patients. Comprehensive geriatric assessment (CGA) is a clinical tool that has been validated to predict mortality and treatment toxicities in elderly patients with cancer by assessing a wide range of health measures (32). A study by *Maione et al* demonstrated a strong association between CGA score and all-cause mortality in non-small cell lung cancer in elderly individuals (33). Furthermore, specific domains of the CGA strongly predicted toxicity to chemotherapy: poor mobility, cognitive impairment, malnutrition, social difficulties and polypharmacy (33). However, despite its clear clinical utility in geriatric oncology, CGA is infrequently used in clinical practice due its timely and resource-intensive nature.

Managing elderly patients with lung malignancy can be challenging in clinical practice. It requires synthesising multiple factors: determining how research is applicable to the individual patient, predicting which treatment regime will provide the optimal quality of life, and ensuring patient autonomy in decision-making. Given these complexities, a multi-disciplinary based approach, which brings together a range of clinical and research expertise, is likely to be highly beneficial. However, our study demonstrates that increasing age was generally associated with lower rates of presentation at a multidisciplinary meeting. Therefore, our central finding of low probability of cancer treatment in the elderly could be, at least in part, due to low levels of multidisciplinary discussion.

Choice of treatment and patient autonomy is important when considering management of elderly patients. In our study, elderly patients appear to have more than double the frequency of declining treatment in our study which could contribute to increased mortality. However, the overall number of study participants who declined treatment was 139, equating to just 4.0% of our study cohort (N=3,481). As such, the contribution of declining treatment to increased mortality in the elderly is likely to be minimal.

One limitation of our study was the narrow spectrum of illnesses used to determine comorbid health in the VLCR. It is possible that clinicians evaluated an individual's fitness for treatment based on health parameters beyond these. However, some studies have demonstrated that comorbidity is poorly predictive of mortality in elderly patients and/or those with advanced stage disease (34-37) although some studies have unsurprisingly demonstrated poorer survival in those with severe comorbidity (38). However, the primary objective of our study was not to analyse the effect of comorbidity on cancer mortality; we used the number of comorbidities merely as a surrogate measure to adjust for confounding in our statistical models, a technique previously used in research literature (39). It is also possible that the natural history of death in elderly patients in the general population contributes to mortality of elderly patients with lung cancer. Unfortunately, our dataset was composed entirely of patients with lung cancer, and thus we were unable to adjust our statistical models for risk of mortality in elderly patients in the general population. However, it has been shown from other studies that mortality between elderly individuals with and without lung cancer is vastly different. *Venuta et al.* noted that life expectancy of patients aged 80 years in the United States is 9.1 years compared to just 14 months for elderly patients with early stage untreated lung cancer (40). The authors concluded that life limitations in this age group are purely related to cancer.

Another limitation of our study was the large number of patients (54.7%) from the VLCR who had missing data and were subsequently excluded from analysis, which may introduce selection bias. Sensitivity analysis of these patients, however, demonstrates even worse survival and under-treatment of the elderly compared to our study subjects. Therefore, our findings are likely to be an under-representation of the true extent of healthcare inequality in the elderly.

5. Conclusion

Compared to younger patients, older patients diagnosed with advanced-stage lung cancer have a disproportionately higher risk of mortality. This is associated with reduced delivery of cancer treatment to older patients, even when performance status and comorbidities are equivalent to younger patients. Possible health care targets for intervention, at an institutional level are; 1) improving culture and reducing stigma and treatment nihilism towards elderly patients; 2) using validated clinical tools to enhance confirmation of suitability of elderly patients for cancer treatment; 3) mandating a multidisciplinary-based approach for all patients, regardless of age or disease stage; and 4) establishing a clinical governance framework that ensures equity in lung cancer care. This study suggests that equitable delivery of lung cancer treatment could lead to improved survival in the elderly.

Table 1. Baseline characteristics by age group

	<60yo (N=679)		60-69yo (N=1,082)		70-79yo (N=1,191)		>80yo (N=529)		Total (N=3,481)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	354	52.1%	609	56.3%	718	60.3%	337	63.7%	2,018	58.0%
Ethnicity										
Oceania	492	72.4%	715	66.1%	722	60.6%	285	53.9%	2,214	63.6%
NW Europe	57	8.4%	191	17.7%	302	25.4%	148	28.0%	698	20.1%
SE Europe	18	2.6%	58	5.4%	74	6.2%	54	10.2%	204	5.9%
N Africa /Middle East	18	2.6%	21	1.9%	29	2.4%	12	2.3%	80	2.3%
SE Asia	45	6.6%	42	3.9%	24	2.0%	9	1.7%	120	3.4%
NE Asia	23	3.4%	20	1.9%	14	1.2%	9	1.7%	66	1.9%
South/Central Asia	12	1.8%	14	1.3%	11	0.9%	9	1.7%	46	1.3%
Americas	8	1.2%	12	1.1%	8	0.7%	1	0.2%	29	0.8%
Sub-Saharan Africa	7	1.0%	8	0.7%	7	0.6%	2	0.4%	24	0.7%
ECOG										
0	328	48.2%	437	40.4%	337	28.3%	108	20.4%	1,210	34.8%
1	272	40.0%	458	42.4%	581	48.8%	237	44.8%	1,548	44.5%
2	59	8.7%	125	11.6%	185	15.5%	105	19.8%	474	13.6%
3	18	2.6%	50	4.6%	80	6.7%	70	13.2%	218	6.3%
4	3	0.4%	11	1.0%	8	0.7%	9	1.7%	31	0.9%
Comorbidities										
Resp	57	8.4%	143	13.2%	192	16.1%	66	12.5%	458	13.2%
Diabetes	45	6.6%	151	14.0%	260	21.8%	106	20.0%	562	16.1%
Renal	6	0.9%	10	0.9%	32	2.7%	10	1.9%	58	1.7%
AMI	22	3.2%	112	10.4%	216	18.1%	137	25.9%	487	14.0%
Comorbid Ca	62	9.1%	185	17.1%	255	21.4%	119	22.5%	621	17.8%
Number of Medical Comorbidities										
0	566	83.2%	741	68.5%	648	54.4%	282	53.3%	2,237	64.3%
1	101	14.9%	274	25.3%	403	33.8%	186	35.2%	964	27.7%
2	10	1.5%	56	5.2%	125	10.5%	50	9.5%	241	6.9%
3	3	0.4%	10	0.9%	13	1.1%	11	2.1%	37	1.1%
4	0	0.0%	0	0.0%	2	0.2%	0	0.0%	2	0.1%
Stage										
1	55	8.1%	130	12.0%	164	13.8%	65	12.3%	414	11.9%
2	55	8.1%	91	8.4%	118	9.9%	50	9.5%	314	9.0%
3	198	29.1%	313	29.0%	352	29.6%	140	26.5%	1,003	28.8%
4	372	54.7%	547	50.6%	557	46.8%	274	51.8%	1,750	50.3%
Histology										
Squamous Cell Ca	93	13.7%	211	19.5%	300	25.2%	126	23.8%	730	21.0%
Adenocarcinoma	426	62.6%	603	55.8%	619	52.0%	277	52.4%	1,925	55.3%
Large Cell Ca	21	3.1%	18	1.7%	21	1.8%	10	1.9%	70	2.0%
NOS	84	12.4%	140	13.0%	130	10.9%	70	13.2%	424	12.2%
SCLC	46	6.8%	87	8.0%	100	8.4%	28	5.3%	261	7.5%

Miscellaneous	10	1.5%	22	2.0%	21	1.8%	18	3.4%	71	2.0%
Cancer Treatment										
Radiotherapy	372	54.7%	516	47.7%	582	48.9%	253	47.8%	1,723	49.5%
Surgery	177	26.0%	279	25.8%	294	24.7%	79	14.9%	829	23.8%
Chemotherapy	489	71.9%	666	61.6%	626	52.6%	140	26.5%	1,921	55.2%
Immunotherapy/TKI	136	20.0%	156	14.4%	125	10.5%	50	9.5%	467	13.4%
Any cancer treatment	634	93.2%	962	89.0%	1,031	86.6%	380	71.8%	3,007	86.4%
Palliative care referral	190	27.9%	282	26.1%	355	29.8%	229	43.3%	1,056	30.3%

HR = Hazard Ratio for mortality, AMI = Acute Myocardial Infarction, Ca = Cancer, ECOG = Eastern Cooperative Oncology Group, SCLC = small cell lung cancer, NOS = not otherwise specified, TKI = tyrosine kinase inhibitors (targeted therapy)

Figure 1. Kaplan–Meier estimate of the probability of survival among patients diagnosed with lung cancer patients, stratified by age

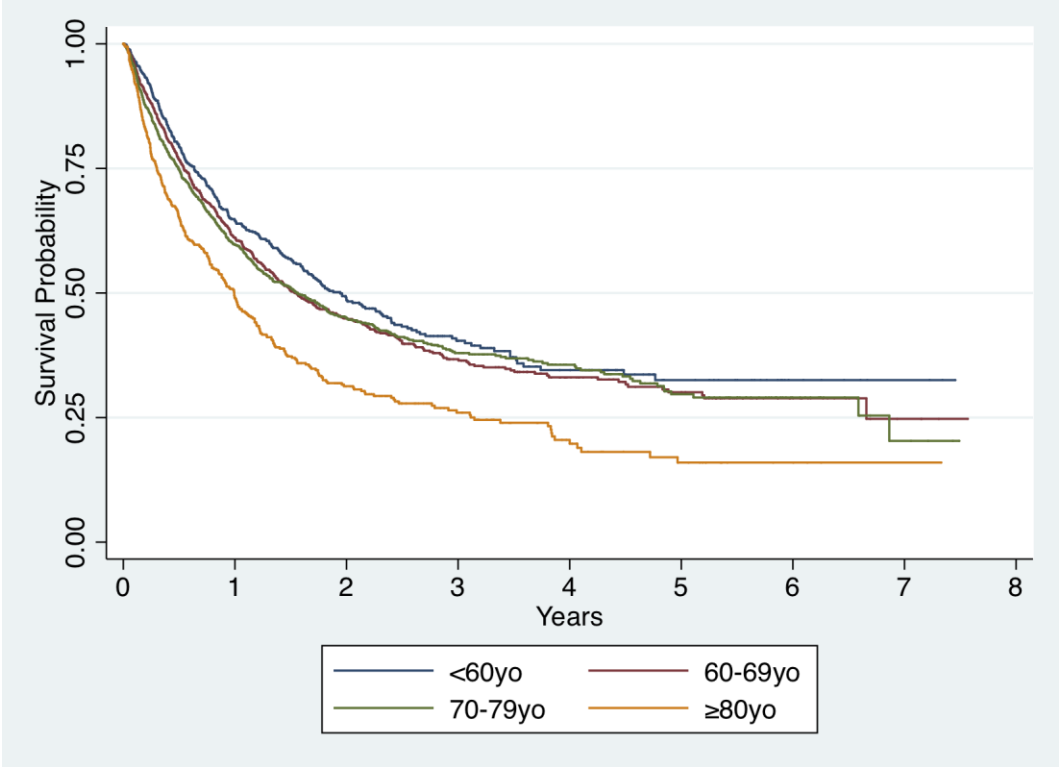


Table 2. Predictors of all-cause mortality.

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p value	HR	(95% CI)	p value
Sex						
Female	<i>ref</i>			<i>ref</i>		
Male	1.20	(1.09, 1.31)	<0.001	1.16	(1.06, 1.28)	0.002
Age Group						
<60	<i>ref</i>			<i>ref</i>		
60-69	1.13	(0.99, 1.29)	0.079	1.09	(0.95, 1.25)	0.238
70-79	1.15	(1.01, 1.31)	0.041	1.07	(0.93, 1.23)	0.324
>80	1.66	(1.43, 1.93)	<0.001	1.31	(1.11, 1.54)	0.001
Ethnicity						
Oceania	<i>ref</i>			<i>ref</i>		
North/West Europe	0.94	(0.84, 1.05)	0.282	0.82	(0.73, 0.93)	0.001
South/East Europe	1.11	(0.92, 1.34)	0.277	1.08	(0.89, 1.31)	0.456
North Africa/Middle East	1.02	(0.75, 1.39)	0.884	1.08	(0.79, 1.47)	0.636
South-East Asia	0.69	(0.52, 0.92)	0.012	0.7	(0.52, 0.93)	0.014
North/East Asia	0.50	(0.33, 0.77)	0.001	0.46	(0.30, 0.70)	<0.001
South/Central Asia	0.71	(0.45, 1.10)	0.122	0.68	(0.44, 1.07)	0.094
Americas	0.72	(0.42, 1.25)	0.245	0.71	(0.41, 1.22)	0.215
Sub-Saharan Africa	0.45	(0.22, 0.90)	0.024	0.59	(0.29, 1.19)	0.141
ECOG						
0	<i>ref</i>			<i>ref</i>		
1	1.67	(1.49, 1.87)	<0.001	1.44	(1.29, 1.62)	<0.001
2	2.91	(2.54, 3.35)	<0.001	2.12	(1.83, 2.45)	<0.001
3	4.27	(3.60, 5.06)	<0.001	2.81	(2.34, 3.37)	<0.001
4	15.85	(10.92, 23.00)	<0.001	9.83	(6.71, 14.41)	<0.001
Number of comorbidities						
0	<i>ref</i>			<i>ref</i>	<i>ref</i>	
1	1.12	(1.01, 1.24)	0.025	1.1	(0.99, 1.22)	0.086
2	1.15	0.96, 1.37)	0.123	1.03	(0.86, 1.24)	0.739
3	1.29	(0.85, 1.94)	0.233	1.01	(0.66, 1.55)	0.967
4	0.66	(0.09, 4.73)	0.683	1.64	(0.23, 11.76)	0.621
Comorbid malignancy						
Not present	<i>ref</i>			<i>Ref</i>		
Present	1.00	(0.89, 1.13)	0.965	1.01	(0.90, 1.14)	0.843
Stage						
1	<i>ref</i>			<i>ref</i>		
2	2.14	(1.60, 2.85)	<0.001	1.93	(1.44, 2.58)	<0.001
3	2.95	(2.32, 3.76)	<0.001	2.59	(2.03, 3.31)	<0.001
4	6.62	(5.25, 8.35)	<0.001	5.6	(4.42, 7.09)	<0.001
Histology						
Squamous cell carcinoma	<i>ref</i>			<i>ref</i>		
Adenocarcinoma	0.94	(0.83, 1.05)	0.284	0.91	(0.80, 1.03)	0.117
Large cell carcinoma	1.12	(0.81, 1.55)	0.501	1.05	(0.76, 1.46)	0.777

NOS	1.46	(1.25, 1.70)	<0.001	1.19	(1.01, 1.39)	0.009
SCLC	1.50	(1.26, 1.79)	<0.001	1.27	(1.06, 1.52)	0.037
Miscellaneous	1.38	(1.01, 1.88)	0.040	0.94	(0.68, 1.30)	0.706
Any Cancer Treatment						
No	<i>ref</i>			<i>ref</i>		
Yes	0.41	(0.36, 0.46)	<0.001	0.57	(0.50, 0.64)	<0.001

HR = Hazard Ratio for mortality, ref = reference group, ECOG = Eastern Cooperative Oncology Group, SCLC = small cell lung cancer, NOS = not otherwise specified

Table 3. Patients presented at multidisciplinary meeting, stratified by stage and age

Age Group	Stage 1 and 2 Disease			Stage 3 and 4 Disease			All Stages		
	n	%	p value	n	%	p value	n	%	p value
<60y	100	90.9%	0.07	439	77.0%	<0.001*	539	79.3%	<0.001*
60-69y	182	82.4%		598	69.5%		780	72.2%	
70-79y	227	80.5%		651	71.6%		878	73.7%	
>80y	91	79.1%		266	64.3%		357	67.1%	
All age groups	600	82.4%		1,952	70.9%		2,552	73.3%	

Table 4. Probability of cancer treatment and death, stratified by stage and age

Stage 1 and 2 Lung Cancer at Diagnosis

Age Group	Odds Ratio*			Hazard Ratio**		
	(Cancer treatment)	(95% CI)	p value	(Death)	(95% CI)	p value
<60y	ref			ref		
60-69y	1.25	0.29, 5.44	0.769	0.84	0.50, 1.40	0.497
70-79y	1.61	0.37, 6.95	0.522	0.97	0.59, 1.58	0.887
>80y	0.54	0.12, 2.41	0.423	1.29	0.75, 2.21	0.354

Stage 3 and 4 Lung Cancer at Diagnosis

Age Group	Odds Ratio*			Hazard Ratio**		
	(Cancer treatment)	(95% CI)	p value	(Death)	(95% CI)	p value
<60y	ref			ref		
60-69y	0.61	0.38, 0.97	0.036	1.12	0.97, 1.29	0.119
70-79y	0.46	0.29, 0.73	0.001	1.05	0.91, 1.22	0.485
>80y	0.24	0.15, 0.38	<0.001	1.28	1.08, 1.51	0.005

* After adjusting for sex, performance status, number of comorbidities and histology.

** After adjusting for sex, ethnicity, performance status, number of comorbidities, comorbid cancer and histology.

ref = reference group, CI = confidence interval

Supplemental Table 1. VLCR definitions of comorbidity

Disease	Definition
Diabetes	Patients receiving oral hypoglycaemic drugs or insulin
Renal insufficiency	Creatinine of greater than 200umol/L or renal replacement therapy
Myocardial infarction	Non-ST elevation myocardial infarction (NSTEMI) or an acute cardiac event requiring coronary intervention (including coronary artery stents, angioplasty, coronary artery bypass grafting).
Respiratory comorbidity	respiratory illness where spirometry demonstrates a forced expiratory volume in 1 second (FEV1) of less than 66% predicted
Neoplastic comorbidity	Patients who have recently been diagnosed or have a past history of cancer other than lung cancer but excluding cutaneous basal or squamous cell carcinoma.

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