Population-based patterns of treatment and survival for patients with stage I and II non-small cell lung cancer aged 65-74 years and 75 years or older

Journal of Geriatric Oncology 10 (2019) 547–554

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Population-based patterns of treatment and survival for patients with stage I and II non-small cell lung cancer aged 65–74 years and 75 years or older

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ARTICLE INFO

Article history:
Received 9 November 2018
Received in revised form 24 January 2019
Accepted 1 March 2019
Available online 12 March 2019

Keywords:
Non-small cell lung cancer
Early stage
Stage I
Stage II
Survival
Surgery
Radiotherapy
SBRT
Older patient

ABSTRACT

Objectives: Insights regarding utilization and survival of surgery and radiotherapy (stereotactic body radiotherapy (SBRT) or conventional radiotherapy (RT)) are lacking for older patients with stage I and II non-small cell lung cancer (NSCLC) in clinical practice.
Methods: Data from the Netherlands Cancer Registry were retrieved for patients ≥65 years with clinical stage I-II NSCLC in 2010–2015. Descriptive analyses, overall survival (OS), and cox regression were stratified for stage I ($n = 8742$) and II ($n = 3439$) and compared age groups (65–74 years vs ≥75 years).
Results: Patients aged 65–74 underwent surgery significantly more often compared to those aged ≥75 (stage I 55% vs 27%; stage II: 65% vs 35%), and received SBRT less often (I: 29% vs 42%; II: 5% vs 11%), conventional RT less often (I: 6% vs 11%; II 10% vs 24%) and best supportive care alone less often (BSC, I: 8% vs 19%; II: 9% vs 25%). One-year OS was significantly higher in patients aged 65–74 compared to those aged ≥75 (I: 87% vs 78%; II: 74% vs 60%); as was five-year OS (I: 49% vs 31%; II: 36% vs 18%). After adjustment for gender, histology, stage, treatment, and comorbidity, hazard ratio (HR) of death was higher for patients aged ≥75 compared to those aged 65–74 (I: HR 1.3, 95% confidence interval (CI) 1.1–1.5; II: HR 1.3 95%CI 1.1–1.7).
Conclusion: Patients aged ≥75 with stage I-II NSCLC had poorer OS, underwent surgery less often, and received SBRT, conventional RT, and BSC more often than patients aged 65–74. In both stages, one-year OS within age groups was similar for surgery and SBRT. However, long-term OS adjusted for prognostic factors was superior for surgery compared to SBRT and remained poorer for those aged ≥75. Prospective research should focus on predictive characteristics for treatment selection and patient-centered outcomes.

1. Introduction

Non-small cell lung cancer (NSCLC) is often diagnosed in older patients, as 65% of patients are ≥65 years and one in four patients is ≥75 years [1]. For stage I and II NSCLC, surgery by video-assisted thoracic surgery (VATS) or thoracotomy is considered standard treatment among patients with potentially resectable disease. Patients who are not willing to accept surgery-related risks or who are inoperable could be offered curative radiotherapy (RT) with Stereotactic Body Radiotherapy (SBRT) or hypofractionated high-dose RT. [2,3] Five-year relative survival rates for patients with stage I and II NSCLC ≥70 years are 54% and 32%, respectively [4].

Surgery is associated with superior survival outcomes in clinical trials including predominantly relatively young and fit patients [4]. With

Abbreviations: BSC, Best Supportive Care; CCMO, Central Committee on Research involving Human Subjects; CI, Confidence Interval; CVA, Cerebral Vascular Accident; DM, Diabetes Mellitus; HR, Hazard Ratio; ICD-O, International Classification of Disease for Oncology; NSCLC, non-small cell lung cancer; OS, Overall Survival; RT, Radiotherapy; SBRT, Stereotactic Body RadioTherapy; TNM, Tumor Node Metastases; VATS, Video Assisted Thoracic Surgery.

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https://doi.org/10.1016/j.jgo.2019.03.001
1879-4068/

the introduction of SBRT, especially older patients and high-risk surgical candidates can receive curative-intent treatment as well [5], with local control rates of 90% after five years [6]. Recent findings indicate similar results between surgery and SBRT for operable patients [7]. Moreover, a large cohort from the National Cancer Database in the United states covering 84,839 patients with early stage NSCLC, found that the 30-day and 90-day mortality was significantly higher after surgery compared to SBRT, especially among patients aged ≥66 years [8]. Data from the Dutch Lung Surgery Audit in the Netherlands indicated that operative mortality is higher among octogenarians with NSCLC compared to patients aged 60–79 years, while the incidence of complications was similar [9]. Several factors correlate with poorer treatment tolerance and survival, such as higher age [10], comorbidity, poorer physical performance [9,11], and larger extent of resection [9,12]. Also, clinical trials state strict eligibility criteria for inclusion regarding performance status, age, and level of organ function in order to minimize the risk of complications [13]. As a result, evidence regarding outcomes of treatment is scarce for older and vulnerable patients [12]. Insights regarding treatment patterns and survival within the older adult population are highly needed in daily clinical practice. As this evidence is currently lacking, our study compares treatment patterns and overall survival (OS) for patients aged 65–74 years and those aged ≥75 years with clinical stage I and II NSCLC in daily clinical practice in the Netherlands.

2. Methods

All patients aged ≥65 years diagnosed with clinical stage I or II NSCLC during 2010–2015 were retrieved from the population-based Netherlands Cancer Registry, which is maintained by the Netherlands Comprehensive Cancer Organization (Fig. 1). Trained registrars have routinely collected data from medical records regarding patient and tumor characteristics of all newly diagnosed patients with cancer in the Netherlands since 1989. Vital status was retrieved from the nationwide population registries network with complete follow-up until February 1st 2018. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry. The Central Committee on Research involving Human Subjects (CCMO) judged that approval of an ethics committee was not required.

The International Classification of Disease for Oncology (ICD-O3) [14] code for pulmonary tumors (C34) was used at the Netherlands Comprehensive Cancer Organization in order to include all patients with NSCLC as well as clinical diagnoses [15]. Patients with other histologies were excluded. Age (65–74 years and ≥ 75 years), gender, histology, and clinical stage were retrieved. Stage of disease was classified according to clinical Tumor Node Metastases (TNM) edition 7 [16]. In Dutch staging guidelines, it is stated that all patients suspected for NSCLC should be staged by PET-CT scan. When the PET-CT scan is positive, lymph nodes are enlarged, and the patient is fit enough, mediastinal staging by EUS/EBUS will be applied [2,17]. For patients without histologic confirmation of the tumor, TNM classification was registered since 2011. A small proportion diagnosed in 2010 did not have a histologic confirmation. In order to classify these patients into stage groups, trends in stage distributions between 2011 and 2015 were compared to those in 2010. In 2011–2015, the increase of patients with stage I NSCLC was similar to the proportion of patients without histologic confirmation in 2010. Therefore, it was decided to classify this group diagnosed in 2010 as stage I NSCLC. Information on comorbidity was available for patients in the southeastern part of the Netherlands only, covering approximately 18% of included patients. Comorbidity was registered according to a slightly adapted version of the Charlson Comorbidity Index (CCI) [18] at the Netherlands Comprehensive Cancer Organization. Retrieved comorbidity data were classified as number of comorbid conditions (0, 1, or ≥ 2), and type of comorbidity (respiratory, cardiovascular, digestive, hypertension, diabetes mellitus (DM), previous malignancy, or cerebrovascular accident (CVA)/hemiplegia). Treatment was categorized as VATS, thoracotomy, SBRT (3–8 fractions), conventional RT, chemotherapy, chemoradiotherapy (chemotherapy and radiotherapy within 90 days of each other), and Best Supportive Care (BSC).

2.1. Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 24.0. All analyses were stratified for stage of disease (I and II) and age groups. Descriptive statistics and OS were compared between age groups (65–74 years and ≥ 75 years) and differences were assessed for significance by the X^2-test for categorical variables and the Mann-whitney *U* test for continuous variables ($P < .05$ two sided). Results were displayed as number (percentage) or median (interquartile range (IQR)). As chemotherapy and chemoradiotherapy covered only small proportions and

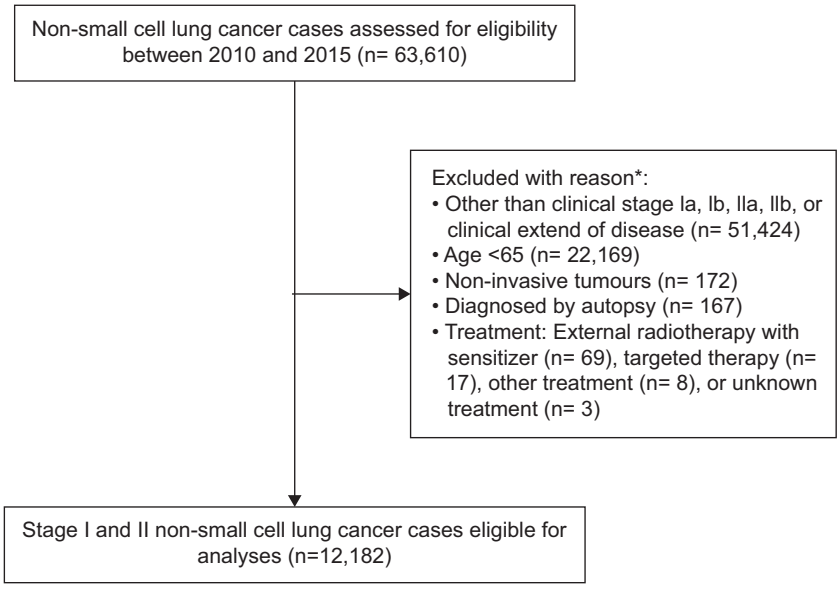


Fig. 1. Flow chart of eligible patients ≥65 years with stage I and II non-small cell lung cancer (2010–2015) * Characteristics of all excluded patients. Multiple characteristics could be applicable to one patient. Therefore, the exclusion numbers cannot be deducted from the total number of non-small cell lung cancer cases in order to calculate the total number of eligible cases.

are not considered regular treatment options for stage I-II NSCLC [2], these were excluded from survival analyses. OS rates were calculated from the date of diagnosis until death or until February 1st 2018 by median, one-year, and five-year OS, and were visualised by the Kaplan-Meier method. Median follow-up was estimated with the reverse Kaplan-Meier method [19]. Hazard Ratios (HRs) for mortality were calculated by Cox proportional hazard regression analyses. HRs were adjusted for factors affecting survival based on previous studies and included in model 1: utilized treatment [7], gender [20], age [4,9,10], stage [21], and histology [22]. In subanalyses, the cohort of the southeastern part of the Netherlands was used to investigate whether number of comorbid conditions [23] was an independent predictive factor for mortality as well, and was added in model 2. Imputation of missing values for comorbidity was not performed for patients outside the southeastern part of the Netherlands, as approximately 80% of outcomes would be imputed. Both OS rates and HRs were displayed with corresponding 95% confidence intervals (95%CI). HR > 1.0 indicates an increased hazard of death. The HR was considered statistically significant when the 95%CI was completely above or below 1.0.

3. Results

In the Netherlands, 12,182 patients aged ≥65 years were diagnosed with stage I-II NSCLC between 2010 and 2015 (Fig. 1), covering 19% of all primary cases of lung cancer. Over half of the study population was aged 65–74 years (53%, Table 1). For stage I NSCLC, patients aged 65–74 years underwent VATS (32% vs 16%) and thoracotomy (23% vs 11%) significantly more often, while SBRT (29% vs 42%), conventional RT (6% vs 11%), and BSC (8% vs 19%) were utilized significantly less often compared to those aged ≥75 years. Two or more comorbid conditions were less often present among patients aged 65–74 years (66%) compared to those aged ≥75 years (73%), whereas 26% and 23% suffered from one comorbid condition, respectively. Patients aged ≥75 years suffered more often from DM ($p = .001$), previous malignancy ($p = .02$), and CVA or hemiplegia ($p = .004$) compared to patients aged 65–74 years. For stage II NSCLC, patients aged 65–74 years underwent VATS significantly more often (25% vs 13%), as well as thoracotomy (40% vs 22%), and chemoradiotherapy (9% vs 5%), while SBRT (5% vs 11%), conventional RT (10% vs 24%), and BSC (9% vs 25%) were utilized significantly less often compared to those aged ≥75 years. Proportions of the number and type of comorbid conditions were comparable between age groups.

Median follow-up was 58 months (95%CI 57–59 months). Fig. 2a and b display that within age and stage groups, OS seemed similar until one year for VATS, thoracotomy, and SBRT. However, survival curves were declining more rapidly after one year among those aged ≥75. After two years, both surgical approaches indicated superior OS compared to SBRT and conventional RT among patients aged 65–74 years for both stages, and among those aged ≥75 years for stage I NSCLC only. Furthermore, SBRT showed superior OS compared to conventional RT. For patients aged ≥75 specifically, VATS showed superior survival after two years in both stages as compared to other treatment options. For stage I, this is consecutively followed by thoracotomy and SBRT. For those aged ≥75 years with stage II NSCLC, OS was similar up until two years for VATS and SBRT and superior with respect to other treatment options, while OS for SBRT and thoracotomy were similar and lower compared to VATS after 3 years.

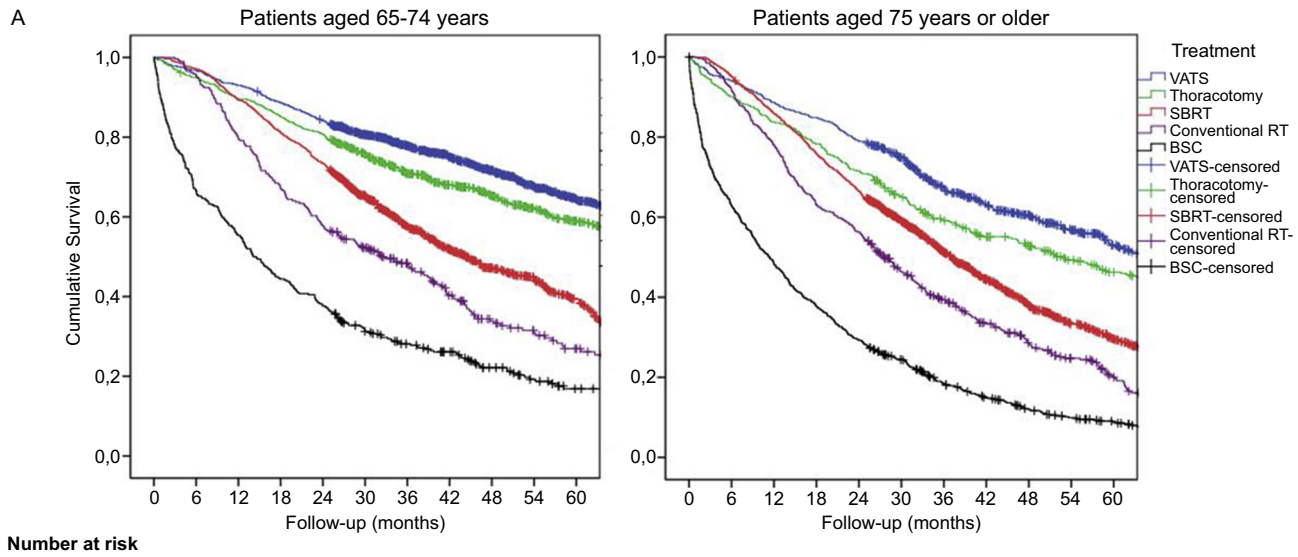
Table 1
Overview of patient and tumor characteristics of older patients with stage I-II non-small cell lung cancer (2010–2015) according to stage and age groups.

Stage	I			II		
Age years n (%)	65–74 4694 (54)	≥75 4048 (46)	P-value	65–74 1774 (52)	≥75 1665 (49)	P-value
Median age years (IQR)	69 (67–72)	79 (77–82)	<0.01[a]	69 (67–72)	79 (77–83)	<0.01[a]
Gender Male %	59	65	<0.01[a]	66	75	<0.01[a]
Histology %			<0.01[a]			<0.01[a]
Squamous CC	31	27		48	51	
Adenocarcinoma	41	27		36	22	
NOS/ large CC	28	46		17	27	
Stage %			0.01[a]			0.30
A	68	66		46	48	
B	32	34		54	52	
Treatment%			<0.01[a]			<0.01[a]
VATS	32	16		25	13	
Thoracotomy	23	11		40	22	
SBRT	29	42		5	11	
Conventional RT	6	11		10	24	
Chemotherapy	1	0,5		3	2	
Chemoradiotherapy	1	0,5		9	5	
BSC	8	19		9	25	
Comorbidity[b]						
Available n (%)	866 (18)	709 (18)		332 (19)	300 (18)	
Number %			0.002[a]			0.42
0	8	4		13	10	
1	26	23		24	23	
≥2	66	73		63	67	
Type %						
Respiratory	45	41	0.06	34	34	0.99
Cardiovascular	51	58	0.06	50	54	0.24
Hypertension	36	38	0.55	34	41	0.08
DM	14	21	0.001	15	19	0.15
Previous malignancy	36	42	0.02	28	29	0.92
CVA/hemiplegia	5	8	0.004	9	12	0.28
Digestive	8	9	0.76	9	7	0.27

Abbreviations: n 'Number' IQR 'InterQuartile Range', CC 'cell carcinoma', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care', CVA 'Cerebrovascular accident', DM 'Diabetes Mellitus'.

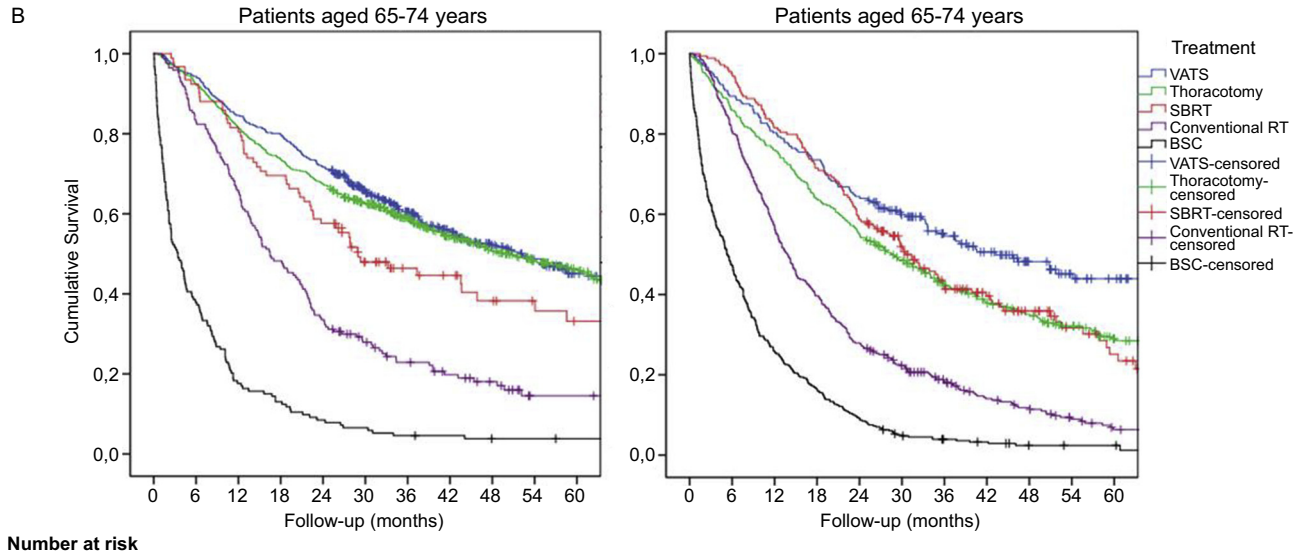
[a] indicates significant differences between age groups.

[b] Subanalyses of 2207 patients (18%) with available information on comorbidity.



Number at risk

VATS	1596	1482	1335	971	661	379	703	624	559	395	289	173
Thoracotomy	1089	975	879	673	525	398	432	362	309	238	195	146
SBRT	1340	1197	984	581	338	188	1709	1466	1135	688	379	205
Conventional RT	292	232	169	112	61	37	446	348	251	151	91	46
BSC	280	128	75	43	25	8	707	322	181	91	45	22



Number at risk

VATS	445	376	319	205	128	69	211	170	137	88	50	30
Thoracotomy	703	572	474	349	246	178	362	275	199	130	99	58
SBRT	92	74	53	26	18	15	179	146	105	56	32	15
Conventional RT	170	112	57	31	18	8	391	222	109	57	31	11
BSC	149	24	10	6	4	3	409	103	35	11	4	3

Fig. 2. (a) Kaplan-Meier survival curves of older patients with stage I non-small cell lung cancer (2010–2015) according to age groups and treatment including the number of patients at risk (VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care'). (b) Kaplan-Meier survival curves of older patients with stage II non-small cell lung cancer (2010–2015) according to age groups and treatment including the number of patients at risk (VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care').

One-year and five-year OS rates were displayed in Table 2. For stage I NSCLC, these OS rates were significantly higher for patients aged 65–74 years (87% and 49%, respectively) compared to those aged ≥75 years (78% and 31%, respectively). After stratification of treatment, both one-year and five-year OS rates were significantly higher for patients aged 65–74 years compared to those aged ≥75 years for all

Table 2
Overall survival rates and median overall survival of older patients with stage I-II non-small cell lung cancer (2010–2015) according to stage, age groups, and treatment.

Stage	I		II	
Age years	65–74	≥75	65–74	≥75
1-year OS % (95%CI) Treatment	87 (86–88)[a]	78 (77–79)[a]	74 (72–76)[a]	60 (57–62)[a]
VATS	93 (92–94)[a]	89 (86–91)[a]	85 (81–88)	80 (75–86)
Thoracotomy	90 (88–91)[a]	84 (80–87)[a]	81 (78–84)	76 (72–80)
SBRT	89 (88–91)[a]	86 (84–87)[a]	80 (72–89)	82 (76–87)
Conventional RT	79 (75–84)	78 (74–82)	66 (59–73)	57 (52–62)
BSC	55 (50–61)[a]	45 (42–49)[a]	18 (12–24)	25 (22−30)
5-year OS % (95%CI)	49 (48–51)[a]	31 (29–32)[a]	36 (34–39)[a]	18 (16–20)[a]
Treatment				
VATS	64 (62–67)[a]	53 (49–58)[a]	45 (39–50)	43 (36–51)
Thoracotomy	59 (56–62)[a]	46 (42–51)[a]	46 (42–50)[a]	29 (24–34)[a]
SBRT	40 (36–43)[a]	30 (27–33)[a]	33 (22–45)	27 (19–36)
Conventional RT	27 (21−33)	20 (16–25)	14 (8.2–21)	6.7 (3.7–9.6)
BSC	17 (12−21)[a]	8.8 (6.5–11)[a]	3.8 (0.7–6.9)	2.3 (0.7–3.9)
Median OS months (95%CI) Treatment	60 (57–63)[a]	33 (32–35)[a]	35 (31–38)[a]	17 (15–18)[a]
VATS	83 (76–91)[a]	65 (57–73)[a]	52 (43–61)	43 (31–56)
Thoracotomy	82 (75–90)[a]	53 (42–64)[a]	50 (42–58)[a]	29 (24–34)[a]
SBRT	44 (40–48)[a]	37 (35–39)[a]	29 (19–39)	30 (26–35)
Conventional RT	32 (25–39)	28 (24–31)	16 (13−20)	14 (12–15)
BSC	14 (12–17)	11 (9.8–13)	34 (2.1–4.7)	5.3 (4.3–6.3)

Abbreviations: 95%CI '95% Confidence Interval', OS 'Overall Survival', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'radiotherapy', BSC 'best supportive care'.
[a] Indicates significant differences when confidence intervals between age groups are not overlapping.

treatments. However, one-year OS was comparable between age groups for conventional RT and five-year OS were comparable for both conventional RT and SBRT. For stage II NSCLC, one-year and five-year OS rates were significantly higher for patients aged 65–74 years (74% and 36%, respectively) compared to those aged ≥75 years (60% and 18%, respectively, Table 2). After stratification of treatment, one-year OS was comparable between age groups for all treatment options. The five-year OS rates were significantly different between age groups for thoracotomy

Table 3
Multivariable cox proportional hazard ratios of older patients diagnosed with stage I-II non-small cell lung cancer (2010–2015) according to stage.

Stage		I		II	
		HR (95%CI)	P-value	HR (95%CI)	P-value
Model 1					
Age	65–74 years	Reference		Reference	<0.01
	≥75 years	1.3 (1.2–1.3)	<0.01	1.1 (0.99–1.3)	
Gender	Male	Reference		Reference	<0.01
	Female	0.79 (0.75–0.84)	<0.01	0.86 (0.78–0.94)	
Histology	Squamous CC	Reference		Reference	
	Adenocarcinoma	0.86 (0.79–0.92)	<0.01	0.92 (0.83–1.0)	0.11
	NOS/large CC	1.0 (0.97–1.1)	0.23	1.0 (0.91–1.1)	0.78
Stage	A	Reference		Reference	
	B	1.5 (1.4–1.6)	<0.01	0.78 (0.72–0.86)	<0.01
Treatment	VATS	Reference		Reference	
	Thoracotomy	1.1 (0.98–1.2)	0.13	1.3 (1.1–1.6)	0.06
	SBRT	1.9 (1.7–2.1)	<0.01	1.3 (1.1–1.6)	0.01
	Conventional RT	2.4 (2.2–2.7)	<0.01	2.7 (2.3–3.2)	<0.01
	BSC	5.0 (4.5–5.5)	<0.01	6.6 (5.7–7.7)	<0.01
Model 2 [a]					
Age	65–74 years	Reference		Reference	
	≥75 years	1.3 (1.1–1.5)	<0.01	1.3 (1.1–1.7)	0.01
Gender	Male	Reference		Reference	
	Female	0.79 (0.68–0.91)	<0.01	0.92 (0.73–1.2)	0.49
Histology	Squamous CC	Reference		Reference	
	Adenocarcinoma	0.93 (0.78–1.1)	0.41	1.1 (0.88–1.5)	0.35
	NOS/large CC	1.1 (0.91–1.3)	0.29	1.1 (0.86–1.4)	0.46
Stage	A	Reference		Reference	
	B	1.5 (1.3–1.7)	<0.01	0.71 (0.58–0.86)	<0.01
Treatment	VATS	Reference		Reference	
	Thoracotomy	1.2 (0.92–1.5)	0.23	0.995 (0.74–1.3)	0.98
	SBRT	1.9 (1.5–2.3)	<0.01	2.5 (1.6–3.8)	<0.01
	Conventional RT	2.6 (2.0–3.4)	<0.01	2.8 (2.0–3.9)	<0.01
	BSC	4.2 (3.3–5.3)	<0.01	7.2 (5.1–10)	<0.01
Number of comorbid conditions	0	Reference		Reference	
	1	1.3 (0.93–1.8)	0.13	0.92 (0.64–1.3)	0.64
	≥2	1.5 (1.1–2.1)	0.01	0.93 (0.68–1.3)	0.66

Abbreviations: HR 'Hazard Ratio', 95%CI '95% Confidence Interval', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care', CC 'Cell Carcinoma', NOS 'Not Otherwise Specified'.
[a] Subanalyses of 2207 patients (18%) with available information on comorbidity.

(46% vs 29%) and SBRT (33% vs 27%), but were comparable for all other treatment options.

The adjusted HR of death are displayed in Table 3. Patients aged ≥75 showed a significant 1.3-fold higher HR of death compared to those aged 65–74 years for both stages (model 2 (including comorbidity as well)). The HR of death was also significantly higher for SBRT (stage I: HR 1.9 (95%CI 1.5–2.3); stage II: HR 2.5 (95%CI 1.6–3.8)) and conventional RT (stage I: HR 2.6 (95%CI 2.0–3.4); stage II: HR 2.8 (95%CI 2.0–3.9)) compared to VATS, and the highest HR of death was seen for BSC (stage I: HR 4.2 (95%CI 3.3–5.3); stage II: HR 7.2 (95%CI 5.1–10)). For patients with stage I NSCLC, females showed a significantly decreased HR of death compared to males (HR 0.79 (95%CI 0.68–0.91)). A significant higher HR of death was seen for patients with stage IB (HR 1.5 (95%CI 1.3–1.7)) compared to stage IA, and for ≥2 comorbid conditions (HR 1.5 (95%CI 1.1–2.1)) compared to no comorbid conditions. For patients with stage II NSCLC, stage IIB was associated with significantly decreased HR of death compared to stage IIA (HR 0.71 (95%CI 0.58–0.86)).

4. Discussion

Evidence regarding treatment options and outcomes are scarce for older patients with NSCLC and evidence-based insights are highly needed for this vulnerable population. The aim of this study was to compare treatment patterns and OS between patients aged 65–74 years and those aged ≥75 years with clinical stage I and II NSCLC in daily clinical practice. Patients aged ≥75 years underwent surgery less often, and received SBRT, conventional RT, and BSC more often than patients aged 65–74 years in both stages. Superior one-year OS was seen for VATS, thoracotomy, and SBRT among patients aged 65–74 years compared to those aged ≥75 years with stage I NSCLC. However, one-year OS was similar between those treatment options and both age groups among patients with stage II NSCLC. Superior long-term OS was seen for VATS and thoracotomy among both age groups with stage I NSCLC and among those aged 65–74 years with stage II NSCLC. However, superior long-term OS for patients aged ≥75 years with stage II NSCLC was found after VATS. After adjustment for known prognostic factors including comorbidity, the HR of death remained significantly higher for patients aged ≥75 years compared to their younger counterparts in both stage groups.

The current study found that older patients with NSCLC undergo surgery less often compared to younger patients [5]. Recently, improvements in survival after both surgery and RT have been found [5,24]. While SBRT is recommended for inoperable patients over non-SBRT radiotherapy techniques [2,25], the superiority of surgical resection over SBRT is debated for operable and older patients [7,26]. In our study, similar one-year OS rates were found for VATS and SBRT within age groups. Comparable short-term survival outcomes for surgery and RT were also found in a retrospective multicenter cohort [27], a large registration database [8], clinical trials including operable patients [7], and a meta-analysis [28]. However, long-term OS in our study was superior for VATS and thoracotomy among patients aged 65–74 years in both stages and for those aged ≥75 years with stage II, whereas only VATS was superior for those aged ≥75 years with stage II NSCLC. SBRT was associated with better OS compared to conventional RT in both age groups, which was also found in a meta-analysis without age-restrictions [25]. Although the adjusted HR of death for both conventional RT and SBRT were increased compared to VATS, this increase was higher for conventional RT than SBRT in our study. SBRT could be a treatment option for older adults with stage I NSCLC, as local control rates of >90% can be achieved after five years [6], and treatment tolerance is acceptable [29]. Moreover, the safety and effectiveness of SBRT for patients aged ≥80 years was previously demonstrated [30], and comparable short term survival rates were previously found for surgery and radiotherapy among patients aged ≥85 years [31], which are partially represented in our dataset as well. A small proportion of patients with stage II NSCLC received SBRT. Although this treatment is not standard for stage II disease, it could be an option for specific situations and is administered to patients with tumors >5 cm in the Netherlands [32]. Although, short-term OS after SBRT within age and stage groups seemed comparable to VATS in our study, long-term outcomes remain to be in favor of surgery in both older age groups. However, SBRT should not be withheld from older patients based on stage alone and it should be kept in mind that surgical patients with long-term survival are a selected subpopulation among older patients with NSCLC and are more likely to be included in clinical trials.

Explanations for poorer OS in older patients are diverse and could depend on a combination of age ≥ 75 years [10,33], short life expectancy [34], (undiagnosed or unforeseen) lymph node metastases [35], poorer physical performance [9,11], and comorbid conditions [2,9]. It was expected that pulmonary comorbid conditions would be different between age groups, impacting treatment choice among the oldest group and negatively impacting OS [9,36,37]. Differences in OS between treatment groups were significant, and it is expected that younger and fitter patients were selected for surgery compared to radiotherapy in both stages [2]. Although we were able to adjust the HR of death for the number of comorbid conditions, adjustment was not optimal as severity of comorbidity was not available. Treatment decisions could also depend on other prognostic factors than those accounted for in this study, such as performance status, cognitive status, pulmonary function, and preferences of the patient [10]. Patient involvement in treatment decision-making is important as almost half of patients with stage I-II NSCLC experience conflicts in treatment decision-making, and one in three patients feel uninformed [38]. This implies that not only patient or tumor characteristics should be taken into account to determine which treatment is the most optimal for each older individual, but patient-centered outcomes should be taken into account as well [39]. A recent study found that health utility, or summarized quality of life, was not significantly different between patients receiving surgery or SBRT for stage I NSCLC [40]. Insights regarding treatment patterns and OS in daily clinical practice would be even more valuable when associated with patient preferences and patient-centered outcomes [38]. This information could improve the treatment decision-making process for both patients and physicians and outcomes for the heterogeneous group of older patients with stage I and II NSCLC.

Strengths of this population-based study were the nationwide coverage and inclusion of unselected patients with clinical stage I-II NSCLC between 2010 and 2015 in the Netherlands. This leads to more generalized results compared to other studies including institutional data. Other strengths were the high quality standard of included data, the completeness regarding obtained treatment, and the availability of information on comorbidity in the southeastern part of the Netherlands. Furthermore, all citizens in the Netherlands have equal access and imbursement to healthcare. Altogether, this leads to the selection of (almost) all patients in the given period, and a description of treatment and survival which is not influenced by financial resources. However, some limitations should be mentioned. As this is an observational study, causal relations cannot be drawn. Dutch practice guidelines indicate that patients who present with a high-risk profile of lung cancer are suspected of stage I NSCLC based on a new or growing [18] FDG-PET positive lesion. These patients are diagnosed with a primary (stage I) lung tumor [41]. Information regarding treatment choice, performance status, radiation dose, hospitalization, completion of treatment, pulmonary function, and adverse events was unavailable. Information on comorbidity was known for 18% of patients. Nevertheless, valuable insights have been gained regarding treatment, OS, and adjusted risks of death for both older age groups and stages. Despite a median follow-up of 58 months, five-year OS rates could have been slightly higher if a longer follow-up period could have been taken into account. The fairly large difference in OS between SBRT and conventional RT could be explained by some patients receiving palliative doses of conventional RT. Unfortunately, information on palliative or curative doses was not available. Also, some tumors can only be treated

with SBRT due to the location and risk of surgery related complications. Furthermore, confounding by indication should be considered, as treatment choice in clinical practice partially depends on patient characteristics such as comorbid conditions. Also, therapeutic nihilism is of significant importance for the interpretation of treatment patterns and outcomes among older patients, as it can be thought that (standard) treatment would be more harmful than beneficial.

Since clinical trials including older patients often suffer from slow accrual and restrictions regarding age, performance and cognitive status and comorbid conditions, large nation-wide cohort studies including big data collection including treatment selection, and patient centered outcomes can help with generalizability and treatment decision making [42]. Also, wishes and expectations of both patients and caregivers should have a more prominent role in the treatment-decision process to gain the most optimal and personal treatment decision [38,43]. Altogether, evidence can be gained for the heterogeneous population with often vulnerable and frail older patients who are not always fit for surgery, in the light of the best evidence, clinician's expertise, and preferences of patients and caregivers.

4.1. Conclusion

Patients aged ≥75 years with stage I and II NSCLC underwent surgery less often than those aged 65–74 years and had poorer OS, even after adjustment for other known prognostic factors. In both stages, one-year OS within age groups was similar for surgery and SBRT. However, adjusted long-term OS was superior for surgery compared to SBRT and remained poorer for those aged ≥75. These findings could form the basis for impactful trials as older patients cannot be compared based on age alone. The perspectives regarding treatment and survival for this heterogeneous and vulnerable group of older patients with stage I-II NSCLC should be optimized by prospective research focusing on predictive patient characteristics for treatment selection and patient-centered outcomes such as complications and quality of life with respect to survival.

Conflicts of Interest

Prof. Dr. D de Ruysscher previously received research grants and fees. These were gained by the institution for previous research and not personally. Other (co-)authors did not declare conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship contributions

Specific contributions to different parts of the manuscript were as follows:

- Study concepts: Ms. Driessen, Mrs. Janssen-Heijnen, and Mrs. Aarts
- Study design: Ms. Driessen and Mrs. Janssen-Heijnen
- Data acquisition: Data managers of the Netherlands Comprehensive Cancer Organization
- Quality control of data and algorithms: Ms. Driessen, Mrs. Aarts, Netherlands Comprehensive Cancer Organization
- Statistical analysis: Ms. Driessen
- Manuscript preparation: Ms. Driessen
- Manuscript editing and review: all authors

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