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Impact of sex and age on adherence to guidelines in non-small cell lung cancer management

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ABSTRACT

Introduction: Age-related disparities in non-small cell lung cancer (NSCLC) treatment are well known, but few studies have assessed the impact of sex on treatment disparities. Disparities in guideline-adherence may explain the superior survival in women with NSCLC. Therefore, we aimed to define patient- and tumor-related factors associated with non-adherence to guidelines in NSCLC management with a special focus on sex and age.

Patients and Methods: Patients with NSCLC who received first-line treatment at the Vaasa Central Hospital between 2016 and 2020 were included in the study. The primary outcome was guideline adherence, defined as adherent, undertreatment, or overtreatment considering performance status. A binary logistic regression model was used to calculate the adjusted odds ratio (aOR) for non-adherence to treatment guidelines depending on patient- and tumor-related factors.

Results: 321 patients were included in the study. Non-adherence was highest in ≥75-year-old women (41.3%), followed by ≥75-year-old men (32.6%), <75-year-old men (27.6%) and lowest in women <75-year-old (19.7%) ($p = 0.035$). Non-adherent care consisted more often of undertreatment in <75-year-old men than women (26.0% versus 12.1%) and overtreatment in <75-year-old women than men (7.6% versus 1.6%). Non-adherence was associated with stage III disease (aOR 2.21; 95% CI 1.07–4.59), poor pulmonary function (aOR 3.69, 95% CI 1.56–8.71), and Charlson Comorbidity Index 1–2 (aOR 2.09; 95% CI 1.09–4.01).

Conclusion: Sex- and age-related disparities in guideline adherence were observed in <75-year-old men and in ≥75-year-olds. Stage III NSCLC was associated with non-adherence.

Age is known to affect lung cancer treatment, but the impact of sex on treatment inequalities is unknown. This study assesses factors affecting how guidelines are followed in non-small cell lung cancer treatment. The population-based study included 321 patients and showed that age and gender affect how guidelines are followed. Strategies to assess problem areas may lead to better care.

Abbreviations

aOR, Adjusted odds ratio;
BMI, Body Mass Index;
BSC, Best supportive care;
CCI, Charlson Comorbidity Index;
CFS, Clinical Frailty Scale;
CI, Confidence interval;
CR, Complete response;
CTCAE, Common Terminology for Adverse Events;
ECOG, Eastern Cooperative Oncology Group;
eGFR, Estimated glomerular filtration rate;
EGFR, Epidermal growth factor receptor;
FEV1, Forced expiratory volume;
IQR, Interquartile range;
NSCLC, Non-small cell lung cancer;
OR, Odds ratio;

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ORR, Objective response rate;
PD, Progressive disease;
PR, Partial response;
PS, Performance Status;
RECIST, Response Evaluation Criteria in Solid Tumors;
SD, Stable disease;
SBRT, Stereotactic body radiotherapy
Twitter handle

Introduction

Despite advances in treatment options, lung cancer remains the leading cause of death worldwide [1]. In Finland, lung cancer caused an estimated 2391 cancer-related deaths in 2020 [2]. During the 21st century, the incidence of lung cancer in males has been decreasing, while the opposite trend has been seen in females [3]. Data show a higher mortality-to-incidence ratio among Finnish males (0.88) than females (0.76) in 2019 [3]. This may indicate that females are being diagnosed earlier or have different treatment patterns, tumor characteristics, or guideline adherent care.

Current guidelines offer several different alternatives for the treatment of non-small cell lung cancer (NSCLC) depending on stage and performance status (PS). Recommended treatments and combinations include surgical resection, chemotherapy, targeted therapy, immunotherapy, radiotherapy, and chemoradiotherapy [4–7]. Finding the optimal treatment for NSCLC is not always obvious and numerous factors may confound the treatment choice. A decision is made based on a combination of patient- and cancer-related factors and aims to strike a balance between risks and benefits. Thus, it is critical that methods for improving treatment tolerance are developed.

One strategy that aims to improve treatment tolerance is the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, which is a widely accepted and guideline-based measure that predicts survival among cancer patients receiving treatment [8–10]. Another scale used specifically to assess fitness among older patients is the Clinical Frailty Scale (CFS). This scale has been used to estimate the possibility of adverse side effects that correlate with poor health outcomes, is associated with mortality, and affects treatment choice and intensity [11]. However, the CFS is not routinely used in the NSCLC treatment context.

Age is an important factor influencing the choice of treatment. Older patients are less likely than younger patients to receive systemic therapy or a referral to an oncologist [12], receive a lung cancer resection [13], or be administered guideline adherent treatment despite reported benefits [14]. While the median age at lung cancer patient diagnosis is 71 years [15], older patients, especially older women, are often underrepresented in clinical trials [16,17]. This may lead to inequities in treatment choice based on a lack of clinical knowledge about specific groups.

While age may influence individual treatment choices, the effect of sex is unclear. Female sex is reported to be a positive prognostic factor in lung cancer survival [18,19], but there is evidence that 50% of the survival disparities are explained by differences in treatment [20]. Studies on sex and guideline adherence in lung cancer are few and controversial, with one study reporting increased risk for women to receive non-adherent care for locally advanced NSCLC [21], and another recent study reporting no sex-based differences in early-stage NSCLC management [22]. Lack of clinical studies, subconscious biases, and restricted clinical experience of less represented groups may create challenges for decision making and increase non-adherence in the form of both over- and undertreatment of certain groups. Whether this is a problem for the management of lung cancer remains unknown. Therefore, this study aimed to examine the patient and tumor-related factors leading to guideline adherence or non-adherence in NSCLC patients with a specific focus on sex and age.

Materials and methods

Study design

This is a population-based retrospective observational study using patient records from the Vaasa Central Hospital, Finland.

Inclusion criteria

Patients with ICD-code C34 who had their first cancer treatment at the Vaasa Central Hospital between 1 January 2016 and 31 December 2020 were identified from patient records. All patients with NSCLC were included, including patients without a pathological confirmation, to get a population-based approximation of guideline adherence. Our study could not include those treated in another hospital or those who did not have contact with the hospital (missing data $n = 7$ (2%) according to Finnish Cancer Registry). The reasons for exclusions were: small-cell lung cancer or other neuroendocrine tumor type, metastasis from another cancer, treatment before 2016, or receiving treatment at another hospital (Fig. 2).

Data extraction

Patient- and tumor-related factors

Patient records were reviewed to obtain patient characteristics, including age, sex, body mass index (BMI), estimated glomerular filtration rate (eGFR), forced expiratory volume (FEV1), smoking status, pack-years, asbestos exposure, comorbidities, CFS, and PS. Patients were defined as non-smokers if they had never smoked before, ex-smokers if they had quit smoking over a year before, or active smokers if they had been smoking regularly within the past year. Comorbidity was measured using the Charlson Comorbidity Index (CCI) [23]. Frailty was assessed using CFS scores which were categorized into three groups: robust (1–2), pre-frail (3–4), and frail ($\geq$5). Given that the CFS is not routinely assessed, scores were determined using the described function level in patient records. PS was obtained using the physician estimate that was reported in the patient records according to the ECOG PS Scale [24]. Tumor-related factors included histopathology and stage as defined in the 8th edition of the TNM staging system [25]. Treatment-related toxicity was assessed using the Common Terminology for Adverse Events (CTCAE) version 5.

Treatment

Information on treatment included delay to treatment, gene test status, treatable mutations, type of first-line treatment, and objective response rate (ORR). ORR was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and was categorized into complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [26]. Delay to treatment was defined as the number of days from referral to the first day of treatment. If a referral was not received, it was defined as the number of days from the hospital arrival to the first day of treatment or decision to provide best supportive care (BSC). The type of treatment received was grouped into five categories: surgical resection, systemic therapy, radiotherapy, palliative radiotherapy, and BSC. Surgical resection included surgical resection alone, neoadjuvant chemoradiotherapy followed by surgical resection, and surgical resection followed by adjuvant therapy. Systemic therapy included chemotherapy, immunotherapy, targeted therapy, and their combinations. Radiotherapy included chemoradiotherapy, stereotactic body radiotherapy (SBRT), and traditional radiotherapy. Palliative radiotherapy and BSC were independent categories.

Outcome

The primary outcome was guideline adherence. Guideline adherence was individualized for each stage and minimum intensity was

determined for the treatment to be considered guideline adherent. Since current Finnish guidelines do not include the most recent types of treatment [4], and most practicing clinicians follow international guidelines, a tailor-made approach based on current international guidelines and the local national recommendations was used in this study (Fig. 1) [4–7,27]. Patients with PS 0–2 required active care to be considered guideline adherent (Fig. 1), while active treatment of patients with PS 3–4 was considered overtreatment. Treatment above the recommended intensity for each stage was also considered overtreatment. The criteria were used to decide on treatment for each patient individually and recorded as adherent or non-adherent under- and overtreatment with the help of lung cancer specialist H.A, who leads the local weekly multidisciplinary lung cancer meeting.

Data analysis and statistical methods

Due to retrospective character of this paper, the sample size calculation was not performed. Patient data were extracted into a premade excel sheet, de-identified, and analyzed using IBM SPSS version 28.0. Due to its skewed distribution, numerical data are presented as medians followed by the interquartile range (IQR) in parentheses. Categorical data are presented as numbers followed by percentages in parentheses. Categorical data were compared using the 2-tailed Pearson Chi-Square test and numerical data were compared using the Mann Whitney *U* test. To analyze patient- and cancer-related factors and treatment-related patterns, the patients were grouped by sex. To analyze the proportion of guideline adherence by age and sex, four groups were formed: men and women <75 years of age and ≥ 75 years of age. The rate of adherent and non-adherent under- and overtreatment in the different groups were compared using the Chi-Square test. The p-values were reported as unadjusted and adjusted with the Bonferroni correction. The number of comparisons used in Bonferroni correction was six.

A binary logistic regression model was performed to assess the odds ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (CI) for the associations between non-adherence and patient- and cancer-related factors. Non-adherence included both under- and overtreatment. A crude model and a model that adjusted for age and sex were performed.

Ethical considerations

This study has the approval of the Vaasa Central Hospital district and the prospective study approval of the National Institute for Health and Welfare of Finland (THL/143/5.05.00/2015.THL 1349/505.00/215) and statistic Finland (TK53–1410–15). It was carried out in accordance with the Finnish Patient Data Protection Law and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Results

Study patients

Of 418 identified patients with ICD-10 code C34, 321 NSCLC patients were included in the study (Fig 2). The Finnish Cancer Registry confirmed that the study reached all patients in the hospital district except for one case diagnosed postmortem.

Patient- and tumor-related factors in men and women

This study included 209 men and 112 women. Both men and women had a median age of 73 years. The smoking status between men and women varied with the proportion of never-smokers being higher in women than in men (26.8% versus 6.7%, p $\leq$0.001). The median pack-years were 40 and 25 in men and women, respectively, and men had a lower FEV1. The CCI scores indicated that men had a higher comorbidity burden than women ($p = 0.035$). Median age, BMI, eGFR, stage, PS, and

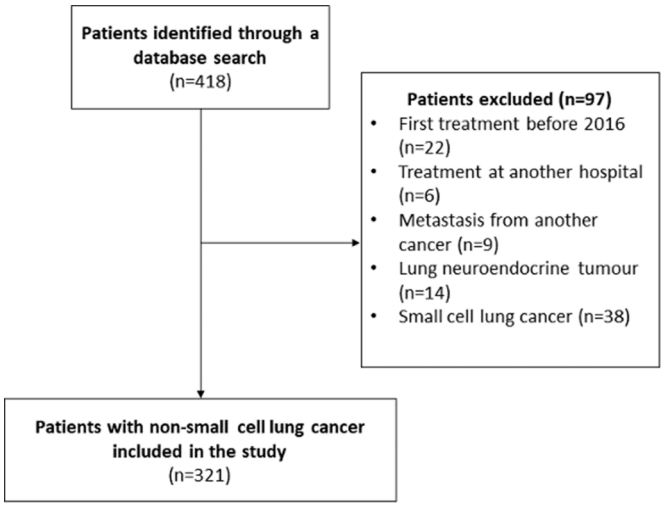

Fig. 2. Study population.

Minimum intensity for guideline-adherence for patients with PS 0-2	
Stage I	• **Preferred approach**: Surgical resection • **Alternative approach**: Stereotactic body radiotherapy • For tumours >4cm and stage IB: Adjuvant therapy • In case of positive surgical margins: Reoperation or postoperative radiotherapy
Stage II	• **Preferred approach**: Surgical resection followed by adjuvant chemotherapy • **Alternative approach**: Chemoradiotherapy
Stage III	• **Preferred approach for resectable tumours**: Surgical resection with neoadjuvant or adjuvant therapy • **Preferred approach for nonresectable tumours**: Chemotherapy or chemoradiotherapy • **Alternative approach**: Individualized multimodal therapy
Stage IV	• **Preferred approach**: Chemotherapy, immunotherapy, targeted therapy or their combinations

Fig. 1. Different approaches for the treatment to be considered guideline adherent. Treatment of patients with PS 3–4 or treatment reserved for higher stages was considered overtreatment, progressive disease during treatment was not considered undertreatment.

CFS did not significantly differ between men and women (Table 1). The median delay to any treatment for men and women was 49 days. Women had a non-significant trend of more treatable mutations (26.4%, $n = 14$) than men (13.3%, $n = 12$, $p = 0.050$), while the amount of gene testing did not significantly differ between the sexes ($p = 0.205$). Treatment results indicated as ORR and guideline adherence did not differ significantly by sex. In general, treatment patterns were similar between men and women (Table 2).

Patient-related factors associated with non-adherence

Of all patients, 70.7% ($n = 227$) were treated guideline adherently and 29.3% ($n = 94$) were treated non-adherently when PS and stage were considered. The results of the univariate and multivariate analyses adjusted for age and sex for patient-related factors are presented in Table 3. After adjusting for age and sex, two variables were associated with non-adherence: FEV1 <50% when compared to FEV1 ≥50% (aOR 3.687; 95% CI 1.561–8.707) and CCI 1–2 when compared to CCI 0 (aOR 2.089; 95% CI 1.088–4.013).

Tumor-related factors associated with non-adherence

The results of the univariate and multivariate analyses adjusted for age and sex for cancer-related factors are presented in Table 4. Stage III was associated with increased OR for non-adherence after adjusting for age and sex (aOR 2.211; 95% CI 1.065–4.592). Patients with PD response had higher odds of having received non-adherent care (aOR 2.364; 95% CI 1.103–5.066).

Table 1
Patient and tumor-related factors by sex.

	Total (n = 321)	Men (n = 209)	Women (n = 112)	p value
Median age in years (IQR)	73 (67, 78)	73 (67, 78)	73 (68, 79)	0.745[a]
Median BMI (IQR)	25.7 (22.9, 28.0)	25.8 (23.0, 27.8)	24.8 (22.3, 28.9)	0.972[a]
Median eGFR (IQR)	85 (67, 95)	85 (67, 95)	84 (68, 94)	0.609[a]
Median FEV1% (IQR)	69 (53, 85)	67 (53, 81)	82 (55, 98)	0.012[a]
TNM stage				
I-II	74 (23.1)	48 (23.0)	26 (23.2)	0.925[b]
III	64 (19.9)	43 (20.6)	21 (18.8)	
IV	183 (57.0)	118 (56.5)	65 (58.0)	
Histologic type				
Adenocarcinoma	189 (58.9)	119 (56.9)	70 (62.5)	0.272[b]
Squamous cell carcinoma	89 (27.7)	64 (30.6)	25 (22.3)	
Other or unspecified	43 (13.4)	26 (12.4)	17 (15.2)	
Smoking history				
Current	127 (39.6)	90 (43.1)	37 (33.0)	<0.001[b]
Former	150 (46.7)	105 (50.2)	45 (40.2)	
Never	44 (13.7)	14 (6.7)	30 (26.8)	
Median pack years (IQR)	40 (13, 50)	40 (23, 50)	25 (0, 40)	<0.001[a]
Known asbestos exposure				
Yes	57 (17.8)	53 (25.4)	4 (3.6)	<0.001[b]
No	264 (82.2)	156 (74.6)	108 (96.4)	
Performance status				
0–2	250 (77.9)	165 (78.9)	85 (75.9)	0.530[b]
3–4	71 (22.1)	44 (21.1)	27 (24.1)	
Charlson comorbidity index score				
0	87 (27.1)	47 (22.5)	40 (35.7)	0.035[b]
1–2	180 (56.1)	122 (58.4)	58 (51.8)	
3–4	39 (12.1)	27 (12.9)	12 (10.7)	
≥5	15 (4.7)	13 (6.2)	2 (1.8)	
Clinical Frailty Scale				
Robust (1–2)	74 (23.1)	46 (22.0)	28 (25.0)	0.832[b]
Pre-Frail (3–4)	112 (34.9)	74 (35.4)	38 (33.9)	
Frail (≥5)	135 (42.1)	89 (42.6)	46 (41.1)	

IQR: Interquartile range; NSCLC: non-small cell lung cancer.
[a] Mann Whitney-U test.
[b] Pearson Chi-Square test, 2-sided.

Table 2
Non-small cell lung cancer treatment by sex.

	Men (n = 209)	Women (n = 112)	p value
Median delay to treatment in days (IQR)	49 (26, 72)	49 (28, 68)	0.810[a]
Median delay to stabilizing or curative treatment in days (IQR)[b]	56 (35, 83)	57 (35, 80)	0.884[a]
Treatment received			
Operation	34 (16.3)	22 (19.6)	0.754[c]
Systemic therapy	70 (33.5)	34 (30.4)	
Radiotherapy	30 (14.4)	14 (12.5)	
Palliative radiotherapy	41 (19.6)	19 (17.0)	
Best supportive care	34 (16.3)	23 (20.5)	
Objective response rate[b]	$n = 134$	$n = 70$	
Complete response	35 (26.1)	25 (35.7)	0.069[c]
Partial response	27 (20.1)	17 (24.3)	
Stable disease	39 (29.1)	9 (12.9)	
Progressive disease	33 (24.6)	19 (27.1)	
Gene test status[b]			
Tested	90 (67.2)	53 (75.7)	0.205[c]
Not tested	44 (32.8)	17 (24.3)	
Existing treatable mutation[d]	$n = 90$	$n = 53$	
Yes	12 (13.3)	14 (26.4)	0.050[c]
No	78 (86.7)	39 (73.6)	
CTCAE during active treatment[c]	$n = 134$	$n = 70$	
0	37 (27.6)	23 (32.9)	0.587[c]
1–2	55 (41.0)	22 (31.4)	
3–4	38 (28.4)	22 (31.4)	
5[e]	4 (3.0)	3 (4.3)	
Guideline-adherence considering stage and PS			
Adherent treatment	147 (70.3)	80 (71.4)	0.164[c]
Non-adherent undertreatment	57 (27.3)	25 (22.3)	
Non-adherent overtreatment	5 (2.4)	7 (6.3)	

IQR: Interquartile range; CTCAE: Common Terminology Criteria for Adverse Events; PS: Performance Status.
[a] Mann-Whitney U test, two-tailed.
[b] Palliative radiotherapy and best supportive care were excluded from the analysis.
[c] Pearson Chi-Square test, 2-sided.
[d] Only gene tested patients were included in the analysis.
[e] 2 infections, 4 cardiovascular events, and 1 cancer death. All grade 5 events had unclear relation to treatment.

Adherent and non-adherent treatment by age and sex

Guideline adherence by age and sex varied from 58.7% to 80.3% ($p = 0.012$) (Fig. 3). Overtreatment and guideline adherence were highest in women <75 years old and undertreatment was highest in women ≥75 years old. When comparing age and sex groups, statistically significant differences were observed between men <75 years old versus women <75 years old ($p = 0.013$), women <75 years old versus women ≥75 years old ($p = 0.003$), and women <75 years old versus men ≥75 years old ($p = 0.010$), but not between older women versus older men ($p = 0.606$), younger men versus older men ($p = 0.583$) or younger men versus older women ($p = 0.188$).

Discussion

This study suggests that sex-related disparities in guideline-adherence occur in patients <75 years old with NSCLC. There is a tendency of overtreatment of women <75 years old and undertreatment of men <75 years old. Furthermore, age ≥75 years leads to more non-adherent treatment. In addition, this study provides important information about factors influencing adherence to guidelines. The results suggest that stage III disease, poor pulmonary function, and moderate comorbidity create challenges for guideline adherent care.

Men <75 years old had higher levels of undertreatment than women <75 years old (26.0% versus 12.1%). Further, women <75 years old were overtreated more often than men in the same age group. Reasons for this remain unclear, but some plausible explanations exist. First, men

Table 3
Analysis of patient-related factors associated with non-adherence to guidelines in patients receiving non-small cell lung cancer treatment.

	Number (%)			Non-adherence OR (95% CI)	
	Adherent 227 (70.7)	Non-adherent 94 (29.3)	*P* value[a]	Crude	Adjusted[b]
Age (years)					
Age < 75	142 (75.1)	47 (24.9)	0.037	Ref ($p = 0.038$)	
Age ≥ 75	85 (64.4)	47 (35.6)		1.67 (1.03 – 2.72)	
Sex					
Male	147 (70.3)	62 (29.7)	0.837	Ref ($p = 0.837$)	
Female	80 (71.4)	32 (28.6)		0.95 (0.57 – 1.57)	
FEV1					
≥ 50%	109 (77.3)	32 (22.7)	0.009	Ref ($p = 0.01$)	Ref ($p = 0.014$)
< 50%	15 (50.0)	15 (50.0)		3.41 (1.51 – 7.71)	3.69 (1.56 – 8.70)
Missing	103 (68.7)	47 (31.3)		1.55 (0.92 – 2.62)	1.46 (0.86 – 2.49)
Charlson comorbidity index score					
0	71 (81.6)	16 (18.4)	0.019	Ref ($p = 0.022$)	Ref ($p = 0.084$)
1–2	115 (63.9)	65 (36.1)		2.51 (1.34 – 4.67)	2.09 (1.09 – 4.01)
3–4	29 (74.4)	10 (25.6)		1.53 (0.62 – 3.77)	1.24 (0.49 – 3.14)
≥5	12 (80.0)	3 (20.0)		1.11 (0.28 – 4.39)	0.93 (0.23 – 3.78)
Clinical Frailty Scale					
Robust (1–2)	59 (79.7)	15 (20.3)	0.111	Ref ($p = 0.115$)	Ref ($p = 0.333$)
Pre-Frail (3–4)	79 (70.5)	33 (29.5)		1.64 (0.82 – 3.30)	1.41 (0.69 – 2.88)
Frail (≥5)	89 (65.9)	46 (34.1)		2.03 (1.04 – 3.97)	1.69 (0.84 – 3.37)
Gene test done					
Yes	135 (59.5)	52 (55.3)	0.492	Ref ($p = 0.493$)	Ref ($p = 0.972$)
No	92 (40.5)			1.19 (0.73–1.93)	0.99 (0.60–1.65)
Mutation status					
Treatable mutation	23 (13.6)	11 (16.4)	0.580	Ref ($p = 0.580$)	Ref ($p = 0.523$)
No mutations	146 (86.4)	56 (83.6)		0.80 (0.37–1.75)	0.77 (0.34–1.72)

OR: odds ratio; CI: confidence interval.
[a] Pearson Chi-Square test, 2-sided, overall *P* value.
[b] Adjusted for age and sex. Age was analyzed as a continuous variable.

had reduced pulmonary function, decreasing their opportunity for surgical resection [28]. Unsurprisingly, FEV1 <50% was more often associated with non-adherence than FEV1 ≥50% in this study. In addition, women who are never-smokers have a disproportionate incidence of lung cancer compared to male never-smokers [29], which may result in increased fitness among younger women with NSCLC in this study. Indeed, it is reported that women have fewer postoperative complications after surgical resection for lung cancer [30], possibly causing a bias in clinical decision-making. There is evidence that disparities in surgical resection contribute to treatment inequities between men and women. An Australian prospective study found that 17% of men and 25% of women received surgical resection within 6 months [20]. Second, men had a higher comorbidity burden, complicating surgical resection and treatment choice. Further, there is evidence of sex-related disparities even in the treatment of underlying comorbidities with women being more actively managed than men with COPD [31]. Whether this is the result of clinician bias or patient- or disease-related factors remain unknown, but more active management may result in better control of the comorbidity, which would allow for more options in treatment choice. While poor pulmonary function and comorbidities affect treatment, non-adherence in this study also required that alternative approaches such as SBRT were not used, and so cannot fully explain the non-adherence, suggesting possible underuse of SBRT. Third, the biological characteristics of cancer vary between men and women. In this study, women had more treatable mutations which would promote a higher amount of individualized treatment and may increase guideline adherence. These observations are in line with general observations that women tend to have more epidermal growth factor receptor (EGFR) mutations and present more often with adenocarcinoma [32]. Fourth, men have a considerably heavier alcohol use than women in Finland [33], which may limit fitness and treatment compliance, resulting in undertreatment. Other factors relating to the undertreatment of men, including socioeconomic factors, remain unclear and warrant further studies.

Age ≥75 years had increased OR for non-adherence. Frailty was associated with non-adherence before adjusting for age and sex. While frailty and old age tend to be linked, this observation suggests that a lower level of frailty in older adults may allow for more guideline adherent care. Since older patients tend to have a higher amount of frailty, prehabilitation that helps patients get ready for cancer treatment such as surgical resection and focuses on reducing frailty may be beneficial. A prospective study on the effect of prehabilitation found that PS was improved and frailty was decreased in high-risk groups, allowing more patients to undergo surgical resection [34]. This could be a strategy to reduce non-adherence in older patients.

To our knowledge, no published studies on NSCLC or lung cancer have examined guideline adherence by age and sex. The current data on this topic is controversial and splintered across different stages. A retrospective cohort study by Kenneth et al. including patients with resectable NSCLC from 2014 to 2019 reported no differences in guideline adherence to adjuvant therapy and adequate lymph node dissection between men and women [22]. In contrast, a registry study by Ahmed et al. found that women with unresectable stage III NSCLC had an increased OR (1.08; $P = 0.002$) for non-adherent care [21]. In the current study, sex was not a factor affecting OR for non-adherence when all ages were taken into account, but men <75 years old were undertreated more often than women <75 years old. The exclusion of all surgically resectable patients in the Ahmed et al. study may have minimized any surgery-related disparities. In addition, patients were treated between 2005 and 2013, and only chemoradiotherapy was considered guideline adherent so individualized multimodal therapy was not an option. Neither study included overtreatment in the analysis. Moreover, Kenneth et al. only included patients with stage 1B to IIIA tumors of at least 4 cm and/or positive lymph nodes with strict NCCN guidelines on the appropriate treatment. At a general level, studies on the effect of sex on guideline adherence are conflicting, with reports of female sex increasing the risk for non-adherent care of pancreatic and bladder cancer [35,36] and one study reporting no differences in care for follicular lymphoma [37]. An increasing rate of non-adherence to guidelines with increasing age has been reported for several studies of lung cancer [14,38,39] and is in line with the observations reported here.

Table 4
Analysis of tumor-related factors associated with guideline non-adherence in patients receiving non-small cell lung cancer treatment.

	Number (%)			OR for non-adherence, CI 95%	
	Adherent 227 (70.7)	Non-adherent 94 (29.3)	*P* value[a]	Crude	Adjusted[b]
TNM stage					
I-II	55 (74.3)	19 (25.7)	0.040	Ref (p = 0.043)	Ref (p = 0.036)
III	37 (57.8)	27 (42.2)		2.11 (1.03 – 4.34)	2.21 (1.07 – 4.59)
IV	135 (73.8)	48 (26.2)		1.03 (0.56 – 1.91)	1.05 (0.56 – 1.96)
Histopathology					
Adenocarcinoma	136 (72.0)	53 (28.0)	0.174	Ref (p = 0.178)	Ref (p = 0.182)
Squamous	57 (64.0)	32 (36.0)		1.44 (0.84 – 2.46)	1.45 (0.84 – 2.50)
Other & unknown	34 (79.1)	9 (20.9)		0.68 (0.31 – 1.51)	0.60 (0.26 – 1.36)
Objective response rate					
Complete response	50 (83.3)	10 (16.7)	0.088	Ref (p = 0.099)	Ref (p = 0.175)
Partial response	34 (72.3)	13 (27.7)		1.91 (0.75 – 4.86)	1.84 (0.72 – 4.71)
Stable disease	39 (69.6)	17 (30.4)		2.18 (0.90 – 5.29)	2.05 (0.83 – 5.04)
Progressive disease	104 (65.8)	54 (34.2)		2.60 (1.22 – 5.52)	2.36 (1.10 – 5.07)

OR: odds ratio; CI: confidence interval.
[a] Pearson Chi-Square test, 2-sided, overall *P* value.
[b] Adjusted for age and sex. Age was analyzed as a continuous variable.

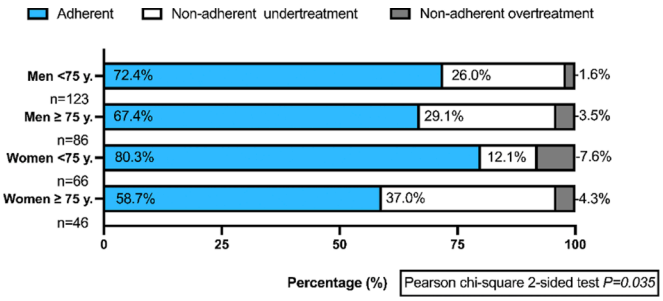

Fig. 3. Treatment patterns by sex and age. Non-adherent treatment increased with age. The amount of non-adherence was lowest in women <75 years old and highest in women ≥75 years old. Statistically significant differences were observed between women <75 years old versus women ≥75 years old (p = 0.008), women <75 years old versus men ≥75 years old (p = 0.031), and men <75 years old versus women <75 years old (p = 0.015). After adjustment using the Bonferroni method, women <75 years old versus women ≥75 years old remained statistically significant.

Stage III lung cancer is a stage where curative treatment is possible and requires multimodal treatment. Stage III was associated with increased non-adherence in the logistic regression analysis when compared to stage I-II disease. Similarly, a study by Ahmed et al. including over 10,000 patients with stage III disease found that only 23% of the patients received guideline adherent treatment [21]. Most guidelines recommend radiotherapy as a part of stage III treatment, but it remains underutilized, especially for patients with stage III disease. A study by Vinod et al. found that actual radiotherapy usage varies from 30 to 62%, while the predicted rate based on indication is 76–81% [40]. While the guideline recommendations for stage III NSCLC varies internationally [41], the importance of chemoradiotherapy in unresectable disease is generally agreed upon [42] and concomitant chemoradiotherapy is considered the treatment of choice for non-resectable stage III disease [43]. The underutilization of radiotherapy and the heterogeneity of stage III disease may explain the increased OR for non-adherence in patients with stage III disease. This emphasizes the importance of multidisciplinary conferences in NSCLC treatment decision making.

Blom et al. [39] and Wang et al. [44] found that advanced and metastatic disease respectively were the ones most associated with non-adherence to guidelines, which differs from our study, where stage III was most associated with non-adherence. However, Wang et al.'s definition of metastatic disease included both IIIB disease with malignant effusion and stage IV disease, and additionally the study only included patients diagnosed between 2003 and 2008, which excludes latest treatment choices. Furthermore, neither of the studies were able to control for PS, even when comorbidities were considered, which potentially explains the discrepancy. It is likely that the number of patients with PS 3–4 is higher for those with more advanced disease, meaning that fewer patients have an indication for active treatment, which is considered by the current study. Additionally, an analysis of the occurrence of overtreatment was not included in either study.

This study has the strength of including a population-based cohort with minimal selection bias, meaning that the results are directly generalizable in the geographic region. Multinational prospective study would have a higher impact. Compared to previous mostly registry-based studies the current study included a more comprehensive dataset and was able to factor in PS when assessing guideline adherence. This study also defined patients who were both over- and undertreated as non-adherent. To our knowledge, previous studies have not been able to include overtreatment due to limitations in available data. While retrospective, this study is a part of a larger ongoing project to improve lung cancer survival and resectability. This includes ongoing prospective studies [45,46] which may contribute to more complete patient records while simultaneously leading to the underrepresentation of treatment-related inequities. In addition, Finland uses a predominantly tax-financed healthcare system with universal coverage and low patient-cost [47], which increases access and reduces socioeconomic differences that may impact guideline adherence. This study is limited by being retrospective, which may introduce bias and lead to missing data. Its sample size also reduced statistical power in some analyses and may have introduced type II errors. Multiple comparisons conducted by age and sex may introduce type I errors, however, we reported p-values adjusted with the Bonferroni correction to account for this.

Conclusions

This study suggests that sex-related disparities exist in guideline-adherent care of <75-year-old patients with NSCLC and indicates that patients ≥75 years old are undertreated even after considering PS. Cause for non-adherent care among men <75 years old warrants further studies. Results also indicate that stage III disease continues to be complex to treat and may contribute to higher rates of non-adherence. Strategies to reduce frailty in older patients and the introduction of alternative treatment modalities to replace pulmonary function-dependent lobectomy and pulmectomy could help to improve guideline adherence. The lesson learned from this study is that for equal care, multidisciplinary case discussions should include all lung cancer patients. In addition, to improve current practice in managing NSCLC it might be beneficial for multidisciplinary teams to follow how much and

why given treatments divide from recommendations. Increased awareness and further studies of sex-related disparities in the treatment of younger men and women are required.

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Data availability statement

Due to Finnish general data protection regulation the data cannot be made public as it contains sensitive data.

CRediT authorship contribution statement

Nelly-Maria Paakkola: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jonatan Lindqvist:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Antti Jekunen:** Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Eero Sihvo:** Methodology, Supervision, Validation, Writing – review & editing. **Mikael Johansson:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Heidi Andersén:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

N-M.P, J.L, A.J, E.S, M.J, and H.A report no conflict of interest.

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