Treatment with curative intent of stage III non-small cell lung cancer patients of 75 years: A prospective population-based study

Rinus Wanders [a], Jessie Steevens [b], Anita Botterweck [a], Anne-Marie C. Dingemans [c], Bart Reymen [a], Angela van Baardwijk [a], Jacques Borger [a], Gerben Bootsma [d], Cordula Pitz [e], Ragnar Lunde [f], Wiel Geraedts [g], Philippe Lambin [a], Dirk De Ruysscher [a,*]

[a] Department of Radiation Oncology (MAASTRO Clinic), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands
[b] Comprehensive Cancer Center The Netherlands, Location Maastricht, Maastricht, The Netherlands
[c] Department of Pulmonology, Maastricht University Medical Center, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands
[d] Department of Pulmonology, Atrium Medical Centre, Heerlen, The Netherlands
[e] Department of Pulmonology, Laurentius Hospital, Roermond, The Netherlands
[f] Department of Pulmonology, St. Jansgasthuis, Weert, The Netherlands
[g] Department of Pulmonology, Orbis Medical Centre, Sittard, The Netherlands

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ABSTRACT

Background: There is little data on the survival of elderly patients with stage III non-small cell lung cancer (NSCLC).

Methods: Patients with stage III NSCLC in the Netherlands Cancer Registry/Limburg from January 1, 2002 to December 31, 2008 were included.

Findings: One thousand and two patients with stage III were diagnosed, of which 237 were 75 years or older. From 228 patients, co-morbidity scores were available. Only 33/237 patients (14.5%) had no co-morbidities, 195 (85.5%) had one or more important co-morbidities, 60 (26.3%) two or more co-morbidities, 18 (7.9%) three or more co-morbidities and 2 patients (0.9%) suffered from four co-morbidities. Forty-eight percent were treated with curative intent. No significant difference in Charlson co-morbidity, age or gender was found between patients receiving curative or palliative intent treatment. Treatment with curative intent was associated with increased overall survival (OS) compared to palliative treatment: median OS 14.2 months (9.6–18.7) versus 5.2 months (4.3–6.0), 2-year OS 35.5% versus 12.1%, for curative versus palliative treatment.

Findings: Patients who received only radiotherapy with curative intent had a median OS of 11.1 months (95% confidence interval [95% CI] 6.4–15.8) and a 5-year OS of 20.3%; for sequential chemotherapy and radiotherapy, the median OS was 18.0 months (95% CI 12.2–23.7), with a 5-year OS of 14.9%. Only four patients received concurrent chemo-radiation.

Interpretation: In this prospective series treating elderly patients with stage III NSCLC with curative intent was associated with significant 5-year survival rates.

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1. Introduction

Non-small cell lung cancer (NSCLC) remains one of the most lethal and frequent cancers world-wide.[1–3] The disease occurs most frequently in the elderly population, with about 50% of the patients being 70 years or older and approximately 25% over the age of 74 years.[1,2,4] With current demographic trends both in Europe, the United States and in major Eastern countries, the absolute number and the proportion of elderly patients with lung cancer will further increase in the coming decades.[1,2] Because of the age distribution and the smoking history of most lung cancer patients, the majority of them present with major co-morbidities at the time of diagnosis, which may render many patients not suitable for aggressive treatments and which will lead to higher non-cancer related deaths in this population.[4,5]

Although concurrent chemo-radiotherapy has become the treatment with the best chance for long-term survival in patients with stage III NSCLC, there are scarce data on the outcome of elderly patients treated with curative intent for stage III NSCLC.[6–13] Elderly patients entered in clinical trials consistently showed more haematological toxicity than the younger group, a finding which was also observed in advanced stage elderly patients.[8,9,12–15] Elderly patients also experienced more non-haematological toxicity, although this varied between trials: In NCCTG 94-24-52, they had more pneumonitis, more oesophagitis in RTOG 94-10, and more renal complications in CALGB 9130.[8,9,13] Despite the increased level of toxicity experienced by the elderly patients, their survival was similar to that observed in younger individuals. The question how to deal with the 75 years and older group with stage III NSLC remains unanswered.[16–19]

In the present study, we investigated in a large prospective population-based registry the outcome of patients treated with curative or palliative intent.

2. Patients and methods

2.1. Netherlands Cancer Registry/ Limburg (NCR/L)

All patients with a pathological diagnosis of NSCLC[20] in south and middle Limburg and with stage III (UICC 6th Edition[21]) from January 1, 2002 to December 31, 2008 were included. Data were obtained from the population-based Netherlands Cancer Registry (NCR) of the Comprehensive Cancer Centre the Netherlands. The NCR/L is a population-based cancer registry, which was established in 1984 and is a department of the Comprehensive Cancer Centre the Netherlands-Location Maastricht. The NCR/L covers the region of mid and southern Limburg, which is situated in the southeast of The Netherlands. On 1 January 2006, the region covered a total of 853,553 inhabitants. The main sources of information are regional hospitals and pathology laboratories from which the NCR/L receives reports on a weekly basis since 1986. After receiving the notification reports, trained registration clerks collect all relevant data of the patients and tumours from the medical records.

Information on topography and morphology was coded according to the International Classification of Diseases for Oncology, 3rd Edition.[21] Tumour stage was recorded in accordance with the tumour–node–metastasis classification system.[21] Completeness of case ascertainment of the NCR/L is very high; for lung cancer, this is estimated to be >95%.[22]

2.2. Co-morbidity

Co-morbidity of all lung cancer patients was scored using the Charlson co-morbidity index (CCI).[23] Co-morbidity was defined as disease that was present at the time of diagnosis and was prospectively retrieved from hospital records.

2.3. Staging and treatment

Only patients without a malignant pleural or cardiac effusion were offered treatment with curative intent. Patients were staged with a whole body ^{18}F-deoxyglucose (FDG)-Positron Emission Tomography (PET) scan and a CT or MRI of the brain unless on a regular CT scan of the chest and the upper abdomen metastases were already visualised. Patients were treated according to standard regional protocols.

According to the regional guidelines, the treatment of choice for patients with stage III (T4 and/or N2-3) NSCLC was concurrent chemo-radiotherapy. Patients with T3N1M0 tumours were treated with a lobectomy and a lobe-specific nodal dissection. Adjuvant chemotherapy was not applied in the studied time period in elderly patients.

In practice, however, the multidisciplinary team, comprising at least a pulmonologist specialised in lung cancer, a thoracic surgeon, a radiation oncologist, a radiologist, a nuclear medicine specialist and a pathologist, was left free to choose the most appropriate treatment for an individual patient. Thus, elderly patients often received sequential chemotherapy and radiotherapy, radiotherapy alone, chemotherapy alone or best supportive care, which could include palliative radiotherapy.

Sequential chemotherapy consisted of cisplatin (75 mg/m^2) or carboplatin (AUC 5) on day 1 and gemcitabine 1250 mg/m^2 on day 1 and 8. Cycles were repeated every 21 days for a total of 3 cycles. The carboplatin dose in milligrams was based on the target AUC (5) × (glomerular filtration rate + 25), with the glomerular filtration rate calculated according to the Cockroft–Gault formula. Standard dose-reduction rules were applied if indicated. In non-progressive patients (RECIST criteria), based on a CT scan of the chest, the primary tumour and the involved lymph nodes were treated with radiotherapy.[24] The dose was specified according to ICRU 50 guidelines.[25] From 2002 to 2005, radiotherapy consisted of a dose of 60 Gy in 30 fractions in 6 weeks. From 2006, individualised accelerated radiotherapy to the primary tumour and the pre-treatment involved lymph nodes on FDG-PET-CT scan was given after induction chemotherapy.[26] The mean radiation dose was 64.8 Gy given in 36 bi-daily fractions of 1.8 Gy with at least 8 h of inter-fraction interval in an overall treatment time of 3.6 weeks.[27] This is a biological

equivalent of a dose of 82 Gy in 41 daily fractions given in 8.2 weeks.

Also from 2006, concurrent chemo-radiation, after 2 cycles or carboplatin-gemcitabine, concurrent cisplatin–vinorelbine (cisplatin 50 mg/m^2 day 2 and 9, vinorelbine 20 mg/m^2 day 2 and 9, cisplatin 40 mg/m^2 day 23, vinorelbine 15 mg/m^2 day 23 and 30; day 1 is the first day of radiotherapy) and radiotherapy to the primary tumour and the lymph nodes involved on FDG-PET-CT was allowed for patients with a WHO performance status 0–1 and without >10% weight loss over the last 6 months. Individualised accelerated radiotherapy with analogous normal tissue constraints as those for sequential chemo-radiotherapy was given.[27] In the first three weeks, 30 twice-daily fractions of 1.5 Gy were given, followed by once-daily fractions of 2 Gy until a mean lung dose of 19 Gy was reached.[28] A mean radiation dose to the tumour and the involved lymph nodes of 65 Gy delivered in 5.5 weeks was given. This corresponds to a biological equivalent of 74 Gy given in 36 daily fractions in 7.4 weeks.

For patients not treated with curative intent, the treatment was left to the discretion of the treating physician. Both best supportive care, which included palliative radiotherapy, and chemotherapy, mainly consisting of carboplatin and gemcitabine were given. Targeted agents were not employed outside of clinical trials in the time periods studied in the present report.

2.4. Follow-up

Patients were seen by the pulmonologist or the radiation oncologist the first weeks after the end of treatment until the acute side-effects resolved to grade 1, and thereafter every three months the first two years, every six months from year 3 to 5 and every year after 5 years. A CT scan or an X-ray of the chest was done regularly or on indication.

2.5. Statistics

Survival was calculated from the date of diagnosis till death using the Kaplan–Meier method with SPSS Statistics version 17.0. Median survival rates are expressed together with their 95% confidence intervals (CI). Other results are expressed as mean ± standard deviation (SD) and their range. Differences between proportions were calculated with Chi-square tests. Differences with a p-value < 0.05 were considered significant.

The minimal follow-up of all patients is 2 years. Survival was updated in January 2011.

3. Results

3.1. Patient characteristics

From January 1, 2002 to December 31, 2008, 1002 patients with stage III NSCLC were diagnosed, of which 545 were less than 70 years old, 220 between 70 and 74 years and 237 75 years or older.

The mean age of the elderly group, i.e. 75 years or older, was 78.9 ± 3.5 years (range 75–90). One-hundred ninety-four patients (81.9%) were male, and 43 (18.1%) female. Seventy-four patients (31.2%) had stage IIIA NSCLC and 163

(68.8%) stage IIIB. The detailed T- and N-stage is depicted in Table 1.

NSCLC-not otherwise specified was the most frequent entity with 108 patients (45.5%), followed by squamous cell cancer (87 patients; 36.7%), adenocarcinoma (40 patients; 16.8%) and bronchiolo-alveolar carcinoma (2 patients; 0.8%).

Most tumours were located in the upper lobe (134 patients; 56.5%), 70 (29.5%) in the lower lobe, 17 (7.2%) in the main bronchus, 5 (2.1%) in the middle lobe, 4 (1.7%) growing directly from one lobe in the adjacent lobe and from 7 patients (3.0%), the exact location could not be retrieved. Hundred thirty-four tumours (56.5%) were right-sided, 102 (43%) in the left lung and in one patient unknown.

From 228 of the 237 (96.2%) elderly patients, co-morbidity scores were available. Only 33 patients (14.5%) had no co-morbidities, 195 (85.5%) had one or more important co-morbidities, 60 (26.3%) two or more co-morbidities, 18 (7.9%) three or more co-morbidities and 2 patients (0.9%) suffered from four co-morbidities. The most frequent co-morbidities were chronic obstructive pulmonary disease (COPD) (73 patients; 32%); myocardial infarction (68 patients; 29.8%), another malignancy in the medical history (62 patients; 27.2%), diabetes mellitus (40 patients; 17.5%) and hypertension (48 patients; 21%). Co-morbidities are summarised in Table 2.

The co-morbidities in the 765 patients younger than 75 years with stage III NSCLC in our region were: No co-morbidities: 242 patients (31.6%), one: 229 patients (29.9%), two: 150 patients (19.6%), three: 87 patients (11.4%), four: 13 patients (2.5%), five co-morbidities: 17 patients (2.2%), missing co-morbidity score: 21 patients (2.7%). The elderly group showed thus more co-morbidities, which were more often multiple. The disease distribution in the co-morbidities was, however, similar in the elderly than in the younger group, except for malignancy in their medical history (data not shown).

3.2. Treatment

One hundred and thirteen patients (47.7%) were treated with curative intent and 124 (52.3%) palliatively. Patients with stage IIIA were more likely getting a treatment with curative intent than individuals with stage IIIB: 46/75 (62.2%) versus 67/163 (41.1%), respectively; $p < 0.001$. From the 124 patients with a T4 tumour, 50 were treated with curative intent (40.3%), in

Table 1 – TNM distribution.		
T- and N-distribution	n	%
T0N3	3	1.3
T1N2	7	3.0
T1N3	5	2.1
T2N2	57	24.1
T2N3	24	10.1
T3N1	8	3.4
T3N2	21	8.9
T3N3	4	1.7
T4N0	36	15.2
T4N1	1	0.4
T4N2	54	22.8
T4N3	17	7.2

Table 2 – Co-morbidities of all patients (n = 228).		
Co-morbidity	n	%
None	33	14.5
COPD	73	32.0
Myocardial infarction	68	29.8
Other malignancy	62	27.2
⩽5 years[a]	37	16.2
6–10 years[a]	11	4.8
>10 years[a]	14	6.1
Hypertension	48	21.0
Diabetes mellitus	40	17.5
Cardiac arrhythmia	34	14.9
Peripheral vascular disease	29	12.7
CVA	18	7.9
Cardiac failure	16	7.0
Cardiac valvular disease	15	6.6
Peptic ulcer	9	3.9
Thrombosis	7	3.1
Diverticulitis	3	1.3
Cardiomyopathy	3	1.3
Rheumatoid arthritis	2	0.9
Chronic inflammatory bowel disease	2	0.9
Dementia	2	0.9
Gastric resection	2	0.9
Psychiatric disorder	1	0.4
Tuberculosis	1	0.4
Parkinson's' disease	1	0.4
Glomerulonephritis	1	0.4
Haemodialysis	1	0.4

n = Number of patients.
COPD: Chronic Obstructive Pulmonary Disease.
CVA: Cerebral Vascular Accident.
[a] Years before current stage III NSCLC diagnosis.

Fig. 1 – Overall survival of patients 75 years or older with stage III NSCLC treated with curative intent (n = 113, blue line) or palliatively (n = 124, green line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the N2 group 67 received therapies with curative intent (53.2%) and in the N3 group 23 patients (43.4%). These differences are significantly different from each other (p < 0.001).

No significant difference in Charlson co-morbidity, age or gender was observed between patients treated with curative or palliative intent, with 50.3% of patients in the curative intent group having two or more co-morbidities versus 59.7% in the palliative group.

The median overall survival (OS) and the survival at 2 years were 14.2 months (95% CI 9.6–18.7) versus 5.2 months (95% CI 4.3–6.0) and 35.5% versus 12.1%, for curative intent versus palliative therapy, respectively (Fig. 1).

Patients who received only best supportive care (n = 85) had a median OS of 3.6 months (95% CI 2.6–4.6), a 1-year survival of 11.8%, a 2-year survival of 4.7% and no survivors at 3 years. When palliative chemotherapy was given (n = 29), the median OS was 7.7 months (95% CI 5.3–10.0), a 1-year OS of 27.6%, a 2-year OS of 20.7% and 1 patient (8.3%) being alive after 5 years. For 85 patients who received only radiotherapy, the median OS reached 11.1 months (95% CI 6.4–15.8), with a 1-, 2-, and 5-year OS of 47.6%, 31.7% and 20.3%, respectively. Fifty-one patients received chemotherapy and radiotherapy. As only four of them got concurrent chemo-radiation, these individuals were included in the same group. Chemo-radiotherapy lead to a median OS of 18.0 months (95% CI 12.2–23.7), with a 1-year OS of 62.7%, 2-year OS of 39.2% and a 5-year OS of 14.9%.
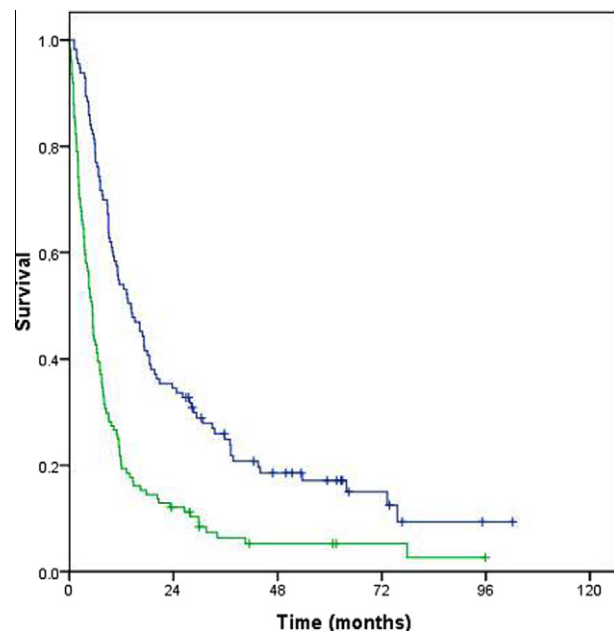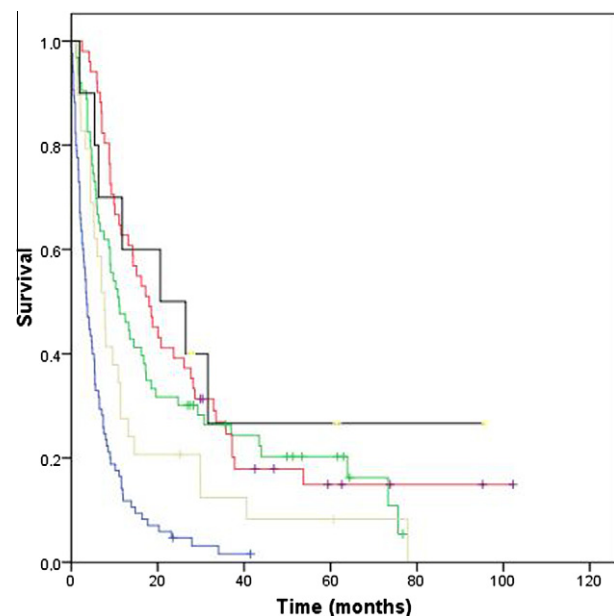

Fig. 2 – Overall survival of patients 75 years or older with stage III NSCLC according to different treatments. Blue: Best supportive care (n = 85); Grey: Palliative chemotherapy (n = 29); Green: Radiotherapy alone (n = 85); Red: Sequential chemotherapy and radiotherapy (n = 51); Black: surgery (n = 10). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Surgery was performed in 10 patients: eight with a T3N1 tumour and two with a T4N0 cancer because of multiple nodes in the same lobe. The median OS in this group was 20.6 months (95% CI 0–43.4), with 1-, 2-, and 5-year survival rates of 60%, 50% and 26.7%, respectively.

3.3. Results are summarised in Fig. 2

Fourty-nine percent of patients younger than 75 years with stage III NSCLC in the same region received treatment with curative intent. This is thus the same as for the elderly. However, of the 765 younger patients, 84 (10.9%) were treated with surgery only: 15 patients had a T4N0 cancer because of multiple nodules in the same lobe and 64 had T3N1 disease. Thirteen patients received induction chemotherapy followed by resection for the following stages: T1N2 (1 patient), T2N2 (7 patients), T4N2 (3 patients) and T2N3 (2 patients).

In the same younger age group in the same time period, 323 patients (42.2%) were treated with chemo-radiation, of which 62 individuals with concurrent chemotherapy and radiotherapy.

Best supportive care was given in 123 younger patients (16.1%), chemotherapy alone in 174 patients (22.7% and radiotherapy alone in 40 patients (5.2%).

The elderly thus received both less sequential and concurrent chemo-radiotherapy than the younger patients and were more likely to be treated with high-dose radiotherapy alone.

4. Discussion

Lung cancer is increasingly a disease of the elderly. On a population basis, about 50% of the patients are over 70 years and 25% 75 years or older.[1–4] In the present series, we investigated the survival of 237 patients 75 years or older with stage III NSCLC. As expected, only 14.5% of these patients did not have co-morbidities. Forty-eight percent were treated with curative intent. No significant difference in Charlson co-morbidity, age or gender was found between patients receiving curative or palliative intent treatment. The overall survival at 2-years was 35.5% for patients treated with curative intent, compared to 12.1% when treated palliatively. Interestingly, even in these elderly stage III NSCLC patients, significant 5-year survival rates could be achieved when treatment with curative intent was given. When treated with radiotherapy only, 20.3% were alive at 5 years, which was 14.9% with sequential chemotherapy and radiotherapy.

Our results thus show that with proper patient selection, reasonable long-term survival rates can be achieved when treating elderly patients with stage III NSCLC with curative intent.

In the literature, scare data are available on the outcome of the elderly with stage III NSCLC.[16–19] Although several subgroup analyses from randomised trials suggest that elderly patients may benefit from treatment similar to younger individuals, only a few patients were 75 years or older and they were already selected for inclusion in studies, thus identifying the fittest of all.[8–13]

Although the definition of the exact age limit of what 'elderly' is diverges between studies, it is clear that the physiolog-ical status of individuals over 75 years differs from younger patients, which may be reflected in changes in pharmacokinetics of drugs and organ reserves.[14,29] The observation that elderly patients have more haematological toxicity after the administration of cytotoxic drugs is consistent with these findings.[8,9,12–14] More important than the chronological age, the patients' functional age should probably determine his capacity to undergo aggressive anti-cancer treatment or not.[29] This includes the evaluation of health, functional status, nutrition, cognition and the psychosocial and economic context.

This could be achieved with the development of better prognostic algorithms and geriatric assessments specifically designed for elderly with lung cancer.[8,9,12–14,30–36] The finding in our series that only four patients received concurrent chemo-radiation reflects the uncertainty of clinicians about the benefits versus the side-effects of this therapy in the elderly.

Although we do not have the performance status of all patients available in the registry, as performance status and co-morbidity are strongly correlated and co-morbidity influences significantly treatment choices, it is reasonable to assume that more objective criteria are needed to assess the elderly patient for which therapy he is likely to have benefit from.[19,29,37,38]

It should be noted that at the time period in this series, stage III included 'wet' T4 tumours with malignant pleuritis or pericarditis. These patients were, therefore, included in this analysis and may also explain the relatively high proportion of stage III patients being treated palliatively. In other series it was observed that elderly patients were more likely to receive palliative treatment, although when fit, they could be treated with curative intent with similar survival to that of younger patients.[39]

As our study is based on the whole population in South and Middle Limburg, The Netherlands, there is no selection bias in our series. On the other hand, although the present study is prospective, it is not randomised. However, the fact that a median survival of 14 months and a 5-year survival of 20% could be achieved by a treatment with curative intent is an argument in favour of radical treatment in suitable elderly patients.

In summary, we have shown in a prospective population registry that in patients over 74 years with stage III NSCLC, treatment with curative intent was associated with long-term outcomes that are comparable with published phase III trials in the younger group. A defeatist approach can thus not be supported. Nevertheless, specific trials for this age group with appropriate assessment and prognostic tools are needed.

Conflict of interest statement

None declared.

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