

ORIGINAL ARTICLE

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Improved overall survival for Stage III NSCLC patients treated with curative-intended therapy from 2010 to 2018—a cohort study in Denmark

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ABSTRACT

Background: Despite advances in treatment strategies and improved clinical outcomes, an unmet need remains for NSCLC patients. With an increased real-world knowledge of NSCLC, clinicians could offer patients optimal tailored treatment and disease management. In this retrospective cohort study, we describe patient characteristics, treatment patterns and modality, and survival in NSCLC patients diagnosed and treated at Aarhus University Hospital, Denmark.

Methods: Data on Stage III NSCLC patients aged ≥ 18 years diagnosed 2010–2018 were obtained from a regional cancer database and linked to national registries for information on socioeconomic and vital status. Patients were stratified by planned treatment intention at diagnosis (curative/palliative). Treatment patterns and overall survival (OS) were estimated using time-to-event methods.

Results: Broad patient and diseases characteristics and multiple treatment options demonstrated the heterogeneity of this patient cohort. Of 851 Stage III NSCLC patients, 599 (70%) and 252 (30%) were offered curative- and palliative-intended treatment, respectively, upon evaluation by a multidisciplinary team (MDT). The most frequent treatment modalities were CRT ($n = 328$; 55%) and RT ($n = 97$; 38%) in the curative and palliative setting, respectively. Age, disease stage, performance status and comorbidity were associated with curative-intended treatment initiation. Curative-intended treatment was associated with an improved OS of 14.6 months (median OS 24.4 months, 95% CI 21.1–27.6). Being offered curative-intended treatment and/or being diagnosed in the more contemporary study period (2016–2018) were significantly correlated with better OS ($p < 0.001$).

Conclusion: Stage III NSCLC is a heterogeneous disease as regards patient and clinical characteristics, multiple treatment options, and outcomes. Age, disease staging, performance status, and comorbidity, as well as MDT evaluation and matching treatment intent, are important determinants of curative-intended treatment. Notably, an NSCLC diagnosis in the more contemporary study period was statistically significantly associated with better OS.

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Stage III non-small cell lung cancer; curative-intended treatment; palliative-intended treatment; treatment intention; survival; real-world evidence

Background

Lung cancer constitutes about 12% of all cancer cases in Denmark [1] and is also the country's leading cause of cancer-related death [2]. Approximately 5000 patients are diagnosed each year [1,3] ranking Denmark tenth in the world as to the highest lung cancer incidence [4]. However, as in most western countries, survival has improved over the last decades with the introduction of new treatments [5,6].

Non-small cell lung cancer (NSCLC) represents roughly 85% of all lung cancers and its treatment depends mainly on the disease stage at diagnosis. Approximately 30% of NSCLC patients present with early-stage (stages I–IIB) disease and receive surgical resection with curative intent as primary treatment; however, 70% of patients already have locally advanced (stage III) or metastatic (stage IV) disease at the

time of diagnosis [7,8], and one out of every four NSCLC patients in Denmark presents with locally-advanced disease with spread to local lymph nodes [9].

Stage III NSCLC patients represent a highly heterogeneous group with disease presentation ranging from apparently resectable tumours with potentially occult microscopic nodal metastases to unresectable tumours with a large degree of nodal involvement [10,11]. The treatment of locally advanced disease is dependent on the number of lymph nodes (N) involved [11]. In Denmark, guidelines recommend that patients with resectable, locally-advanced NSCLC (N1 disease) should be evaluated for surgery or concomitant chemoradiotherapy (CRT) with 66 Gy/33 F and platinum-containing combination chemotherapy (CT), while patients in a poor general condition or with significant comorbidity should be

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evaluated for 66 Gy/30-33F radiotherapy (RT) without CT [12]. In contrast, current standard of care (SoC) for unresectable disease (N2 disease) is either curative CRT with 66 Gy/33F and platinum-containing combination CT followed by active surveillance or palliative RT, or the best supportive care for CRT-ineligible patients [13]. Notably, national guidelines for patients eligible for curative-intended treatment remained unchanged for a decade until 2021 when patients with $a > 25\%$ expression of programmed death-ligand 1 (PD-L1) and who had completed and responded to CRT were recommended for a 12-month treatment of adjuvant therapy with durvalumab, a novel immunotherapy of the PD-L1 inhibitor class and one of the immune checkpoint inhibitors (ICIs) that have transformed NSCLC treatment [14–16].

Multidisciplinary teams (MDTs) have become fundamental to evaluating the patients, including all aspects of their disease (e.g., medical history, current condition, and all imaging and pathology findings), and to making the final decision regarding diagnosis, staging, and optimal treatment strategy [17]. Today, the MDT is considered indispensable to ensuring that the therapeutic pathway, including treatment options and intent decisions, is as accurate as possible and in line with current guidelines and available contemporary treatments.

Increased knowledge of current lung cancer management in clinical practice and its correlation to survival for Stage III NSCLC patients is vital for clinicians to offer optimal tailored

treatment. Thus, our aim was to determine and describe the patient characteristics, treatment patterns, and survival with respect to the treatment modality of Stage III NSCLC patients diagnosed and treated during 2010–2018 in Aarhus County, Denmark.

Methods

Study design and data sources

This retrospective cohort study utilized data from electronic medical records of a regional, clinical cancer database at the Department of Oncology, Aarhus University Hospital, Denmark. Patient-level data on characteristics, diagnostic work-up, treatment modalities, and clinical outcomes were linked with nationwide registry data on vital status from the Danish Civil Registration System and information on educational level from Statistics Denmark. A unique, personal identification number assigned to all individuals resident in Denmark enabled accurate individual-level data linkage across these data sources.

This study required neither approval from the Research Ethics Committee as it utilized data from a quality assurance database nor informed patient consent as it was a retrospective study.

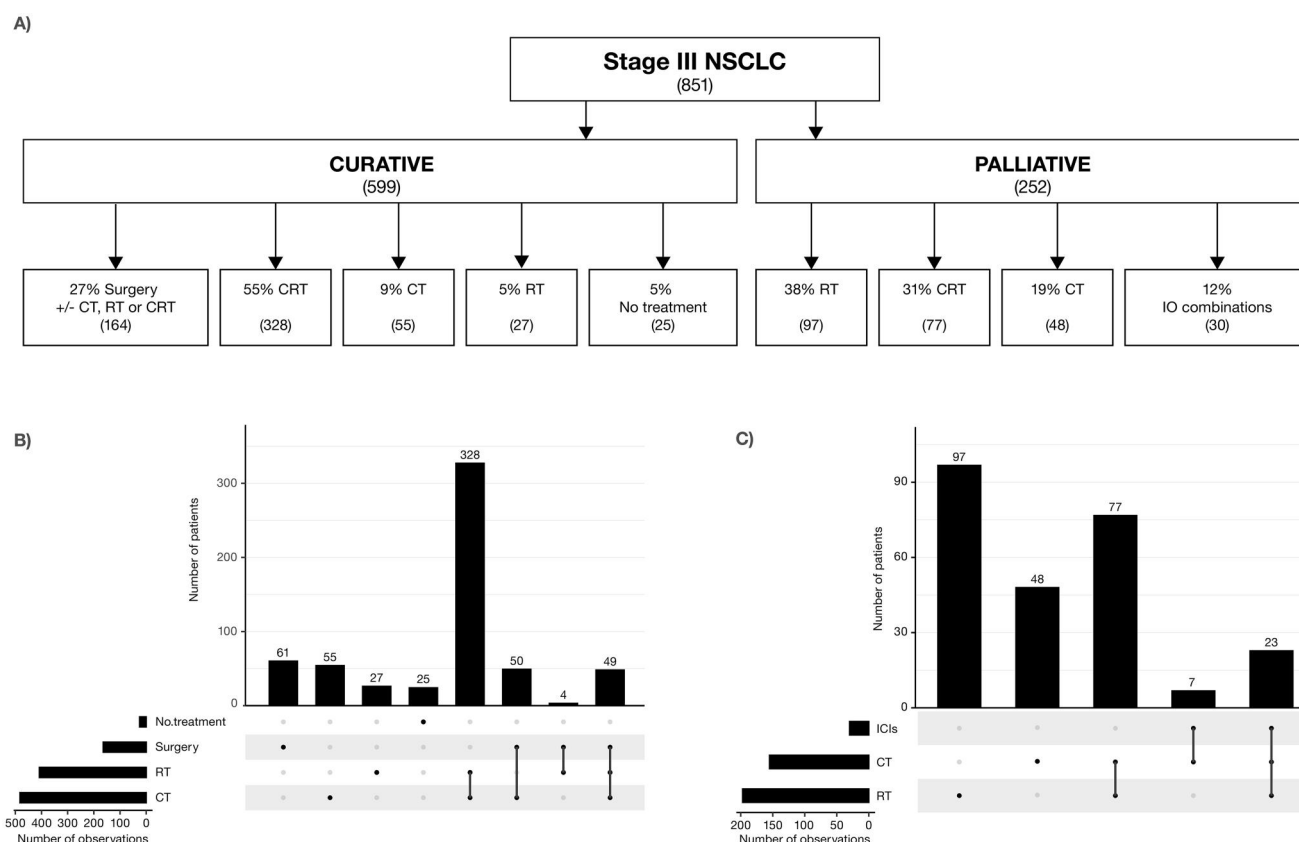


Figure 1. The study cohort included 851 Stage III NSCLC patients with complete records of treatment intention at baseline. (A) Patients are described by treatment intention (curative and palliative) and modality of treatments, where CRT: chemoradiotherapy; CT: chemotherapy; ICI: immune checkpoint inhibitors; IO: Immunotherapy; and, RT: radiotherapy. The number of patients is depicted in brackets. The upset plots show the first treatment modality offered to Stage III NSCLC patients in the (B) curative ($N = 599$) and (C) palliative ($N = 252$) settings, respectively, at first visit.

Study population and outcomes

Incident Stage IIIA and IIIB NSCLC patients aged ≥ 18 years diagnosed and treated at the Department of Oncology, Aarhus University Hospital, Denmark between 1 January, 2010 and 1 March, 2018 were included from the date of their diagnosis (baseline) and followed until death, emigration (censored), loss of follow-up or end of study (1 March 2020), whichever occurred first. All eligible patients had been routinely evaluated by an MDT at the centre. Information on patient characteristics (sex, age, year of diagnosis, smoking status, comorbidities [modified Charlson Comorbidity Index, 0, 1, 2+], performance status [ECOG-based performance score, PS: 0-3], diagnostic work-up (e.g., histology and disease stage), civil status (widow, single, divorced, married) and level of education (short/basic/long [18]), as well as initial treatment modalities were captured at baseline, whereas clinical outcomes for all Stage IIIA and IIIB NSCLC [19] were captured during follow-up.

Treatments were described by stratifying patients according to planned treatment intention at diagnosis, i.e., curative or palliative and by treatment modality, i.e., surgery, ICIs, CT, and RT. Patients were considered for palliative care either when the tumour and lymph nodes were too large to be contained in a radiation field or if the patients were too comorbid to receive CT and/or RT in curative doses. Overall survival (OS) was assessed during follow-up.

Statistical methods

Baseline patient and tumour characteristics were described using the median (m) and interquartile range (IQR) for numerical variables and, counts and proportions for categorical variables. Descriptive statistics were presented as stratified by treatment intention, while the absolute number and proportion of patients receiving different treatment modalities were plotted visually.

The characteristics of Stage III patients and the odds ratio (OR) of receiving curative-intended treatment at diagnosis were estimated using logistic regression models.

Survival analyses were based on complete case data for treatment intention (observations with missing values were excluded); therefore, of 851 Stage III NSCLC patients with complete case data, statistical analyses were performed in 813 patients with ≥ 1 record per variable of interest (i.e., with complete information on all variables used in the analyses). Time-to-death was estimated using time-to-event methods censoring for loss to follow-up or end of follow-up. OS was presented in Kaplan-Meier plots stratified by treatment intention and treatment modalities. The relative risk for all-cause mortality was estimated using Cox proportional hazards regression with time since treatment started as the time scale and including specific variables (e.g., treatment intention, sex, age, year of diagnosis, smoking status, and education) in the multiple regression model. The proportional hazards assumption was evaluated by plotting Schoenfeld residuals against time.

The variables of primary interest were treatment intention, year of diagnosis, and treatment modalities for both curative-intended treatment (CT and/or RT, surgery) and palliative-intended treatment (CT and/or RT). No adjustment for multiple testing was made as this was a descriptive study. All estimates from regression modelling were presented with 95% confidence intervals (CIs). The statistical software R v.4.2.1 [20] was used for all statistical analyses.

All patient and tumour characteristics were included in the survival analysis to address potential bias and confounding factors.

Results

A total of 851 NSCLC patients with complete records of treatment intention were included in the analyses, of whom 599 (70%) and 252 (30%) were offered curative-intended treatment and palliative-intended care, respectively (Figure 1(A)). Among Stage III patients treated with curative intent, 164 (27%) underwent surgery $\pm$ CT, RT or CRT, and 328 (55%), 55 (9%), and 27 (5%) received CRT, CT and RT, respectively. However, 25 (5%) patients were not offered any treatment

Table 1. Characteristics of Stage III NSCLC patients at baseline ($N=851$) by treatment intention.

	Curative	Palliative	P
<i>n</i> (%)	599 (70.4)	252 (29.6)	
Median age [IQR]	68 [61-73]	72 [66-79]	
Age (%)			
<60	126 (21.0)	29 (11.5)	<0.001
60-69	231 (38.6)	55 (21.8)	
70-79	211 (35.2)	116 (46.0)	
>80	31 (5.2)	52 (20.6)	
Sex			
Male	317 (52.9)	142 (56.3)	0.401
Female	282 (47.1)	110 (43.7)	
Year of diagnosis			
2010-2012	175 (29.2)	79 (31.3)	0.172
2013-2015	183 (30.6)	61 (24.2)	
2015-2018	241 (40.2)	112 (44.4)	
Stage			
IIIA	429 (71.6)	120 (47.6)	<0.001
IIIB	170 (28.4)	132 (52.4)	
Histology			
Adenocarcinoma	349 (58.3)	126 (50.0)	0.076
Squamous cell carcinoma	220 (36.7)	113 (44.8)	
Other	30 (5.0)	13 (5.2)	
Comorbidity score			
0	327 (54.6)	109 (43.4)	0.002
1	129 (21.5)	55 (21.8)	
2+	143 (23.9)	88 (34.9)	
Performance Status			
0	248 (42.2)	43 (17.1)	<0.001
1	277 (47.1)	97 (38.5)	
2/3	63 (10.7)	112 (44.4)	
Smoking			
Previous	386 (64.4)	154 (61.1)	0.647
Current	186 (31.1)	85 (33.7)	
Never	27 (4.5)	13 (5.2)	
Civil status			
Widow	75 (12.5)	47 (18.7)	0.137
Divorced	107 (17.9)	41 (16.3)	
Married	360 (60.1)	140 (55.6)	
Single	57 (9.5)	24 (9.5)	
Educational level			
Short	249 (42.9)	139 (57.2)	<0.001
Basic	231 (39.8)	81 (33.3)	
Long	101 (17.4)	23 (9.5)	

IQR:interquartile range.

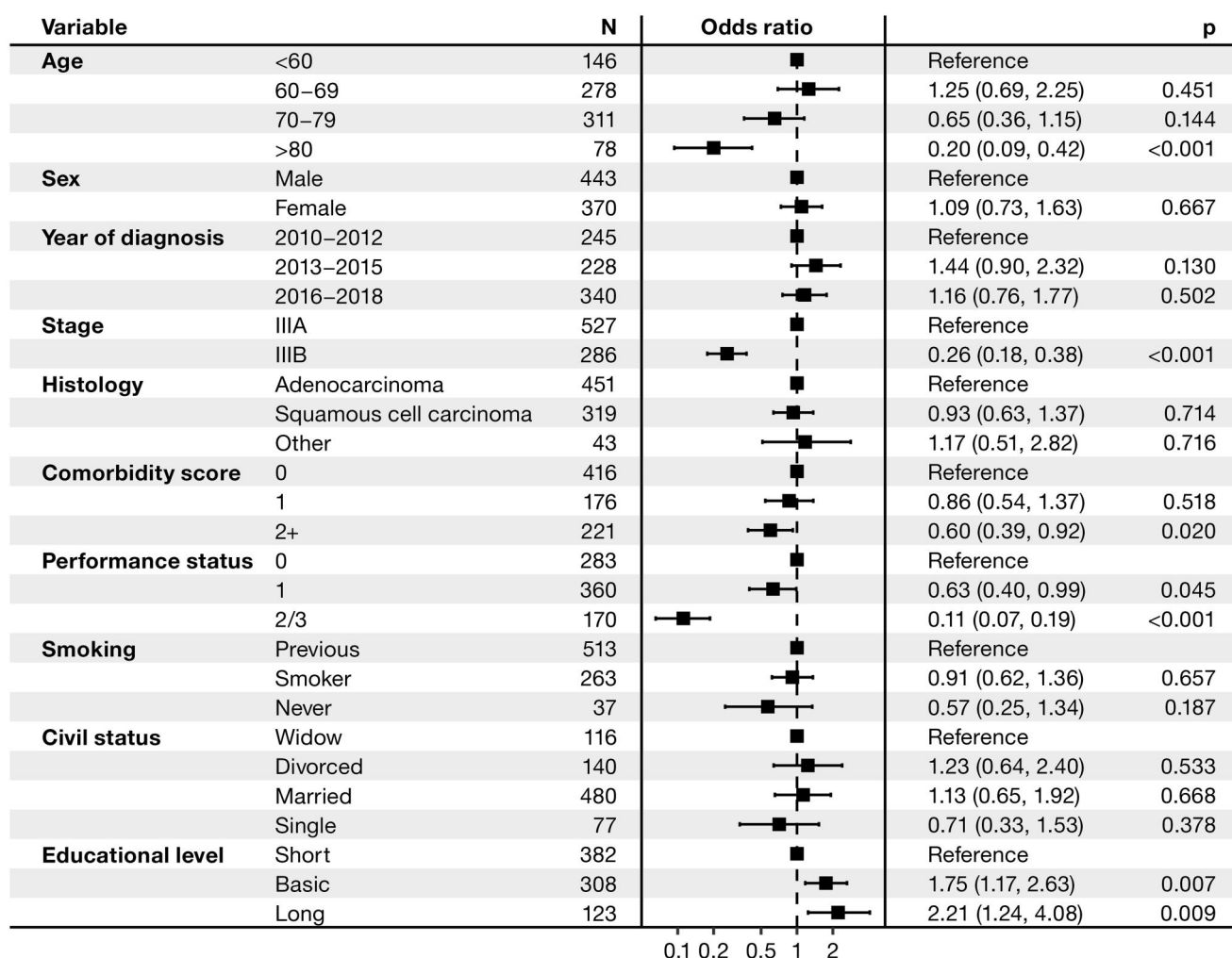


Figure 2. The Forest plot shows the risk (odds ratio) of initiating curative-intended treatment as opposed to palliative-intended treatment at baseline. The odds ratios were estimated using a mutually adjusted logistic regression model.

having died before treatment initiation (Figure 1(B)). Among the 252 patients offered palliative-intended care at first visit, 97 (38%) received RT (typically 8 Gy/1fx, 20 Gy/4fx, or 30 Gy/10fx), 77 (31%) CRT (CT at standard doses; RT at palliative doses), 48 (19%) CT only, and 30 (12%) ICIs combined with CT or CRT (Figure 1(C)).

On average, patients in the curative setting were younger than those offered palliative care (mean age 66.4 vs. 71.8 years, respectively), had less comorbidity (54.6% vs. 43.3%, respectively, for comorbidity score 0, $p = 0.002$). The proportion of patients in the curative and palliative groups were similar across the years of diagnosis ($p = 0.172$). Most patients in the curative setting (71.6%) were diagnosed as Stage IIIA compared to 47.6% in the palliative setting ($p < 0.001$) and presented with a significantly better performance status (89% curative vs. 55.6% palliative, PS = 0–1, $p < 0.001$). Although there were no statistically significant differences between the two groups as regards to sex, smoking status, or civil status, there was a statistically significant difference in the educational level with 57.2% of palliative care patients having a short education compared to those in the curative setting (42.9%) (Table 1).

The patient age, disease stage, performance status and comorbidity score were all associated with curative-intended

treatment initiation. The odds of initiating curative-intended treatment for patients aged >80 years was five times lower than those aged <60 years, OR 0.20 (95% CI 0.09–0.42). Stage IIIB patients were less likely to be offered curative-intended treatment than Stage IIIA patients, OR 0.26 (95% CI 0.18–0.38), as were those with poor (PS = 2/3) versus those with good performance status (PS = 0), OR 0.11 (95% CI 0.07–0.19). In contrast, patients with a basic or long education were more likely to receive curative-intended treatment (OR 1.75 [95% CI 1.17–2.63]) than those with a short education (OR 2.21 [95% CI 1.24–4.08]). Sex, year of diagnosis, smoking status, histology, and civil status were not statistically significantly associated with specific treatment intention (Figure 2).

The median follow-up time was 24 and 10 months for curative- and palliative-treated patients, respectively. Patients offered curative-intended treatment showed a median OS that was 14.6 months longer (mOS 24.4 months, 95% CI 21.1–27.6) than the median OS in patients offered palliative-intended treatment (mOS 9.8 months, 95% CI 8.00–11.7). Five-year survival could only be estimated for patients with curative-intended treatment with 16% (95% CI 10–25%) still alive 5 years post diagnosis (Figure 3(A)).

Median survival for patients offered surgery ($n = 164$) as curative-intended treatment was 40.1 months (95% CI 33.1–

57.5) compared to patients offered CRT ($n=328$) (25.8 months [95% CI 23.7–29.2]) (Figure 3(B)). Median survival for patients in the palliative care setting ($n=252$) was 6.1 (95% CI 5.5–7.5), 13.1. (95% CI 9.0–17.2), and 10.7 months (95% CI 8.8–13) for those offered RT alone, CT alone, and CRT, respectively (Figure 3(C)).

Finally, the association between treatment intention and mortality was investigated. Interestingly, being offered curative-intended treatment (HR 0.44, 95% CI 0.36–0.53) and being diagnosed with NSCLC during the most recent years of the study period (2016–2018) (HR 0.62, 95% CI 0.50–0.76) were significantly associated with better OS ($p < 0.001$). In contrast, poor performance status (PS = 2/3) (HR 2.11, 95% CI 1.64–2.72) and being diagnosed with Stage IIIB versus IIIA (HR 1.40, 95% CI 1.17–1.67) were associated with an increased risk of mortality (Figure 4).

Discussion

In this retrospective study of Stage III NSCLC patients in Denmark, we mapped the contemporary management of NSCLC in a real-world setting and identified key variables correlated with the treatment options offered to these patients and the resultant survival outcomes.

Our study cohort of Stage III NSCLC patients presented with wide-ranging ages, including >80 years, and variable disease stages, histological tumour profiles, and performance status. Most patients ($n=696$, 82%) were aged >65 years, and about 50% of those receiving curative-intended treatment had comorbidity scores of ≥ 1 . Most of the patients who were offered curative-intended treatment received CRT followed by surgery $\pm$ combinations of CT/RT, while palliative patients received mostly RT/CRT. The intent of surgery was different in the two care settings; typically, oligo-metastases such as single brain metastases are removed surgically prior to CT and RT with curative intention, while surgery is used in cases of distant metastases resulting in spinal cord compression or malignant fractures in the palliative setting. Our results are in line with previous studies [13,21,22] describing Stage III NSCLC as a highly heterogeneous group of patients with differences in disease characteristics, as well as treatment options and goals. Hence, due to the heterogeneity and complexity of our Stage III cohort, MDTs employed at the Aarhus centre seem to be very important to evaluate patients, prior to deciding and offering the optimal treatment pathway recommendation, be it curative or palliative.

Notably, we found that patient age, disease stage, performance status, and the comorbidity score may influence the treatment options offered to and received by the patients, as well as subsequent outcomes. In our study, these factors were all associated with curative-intended treatment initiation. We found that the likelihood of initiating curative-intended treatment for patients aged >80 years, for example, was five times lower than those aged <60 years. Treatment of elderly patients is hampered by their relative frailty and comorbidity [21], although older patients with advanced NSCLC may benefit from CRT [21] and ICIs as much as

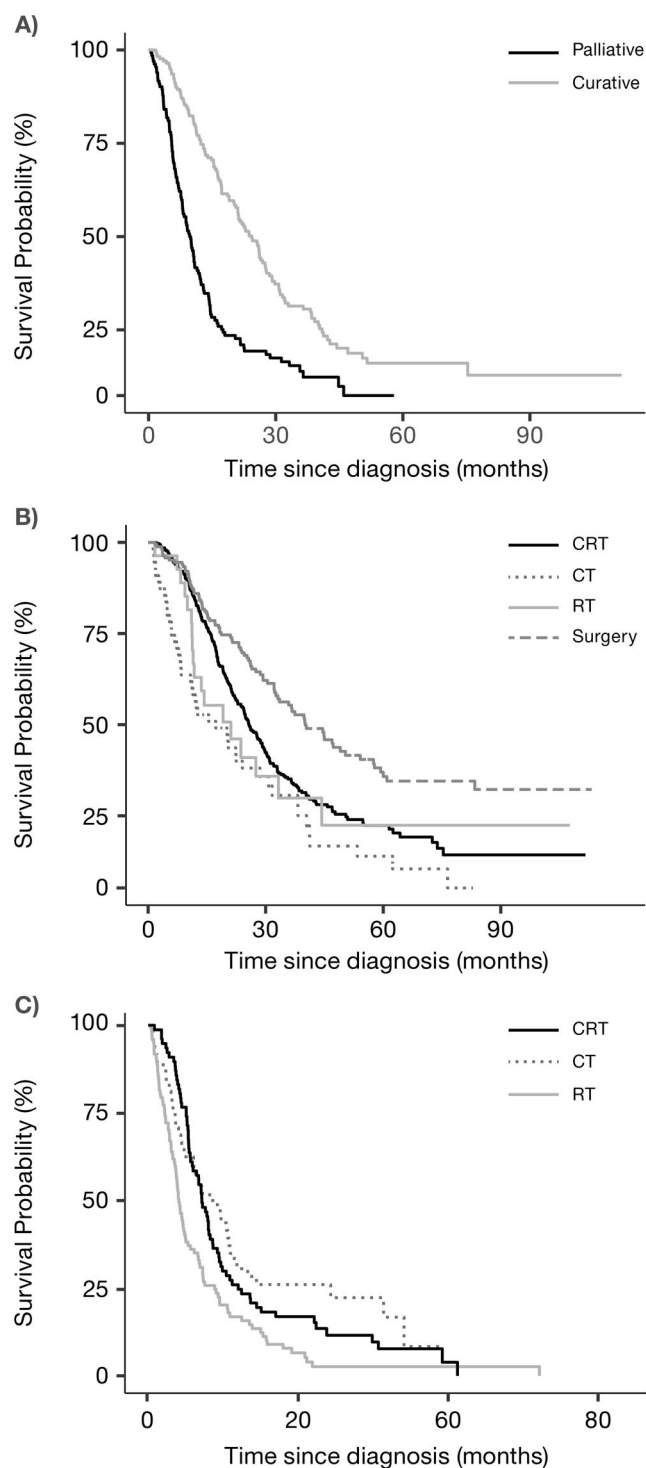


Figure 3. The overall survival stratified by treatment intention (curative or palliative) is shown at first visit (a), as well as survival by treatment modality, where CRT: chemoradiotherapy; CT: chemotherapy; and, RT: radiotherapy for patients offered curative-intended treatment or (C) palliative-intended treatment.

younger, fitter patients [23]. Meanwhile, the patient performance status subjectively assessed by the clinician upfront is essential for a patient to be offered the correct treatment, and its continual assessment at each visit ensures that the patient's PS is maintained throughout the treatment journey. Stage III NSCLC patients with PS ≥ 2 (i.e., poor performance) represent around 14% of the real-world population [24], and

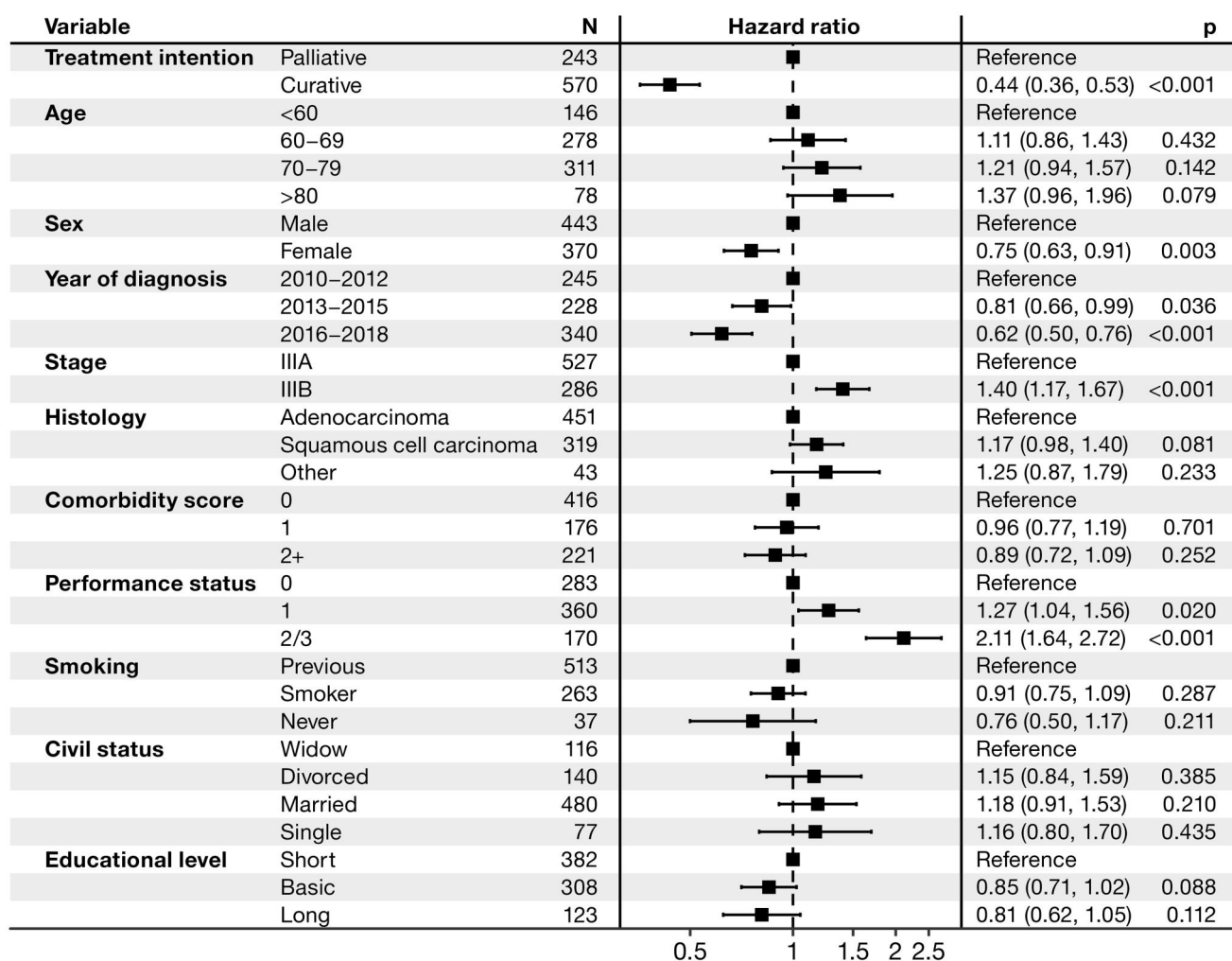


Figure 4. The hazard ratios for overall survival are shown with estimates obtained using a mutually adjusted Cox proportional hazards model.

in our study we found that such patients were less likely to receive curative-intended treatment than those with good performance. Notably, the latter is recommended for a patient to be offered curative-intended treatment [25] and is associated with better outcomes [26,27], while poorer performance is linked to worse OS in a real-world setting [6]. Thus, earlier NSCLC diagnosis when a patient has a higher PS and curative-intended treatment is initiated [3,13] will positively influence both survival outcomes and a clinician's ability to maintain as good a PS and quality of life as possible for the patient.

Importantly, we also found an improved OS of 14.6 months in patients who received curative-intended as opposed to palliative-intended treatment. Overall survival has generally improved for Stage III NSCLC, possibly due to more targeted and personalized patient selection, improved diagnostic imaging, new radiation modalities, and increased availability of additional and subsequent treatment pathways [28]. Notably, SoC for Stage III NSCLC changed after the 5-year follow-up of the PACIFIC study, which showed robust and sustained OS and durable progression-free survival benefit with durvalumab following CRT [29]. Approximately 42.9% of patients randomly assigned to durvalumab remained alive at 5 years and 33.1% of patients randomly assigned to

placebo remained alive and free of disease progression, establishing a new benchmark for SoC in this setting [29]. Since this novel treatment was only available from 2018, durvalumab is unlikely to have substantially impacted the survival outcomes we observed in our study population. However, we found that being offered curative-intended treatment and being diagnosed with NSCLC in the most recent years of the study period was significantly associated with a better OS, whilst poor performance status and a Stage IIIB diagnosis were associated with an increased risk of mortality.

Treatment choice for NSCLC is multifactorial and includes a patient's disease stage, performance status, comorbidities and patient preference [30]. Two vital factors that influence treatment decisions and thus outcomes in this population, however, are the clinician and the patient. Clinicians, with expert guidance from the MDT, will offer patients the optimal tailored treatment pathway but ultimately, it is the patient who will decide their final treatment pathway based on the clinician's recommendation and partly on their understanding of the risk-benefit they are willing to accept for curative-intended versus palliative-intended treatment. To this end, we found that patients with a long education [18] were more likely to receive curative-intended treatment than

less well-educated patients, highlighting a pressing need for them to be able to evaluate information provided by their clinicians. Since NSCLC treatment has improved over the last decade and current SoC now incorporates better CRT strategies [21] and novel immunotherapies, such as the PD-L1 inhibitors [29], more clinicians and patients may opt for the curative approach—if recommended by the MDT—with greater confidence.

The main strengths of our study are its comprehensive data set and long-term follow-up of a large, unselected cohort of Stage III NSCLC patients diagnosed and/or treated in a contemporary, real-world setting. The MDT at Aarhus University Hospital thoroughly evaluated all eligible patients, thereby enabling a reliable and high-quality assessment of clinical outcomes. The unique data set comprised clinical data from electronic medical records that included treatment information with mandatory registration practise by the treating physician, and reliable registry data on vital status with accurate linkage across all data sources.

Nevertheless, these findings should be interpreted with some caution. The stratified analyses based on few observations may have resulted in less precise effect estimates. Only data for curative-intended treatment were available for the 5-year survival outcome analyses. The change in national education levels and SoC during the almost decade-long study period may have influenced outcomes, as exemplified by improved survival outcomes in the contemporary study period, and the study period may not have captured all new treatments currently available. Finally, while our findings reflect those of other studies, this was a single-centre study of patients diagnosed and/or referred for cancer treatment at Aarhus University Hospital, Denmark.

In conclusion, our retrospective study of Stage III NSCLC patients in Denmark has confirmed the heterogeneity of this patient population as regards their characteristics, treatment pathways and modalities, and associated survival outcomes. The study also shows that patient age, performance status, and prevalence of comorbidities are the most important determinants of treatment intention. In fact, Stage IIIA patients, <60 years old, with PS 0-1 and a low comorbidity score were the most suited to curative-intended treatment. Our results show that despite a dismal prognosis [31], many patients are offered curative-intended treatment and show better OS. This positive trend in survival may reflect a per-patient targeted work with improvements in pre-treatment staging and MDTs in place in Aarhus. With the revised guidelines now incorporating novel ICIs, assuming an earlier diagnosis and that a good performance status is maintained during treatment, the hope for a cure for Stage III NSCLC patients has increased during the last few years.

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Authors' contributions

All authors contributed to study conception, design, and data interpretation. PM, AJ, and EM contributed to data acquisition. KKA performed statistical analyses. The authors participated in drafting, critically reviewing the manuscript and approved the final version to be published.

Ethical approval

This study required no approval from the Research Ethics Committee as it utilized data from a quality assurance database at Midtjylland Denmark Region.

Patient consent

Informed patient consent was not required for this retrospective study. Improved overall survival for Stage III NSCLC patients treated with curative-intended therapy from 2010 to 2018—a cohort study in Denmark.

Disclosure statement

PM, AJ, and EM declare no competing interests. MK and SC are employees of the study sponsor, AstraZeneca. KKA is an employee of Omicron ApS of which AstraZeneca is a client.

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Data availability statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at [https://astrazenecagrouptrials.pharmacm.com/ST/ Submission/Disclosure](https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure)

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