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Effect of adherence to treatment guidelines on overall survival in elderly non-small-cell lung cancer patients

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ABSTRACT

Objectives: Mean age at diagnosis of lung cancer is increasing with increasing age in Western populations. The present study was designed to evaluate the effect of adherence to first-line treatment guidelines on overall survival (OS) in elderly patients with non-small-cell lung cancer (NSCLC) and reasons for non-adherence to treatment guidelines.

Materials and methods: All patients aged ≥ 65 years diagnosed with NSCLC in Ostrobothnia, Finland, during the years 2016 to 2020 were identified from hospital registries. Adherence of first-line treatment to contemporary treatment guidelines was analysed based on diagnosis, tumour stage and performance status (PS), as was the effect of adherence on OS.

Results: A review of hospital registries identified 238 NSCLC patients aged ≥ 65 years. Guideline adherence by stage decreased significantly with age, with 66.4% of patients aged 65 to 74 years, but only 33.3% of those aged > 80 years treated according to guidelines ($p < 0.001$). Other factors associated with non-adherence to guidelines included poor PS, frailty, and limited lung function. Of the patients with PS 0–2, 26.9% were under-treated according to guidelines. Reasons for under-treatment included comorbidities, decreased lung function, physician decision to reduce treatment intensity or recommend best supportive care, patient choice and PS decline before treatment initiation. Guideline adherence increased overall OS of elderly NSCLC patients in all stages. Elderly PS 2 patients appear to benefit from guideline adherence and active treatment. In contrast, active treatment did not benefit patients with PS 3–4.

Conclusions: Guideline adherence was associated with increased OS in elderly NSCLC patients. Almost 10% of elderly and otherwise fit NSCLC patients were not treated according to guidelines and could have benefitted from more intensive treatment.

1. Introduction

Lung cancer in 2020 was the second most common type of cancer diagnosed and the leading cause of cancer deaths worldwide, with 1.8 million deaths. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers, with a high mean age at diagnosis, including over 50% of NSCLC patients being aged > 65 years at diagnosis [1]. Nevertheless, randomised controlled trials, which provide the basis for current treatment guidelines, have mostly included younger patients [2–5]. Patients in clinical trials usually have better performance status (PS) than real-world patients treated in ordinary clinical practice. Research on how new treatment modalities reach and benefit elderly and sometimes frail NSCLC patients is limited.

Lung cancer treatment guideline recommendations are based on performance status (PS), tumour stage and tumour type. A recent review concluded that treatment should be guided by patient characteristics, not by age [6]. The 2017 Finnish lung cancer guidelines do not include the most recent types of treatment. Most Finnish physicians diagnosing and treating lung cancer follow the most recent international guidelines, such as those of the European Society for Medical Oncology (ESMO),

Abbreviations: PS, performance status; OS, overall survival; CFS, clinical frailty scale; SBRT, stereotactic body radiotherapy.

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with additional viewpoints adapted from the National Comprehensive Cancer Network (NCCN) and the American College of Chest Physicians (ACCP) [7–9].

The Vaasa Central Hospital district in Finland includes a large subpopulation of elderly lung cancer patients receiving active treatments. The association of treatment outcomes with adherence to national and international guidelines has not been determined in elderly NSCLC patients. This study was designed to evaluate the effects of adherence to real-world treatment guidelines on patient survival, to determine the percentage of these patients being under-treated exists, and to evaluate the reasons for non-adherence to international guidelines in elderly NSCLC patients.

2. Materials and methods

2.1. Study population

The database of Vaasa Central Hospital was searched to identify NSCLC patients aged ≥ 65 years with an ICD-10 diagnosis code of C34 during the years 2016 to 2020. Vaasa Central Hospital is a tertiary centre for lung cancer patients, with a Department of Pulmonary Medicine for diagnosis and a Department of Oncology for radiotherapy and medical treatments with more than ten physicians working with lung cancer. Lung cancer surgery is performed at the Central Hospital of Central Finland in Jyväskylä [10].

2.2. Patient, tumour and treatment characteristics

Patient characteristics were obtained from hospital files. These characteristics included age, sex, and medical history. Occupation was classified by International Standard Classification of Occupations (ISCO) skill level, with occupations at skill levels 1 and 4 having the lowest and highest levels of education, respectively [11]. Validated tools for evaluation included the Clinical Frailty Scale [12], the Charlson Comorbidity Index (CCI) [13,14], and World Health Organisation [WHO] PS. A body mass index (BMI) ≥ 30 kg/m^2 was defined as the cut-off for obesity. In classifying smoking status, patients were defined as never smokers if they had smoked less than one pack during their lifetime; as ex-smokers if they had quit smoking >1 year earlier; and as current smokers if they had quit within the previous year or were still smoking. Tumour characteristics included pathological diagnosis, mutation status and clinical stage according to latest TNM classification (8th) [15]. First-line primary treatment was classified as best supportive care, surgery, stereotactic body radiotherapy (SBRT), radiotherapy, chemoradiotherapy, chemotherapy, immunotherapy, targeted therapy, or combinations of these treatments. The main clinical outcome variable was OS, obtained from the Finnish Death Registry. Deaths were classified as due to cancer or of other causes. The follow up ended on 15 October 2021.

Two aspects of guideline adherence were analysed. First, treatment was classified as adherent to guidelines or as under- or over-treatment by comparing actual treatment with the recommendations for each TNM stage of NSCLC. Comparisons were assessed by two independent observers, with any disagreements resolved by consensus after discussion with a senior consultant (HA). Guideline adherence according to TNM stage was evaluate retrospectively by comparisons with contemporary international guidelines, including ESMO, NCCN, and ACCP guidelines, and the latest (2017) Finnish guidelines [7–9,16,17]. The minimum limits for guideline adherence by stage are summarised in Table 1.

Second, the reasons for treatment divergence from guidelines were determined by analysing individual patient files. Patients were classified into five groups based on PS and adherence to guidelines. Patients with PS 3–4 receiving active treatment in PS 3–4 were classified as (1) being over-treated or (2) receiving best supportive care, including palliative radiotherapy. Patients with PS 0–2 were classified either as (3) being treated according to guidelines, (4) being under-treated, defined as treatment intensity below guidelines or (5) being over-treated, defined as treatment intensity above guidelines.

Table 1
Minimum intensity treatment for each stage of NSCLC to be considered guideline adherent.

Stage I	Surgery was the primary recommendation, although SBRT was considered an option if surgery was associated with too high risk. Adjuvant chemotherapy was recommended for stage IB or when the tumour was > 4 cm; and postoperative radiotherapy was indicated if operation margins were positive and additional resection impossible.
Stage II	Surgery was the primary recommendation, followed by recommended adjuvant chemotherapy. Chemoradiotherapy was an option if surgery was associated with too high risk.
Stage III	Surgery was the primary recommendation, accompanied by neoadjuvant or adjuvant therapy. Chemotherapy was recommended if the tumour was not resectable or surgery was associated with too high risk; e.g. N2 positive tumours. Chemoradiotherapy was also the primary recommendation for stage IIIB. Individualised multimodal treatment was also considered guideline adherent.
Stage IV	Recommendations included targeted therapy, immunotherapy, chemotherapy, or their combinations. The use of a single chemotherapy agent or reduced doses was not considered undertreatment.

Reasons that treatment intensity was lower than recommended in guidelines were determined by reviewing patients' medical files. Reasons for non-adherence to guidelines were classified as PS 0–1 and age, PS 2 and age, patient preference, comorbidities, low lung function, PS decline and disease progression before the start of treatment.

2.3. Statistical analysis

All data were analysed with IBM statistics SPSS 27 software (IBM, Armonk, NY, USA). Adherence to guidelines compared in groups of patients using chi-square tests and z-tests. Guideline adherence was analysed in age cohorts with 5-year intervals. A P-value < 0.05 was considered statistically significant.

Survival was analysed using Cox regression and Kaplan–Meier survival analyses, with groups compared by log-rank tests with hazard ratios (HR). Median OS was determined, along with 95% confidence intervals (95% CI). Guideline adherence association to survival was analysed in multivariable cox proportional hazard analyses.

The odds ratios (ORs) of receiving guideline adherent treatment compared with non-adherent treatment according to tumour stage were calculated using binary logistic regression analyses. These crude analyses identified factors associated with guideline-based treatment, which were subsequently included in binary multivariate analysis. ISCO skill level, forced expiratory volume in 1 s (FEV1) and BMI were not included in the adjusted analysis because of missing data. Due to their similarity, PS and was not included in the analysis of clinical frailty scale (CFS), and CFS was not included in the analysis of PS.

3. Results

3.1. Patient characteristics

A total of 238 NSCLC patients aged ≥ 65 years were evaluated for first-line treatment at Vaasa Central Hospital during the years 2016 to 2020 (Fig. 1). This population-based cohort includes all, also frailest patients in the area. Patient characteristics are presented in Table 2. Of these patients, 155 (65.1%) were men and 83 (34.9%) were women, with a median age of 75 years (65 to 93 years). One hundred patients (42.0%) classified as PS 1, whereas 45 (18.9%) were classified as PS 3–4, indicating severely impaired PS, and 39 (16.5%) were classified as CFS 7–9, indicating severe frailty. Thirty-seven (15.5%) patients had a CCI index ≥ 3, and 192 (91.0%) had an ISCO skill level ≤ 2, indicating a low

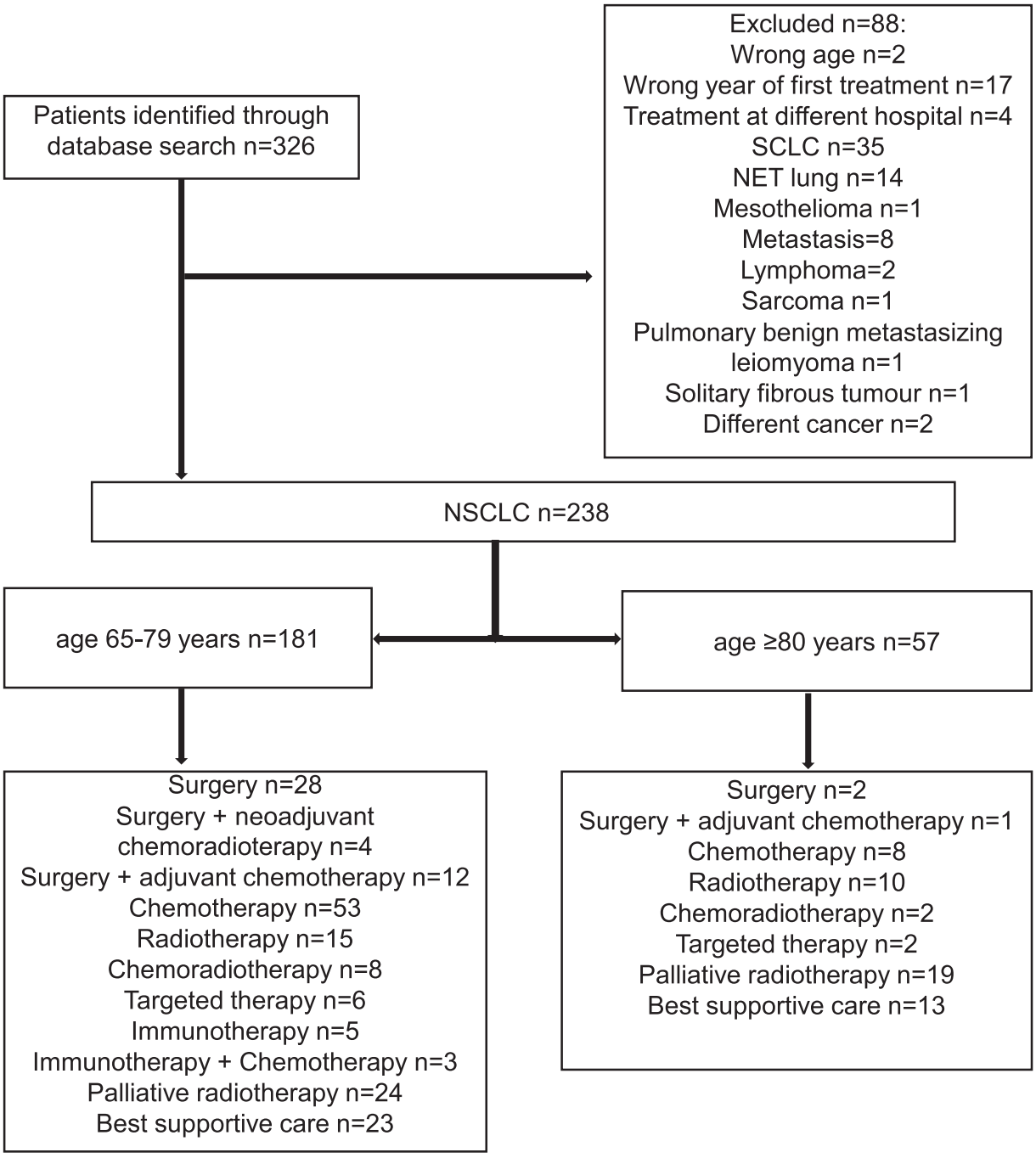

Fig. 1. Flow chart of the study and treatment modalities in NSCLC patients aged 65–79 and ≥ 80 years.

socioeconomic status based on occupation. Most patients were smokers, with only 32 (13.4%) being never smokers. Of these patients, 109 (45.8%) were diagnosed with stage I–III disease, indicating that curative therapy was a possibility. At the time of treatment-decision 219 (92.0%) had histological diagnosis and of those 188 (85.8%) had molecular diagnosis.

Treatment activity decreased with increasing stage, from 100% to 52.7%, with actual treatments in age group described in Fig. 1. For example, immuno-oncology (IO) treatments were administered only to the younger age group, and the percentage of patients receiving surgery, adjuvant and neoadjuvant treatments decreased with increasing age. Fig. 2 shows the proportion of patients in each age group receiving stage-based guideline adherent and non-adherent treatment. These percentages became equal in patients aged 80–84 years, with adherence to guidelines significant decreasing with age ($p = 0.001$).

3.2. Factors associated with guideline adherence

Adjusted multivariable logistic regression analysis showed that factors associated with guideline adherence by stage included age, PS, CFS, and FEV1 (Table 3). ORs for adherence to guidelines were lower in patients aged ≥ 85 than in those aged 65–69 years (OR 0.13; 95% CI: 0.03–0.61); in patients with PS 2 (OR 0.16; 95% CI: 0.07–0.34) and PS 3–4 (OR 0.02; 95% CI: 0.01–0.06) compared with PS 0–1; in patients with CFS 5–6 (OR 0.10; 95% CI:0.03–0.27) and CFS 7–9 (OR 0.03; 95% CI: 0.01–0.12) compared with CFS 1–2; and in patients with FEV1 < 50% (OR 0.13 95% CI: 0.03–0.56) compared with FEV1 ≥ 50%. ISCO skill level, CCI–index, obesity and year of diagnosis were not associated

Table 2
Demographic and clinical characteristics of NSCLC patients aged ≥ 65 years in Vaasa Central Hospital district between 2016 and 2020.

	Patients (N = 238)
Sex	
Male	155 (65.1%)
Female	83 (34.9%)
Median age at start of treatment (range), yr	75 (65 to 93)
WHO PS	
0	21 (8.8%)
1	100 (42.0%)
2	72 (30.3%)
3	42 (17.6%)
4	3 (1.3%)
Clinical frailty scale	
1	7 (2.9%)
2	40 (16.8%)
3	44 (18.5%)
4	48 (20.2%)
5	29 (12.2%)
6	31 (13.0%)
7	33 (13.9%)
8	3 (1.3%)
9	3 (1.3%)
Charlson comorbidity index	
0	54 (22.7%)
1	76 (31.9%)
2	71 (29.8%)
3	18 (7.6%)
≥4	19 (7.9%)
ISCO skill level	
1	39 (18.5%)
2	153 (72.5%)
3–4	19 (9.0%)
Smoking history	
Never smokers	32 (13.4%)
Ex-smokers	124 (52.1%)
Current smokers	82 (34.5%)
T-stage	
T1a	6 (2.5%)
T1b	26 (10.9%)
T1c	14 (5.9%)
T2a	41 (17.2%)
T2b	25 (10.5%)
T3	55 (23.1%)
T4	71 (29.8%)
N-stage	
N0	77 (32.4%)
N1	29 (12.2%)
N2	73 (30.7%)
N3	59 (24.8%)
M-stage	
M0	109 (45.8%)
M1a	52 (21.8%)
M1b	15 (6.3%)
M1c	62 (26.1%)
Stage	
I	45 (18.9%)
II	16 (6.7%)
III	48 (20.2%)
IV	129 (54.2%)
Percentage of active treatment per stage	
I	45 (100.0%)
II	14 (87.5%)
III	32 (66.7%)
IV	68 (52.7%)
Histology	
Adenocarcinoma	148 (62.2%)
Squamous cell carcinoma	69 (29.0%)
Other	2 (0.8%)
Unknown, biopsy not available	19 (8.0%)

Data are reported as n (%) or median (range).

with guideline adherence by stage.

3.3. Patterns of guideline non-adherence for each stage

Of the 238 patients in the study cohort, 193 (81.1%) were diagnosed with PS 0–2, including 123 (51.7%) who received guideline-adherent treatment, six (2.5%) who received higher intensity treatment and 64 (26.9%) who were undertreated. Most patients with PS 3–4 were treated according to guidelines with best supportive care, which included palliative radiotherapy when needed. However, five patients (2.1%) with PS 3–4 were overtreated according to international guidelines.

Analysis of the 64 undertreated patients with PS 0–2 identified six different patterns (Fig. 3). Of these 64 patients, 22 (34.4%) had PS 0–1. Only two resectable patients fit for surgery were not treated because of patient preference. Some elderly patients had living wills, specifying that they receive best supportive care rather than active treatment. Physicians did not recommend treatment for PS 2 patients with comorbidities, especially for those with low lung function. However, these patients were not evaluated by stair climbing or spiroergometric tests. Physicians seemed to choose lower intensity systemic treatment rather than chemoradiotherapy for older patients with stage III NSCLC. During the delay between diagnosis and the start of treatment, 17 patients showed disease progression with a decline in, PS, precluding any active treatment.

3.4. Guideline adherence and survival

The median OS in this patient cohort was 12.5 months (95% CI: 9.9–15.2 months). Of these 238 patients, 121 (50.8%) survived >1 year, women and men having the same 1-year survival rates (50.6% vs 51.0%, $p = 0.957$). OS differed significantly in patients at all stages who did and did not receive guideline-adherent treatment. Comparisons of patients who received guideline-adherent and non-adherent treatments showed that the median OS in stage I–II patients was 63.2 months (95% CI: 48.3 months-NR) and 26.5 months (95% CI: 10.9–42.1 months), respectively; the median OS in stage III patients was 42.2 months (95% CI: 8.1–76.4 months) and 11.5 months (95% CI: 8.2–14.8 months), and the median OS in stage IV patients was 11.0 months (95% CI: 7.3–14.7 months) and 1.4 months (95% CI: 0.6–2.3), respectively ($p < 0.001$ each).

In Cox regression survival analysis, guideline adherence for stage was associated with increased survival in univariate (HR 0.28; 95% CI: 0.21–0.39) and in multivariable (HR 0.44; 95% CI: 0.29–0.67) proportional hazard model adjusted to age, sex, PS, and stage.

PS 0–2 patients were classified into those who received guideline adherent treatment, high-intensity treatment, and under-treatment, and PS 3–4 patients were classified into those who received guideline-adherent best supportive care and over-treatment (Fig. 3). Cox survival analyses showed that PS 0–2 patients who received high intensity treatment had the best prognosis and that the prognosis of PS 0–2 patients who received guideline-adherent treatment did not differ from those who received high-intensity (hazard ratio [HR] 2.2; 95% CI: 0.5–9.1). Compared with guideline-adherent PS 0–2 patients, undertreated PS 0–2 patients had a poorer prognosis (HR 6.3; 95% CI: 1.5–26.0). Overtreated PS 3–4 patients (HR 12.1; 95%CI: 2.3–63.5) had a similar prognosis as PS 3–4 patients who received best supportive care (HR 17.5; 95% CI: 4.2–73.9) (Fig. 4).

4. Discussion

The optimal treatment of elderly frail patients with NSCLC has not been determined, especially as Western populations' age and treatment alternatives have increased. Treatment selection is based on tumour stage, histology and mutational profile as well as patient characteristics, including PS. Individualized treatments are given according to detailed treatment guidelines. In the present study, 26.9% of patients received guideline non-adherent treatment after adjustment for PS. About one-

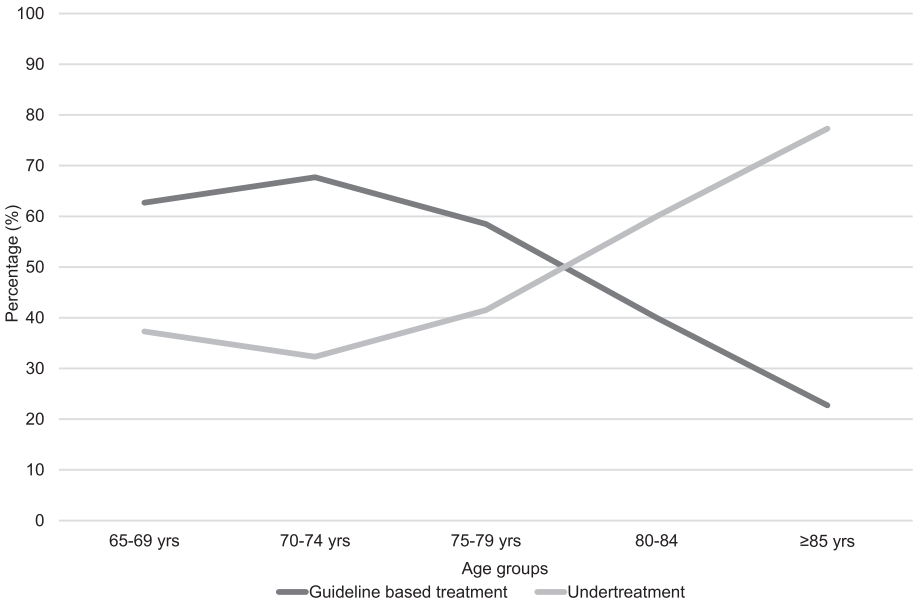

Fig. 2. Association of guideline adherent treatment based on tumour stage with patient age.

third might have benefitted from more intensive treatment and even greater number from a more rapid diagnostic process and rehabilitation before treatment evaluation. This population-based retrospective study showed that guideline adherent treatment increased OS in elderly patients with all stages of NSCLC.

Of the patients in this study, only 56% received guideline adherent treatment according to stage. Similarly, only 59% of surgically treated stage II–III NSCLC patients of all age groups received adjuvant chemotherapy, with the major cause of non-adherence to guidelines being unfit clinical condition [18]. That study also reported that most stage IIIB patients did not receive chemoradiotherapy. Compared with historical reports, guideline adherence among elderly patients has been lower, with a study in veterans aged > 65 years reporting that 51% with local disease, 35% with regional disease and 27% with metastatic disease received first-line treatment adherent to guidelines [19]. Another study reported that 66% of patients of all ages received guideline adherent treatment, and that under-treatment was associated with high stage and PS 2 [20]. Diagnoses and stagings made inconsistent with guidelines has been reported in patients with stage III NSCLC [21]. To avoid, inconsistent diagnosis we have an early multidisciplinary meeting that plans diagnostic tests such as position emission tomography, brain scans, combined systematic endoscopic ultrasound staging, and large-scale molecular tests. Treatment decisions including postoperative treatment are discussed in a weekly multidisciplinary meeting with a check list referral. Adjuvant immunotherapy following chemoradiotherapy has become a standard treatment for selected patients with stage III disease and is included in current treatment guidelines [22]. However, adherence to this recommendation among elderly patients remains to be investigated as it has not yet been generally implemented in Finland and was not included in guidelines available in 2016 when the first patients in this retrospective cohort were treated.

Non-respiratory comorbidities did not decrease guideline adherence. Moreover, most observed comorbidities were chronic and being treated. Occupational skill level did not significantly affect the likelihood of receiving guideline adherent treatment, in contrast to an earlier report, which found that lower educational level and residence in a rural county were associated with a lack of adherence to guidelines in patients with stage III NSCLC [23]. In our study population, only 9.0% of the NSCLC patients had a high occupational level, a much lower percentage than in the general population of Ostrobothnia [24].

The strengths of this study were an unselected population-based cohort including the frailest and severely affected patients and comprehensive overview of the diagnostic and treatment pathways. The year of treatment was not associated with adherence to guidelines, even during 2020, indicated that the ongoing covid-19 pandemic had no effect in Ostrobothnia. No structural changes to the lung cancer process were made during the study period. The lung cancer team consists of more than ten physicians attending to weekly multidisciplinary meetings. The experience and personal preferences of treating clinicians may affect treatment choice to a greater degree in frail elderly patients with comorbidities. Owing to retrospective setting reasons to guideline-non-adherence were limited to those reported by a physician. Approximately 100 patients per year in the area of Vaasa Central Hospital have a new lung cancer diagnosis lung cancer, with about 20% eligible for surgery. The 5-year OS rate of lung cancer patients in Finland was 15% in 2018, including 23% of patients aged 0–54 years, 15% in patients aged 55–74 years, and 8% in patients aged ≥ 75 years [25]. These age-associated differences in OS rates suggest the possibility of age-related inequalities in NSCLC care. Although OS rates of all lung cancer patients are improving in all Nordic countries, they vary among these countries and being higher in women than men [26]. The 1-year OS rate of elderly NSCLC patients in Ostrobothnia was higher than the 1-year OS rate for all age groups throughout Finland.

Guideline adherence was associated with increased OS at all stages, especially in patients with PS 0–2 and early-stage disease. Treatment intensity should be based on PS and frailty. For example, active treatment had no survival benefit compared with best supportive care in PS 3–4 patients, and results in patients with stage IV tumours indicated that over-treatment may harm the frailest patients. Guideline adherence is associated with the quality of care and decreases inequalities based on an objective assessment of disease. In agreement with previous findings [27], guideline adherence decreased with increasing age ($p = 0.001$), as older patients are less likely to undergo surgery, radiotherapy, chemotherapy, and combination treatment than younger patients [28]. For example, a study of 36,203 NSCLC patients aged > 65 years found that surgery decreased with age in patients with stage I tumours and surgery and adjuvant chemotherapy or chemoradiotherapy decreased with age in patients with stage III disease [27].

High intensity treatment of patients with stages I–III did well. Based on 2017 Finnish guidelines, these patients were over-treated, emphasizing the importance of updating guidelines based on new information. Diagnostic procedures and subsequent lung cancer treatment have

Table 3
Odds ratios (OR) of receiving guideline adherent treatment based on stage compared with non-adherent treatment in elderly patients diagnosed with non-small-cell lung cancer (NSCLC) in Ostrobothnia, Finland, between 2016 and 2020.

	Guideline adherent		Guideline non-adherent		P-value	Crude		Adjusted	
	n	(%)	N	(%)		OR	(95% CI)	OR	(95% CI)
Sex					0.866				
Male	86	(55.5)	69	(44.5)		Reference		Reference[A]	
Female	47	(56.6)	36	(43.4)		1.05	(0.61–1.79)	0.74	(0.32–1.69)
Age at diagnosis, years					0.001				
65–69	32	(62.7)	19	(37.3)		Reference		Reference[A]	
70–74	43	(66.2)	22	(33.8)		1.24	(0.58–2.69)	1.36	(0.49–3.81)
75–79	39	(60.0)	26	(40.0)		0.84	(0.39–1.77)	1.13	(0.41–3.10)
80–84	14	(40.0)	21	(60.0)		0.40	(0.16–0.96)	0.54	(0.16–1.79)
≥85	5	(22.7)	17	(77.3)		0.18	(0.06–0.56)	0.13	(0.03–0.61)
Year of diagnosis					0.616				
2016	24	(51.1)	23	(48.9)		Reference		Reference[A]	
2017	26	(66.7)	13	(33.3)		1.92	(0.80–4.61)	2.30	(0.74–6.74)
2018	27	(51.9)	25	(48.1)		1.04	(0.47–2.28)	1.69	(0.59–4.83)
2019	23	(54.8)	19	(45.2)		1.16	(0.50–2.67)	2.05	(0.66–6.45)
2020	33	(56.9)	25	(43.1)		1.27	(0.58–2.74)	1.60	(0.60–4.28)
WHO PS					<0.001				
0–1	99	(81.8)	22	(18.2)		Reference		Reference[A]	
2	30	(41.6)	42	(58.3)		0.16	(0.08–0.31)	0.16	(0.07–0.34)
3–4	4	(8.9)	41	(91.1)		0.02	(0.01–0.07)	0.02	(0.01–0.06)
CFS					<0.001				
1–2	37	(78.7)	10	(21.3)		Reference		Reference[B]	
3–4	68	(73.9)	24	(26.1)		0.77	(0.33–1.77)	0.72	(0.27–1.88)
5–6	20	(33.3)	40	(66.7)		0.14	(0.06–0.33)	0.10	(0.03–0.27)
7–9	8	(20.5)	31	(79.5)		0.07	(0.03–0.20)	0.03	(0.01–0.12)
CCI					0.278				
0	36	(66.7)	18	(33.3)		Reference		Reference[A]	
1	42	(55.3)	34	(44.7)		0.62	(0.30–1.27)	1.10	(0.43–2.84)
2	34	(47.9)	37	(52.1)		0.46	(0.22–0.96)	0.86	(0.32–2.30)
3–4	18	(60.0)	12	(40.0)		0.75	(0.30–1.89)	1.93	(0.52–7.16)
≥5	3	(42.9)	4	(57.1)		0.38	(0.08–1.86)	0.31	(0.05–2.03)
BMI, kg/m^2					0.557				
<30	100	(63.3)	58	(36.7)		Reference		Reference[D]	
≥30	22	(68.8)	10	(31.2)		1.28	(0.57–2.88)	1.27	(0.41–3.97)
ISCO skill level					0.488				
1	22	(57.9)	16	(42.1)		Reference		Reference[E]	
2	83	(54.2)	70	(45.8)		0.86	(0.42–1.77)	1.57	(0.56–4.41)
3–4	13	(68.4)	6	(31.6)		1.58	(0.49–5.04)	1.92	(0.39–9.33)
FEV1					<0.001				
≥50	90	(76.9)	27	(23.1)		Reference		Reference[C]	
<50	10	(41.7)	14	(58.3)		0.12	(0.09–0.54)	0.13	(0.03–0.56)
Smoking status					0.728				
Never smokers	18	(56.3)	14	(43.8)		Reference		Reference[C]	
Ex-smokers	72	(58.1)	52	(41.9)		1.01	(0.49–2.36)	1.05	(0.32–3.38)
Current smokers	43	(52.4)	39	(47.6)		0.86	(0.38–1.95)	0.53	(0.14–1.92)

*data missing on FEV1 for 97 patients, on ISCO for 28 patients, and on BMI for 48 patients.
A Adjusted for sex, age, treatment year, PS, CCI, and smoking status.
B Adjusted for sex, age, treatment year, CFS, CCI, and smoking status.
C Adjusted for sex, age, treatment, year, PS, CCI, smoking status and FEV1.
D Adjusted for sex, age, treatment year, PS, CCI, smoking status and BMI.
E Adjusted for sex, age, treatment year, PS, CCI, smoking status and ISCO.

improved markedly over the last decade [29–31]. Mini-invasive video-assisted thoracoscopy (VATS) surgery has reduced perioperative morbidity and mortality rates, allowing a higher percentage of elderly high-risk patients to undergo surgical treatment [30,31]. In addition, advances in SBRT have improved the possibilities of curative treatment with limited toxicity in the most fragile patients [29,32]. Compared with radiotherapy alone, intensive treatments such as chemoradiotherapy for locally advanced disease may improve OS in elderly patients [33]. Although chemotherapy has been the standard treatment for advanced lung cancer, new insights into lung cancer biology have improved treatments for distinct molecular subtypes of NSCLC [6]. Recent advances include targeted therapies, immunotherapy [34] and chemo-immunotherapy [35].

Better guideline adherence to functional assessment prior to curative treatment, such as surgery and radiotherapy, may allow the selection of elderly patients for treatment. The stair climbing test is a simple way to evaluate risk before surgery among elderly NSCLC patients with low FEV1 [31]. The ability of this test to evaluate risk evaluation before other treatment modalities such as chemoradiotherapy has not been determined. Prehabilitation of intermediate risk patients may also increase the number of elderly NSCLC patients eligible for curative treatment. Preoperative pulmonary rehabilitation has been shown to reduce morbidity and mortality risks in frail NSCLC patients [36]. Postoperative exercise and high-intensity training have also been shown to reduce morbidity and mortality rates. For example, high-intensity endurance and strength training resulted in clinically significant improvements in peak oxygen uptake and quality of life following lung cancer surgery [37]. A study addressing daily exercise before chemoradiotherapy showed that moderate-to-high intensity cycle ergometer exercise was well-tolerated by patients with locally advanced NSCLC [38].

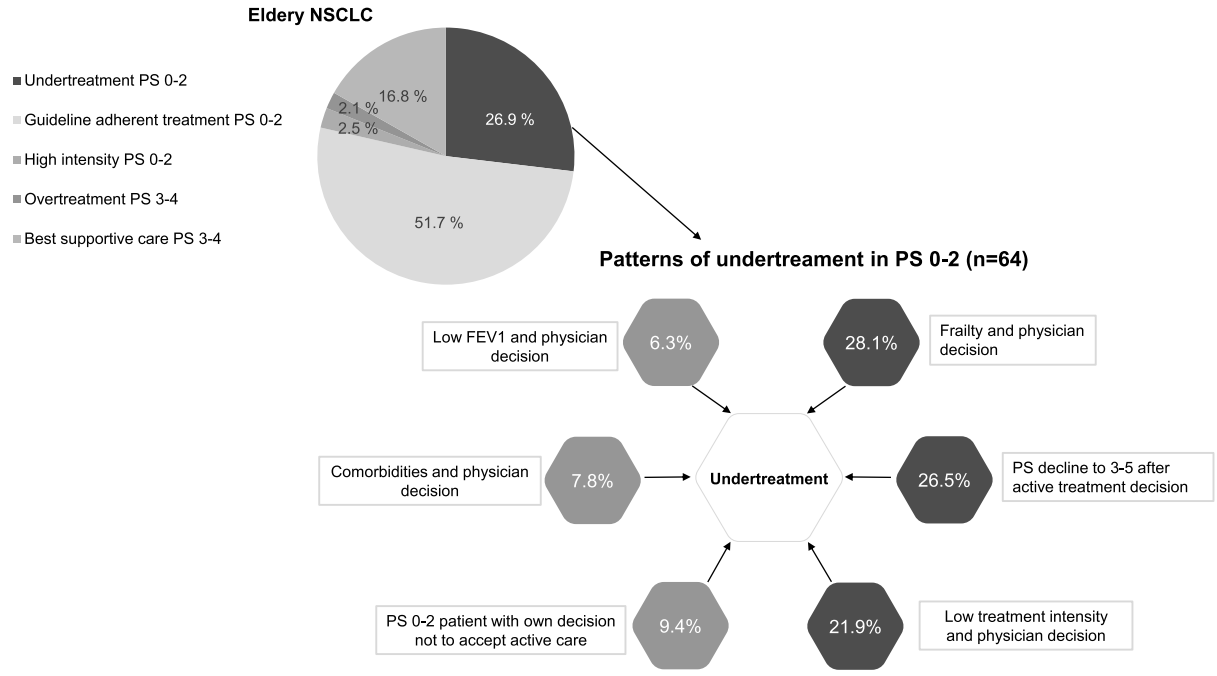

Fig. 3. Patterns of non-adherence to treatment guidelines in elderly NSCLC patients.

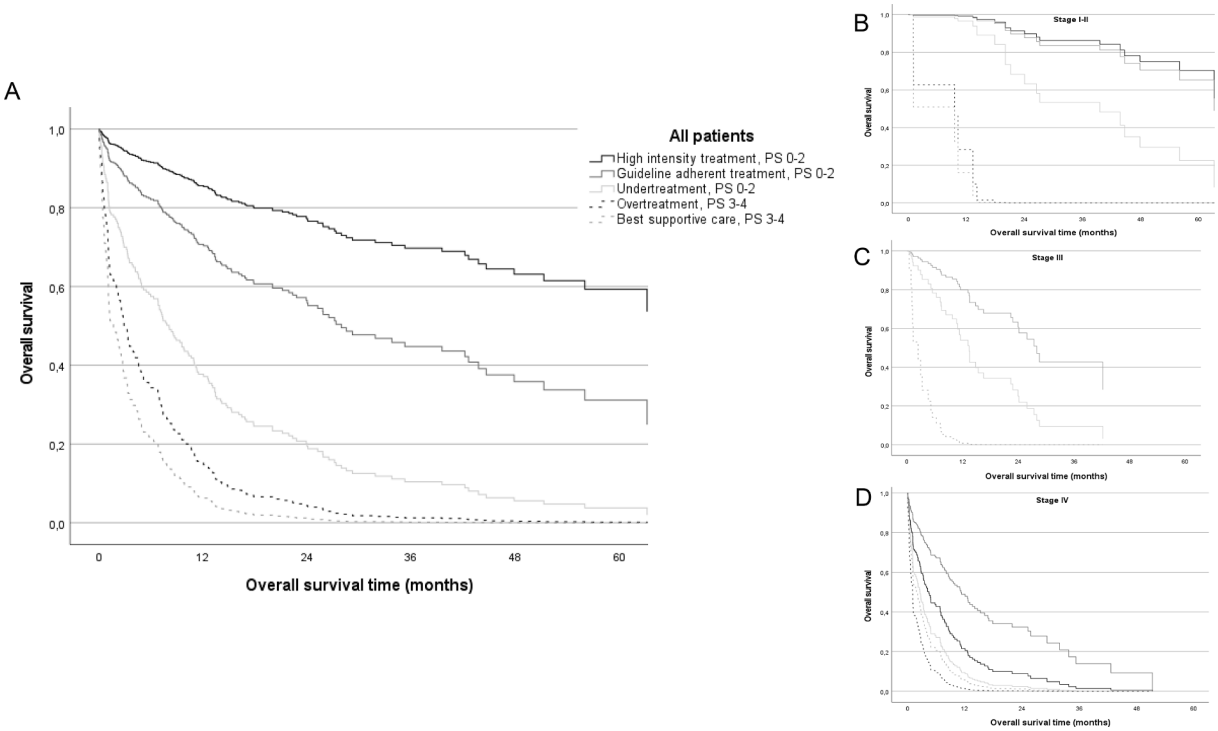

Fig. 4. (A) Cox regression curves for 5-year overall survival stratified by adherence to treatment guidelines. Patients with PS 0–2 were classified into those who received high intensity treatment, guideline adherent treatment, and undertreatment, whereas patient with PS 3–4 were classified into those who received overtreatment and best supportive care. Further sensitivity analyses for patients with (B) stage I–II, (C) stage III, and (D) stage IV NSCLC.

5. Conclusion

In this retrospective observational study, guideline adherence was associated with improved survival of elderly NSCLC patients. Guideline adherence decreased with higher age, PS, frailty and clinical stage. About 10% of elderly NSCLC patients may benefit from more intensive guideline adherent treatment. Rapid diagnosis, including early rehabilitation to avoid decreasing PS and progressive disease, may also be important. In addition, geriatric evaluation within treatment assessment might reduce variations in clinicians' treatment decisions in elderly NSCLC patients. Prospective studies are needed to determine whether geriatric evaluation leads to increased guideline adherence and improved overall results.

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CRediT authorship contribution statement

Jonatan Lindqvist: Conceptualization, Methodology, Visualization, Investigation, Formal analysis, Writing – review & editing. **Antti Jekunen:** Supervision, Writing – review & editing. **Eero Sihvo:** Methodology, Writing – review & editing. **Mikael Johansson:** Supervision, Writing – review & editing. **Heidi Andersén:** Conceptualization, Methodology, Validation, Investigation, Formal analysis, Supervision, Writing – review & editing, Funding acquisition.

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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