INTRODUCTION

More than two-thirds of lung cancer cases currently diagnosed are in people over 65 years of age. Indeed, the mean age at diagnosis is 71 years old,1 most patients being frail patients with comorbidities that may limit their prognosis and tolerance of treatment.2–4 Therefore, it is becoming increasingly important to establish which management approach is most effective in elderly patients with locally advanced lung cancer. A meta-analysis5 demonstrated the superiority of concomitant chemotherapy and radiotherapy over sequential chemotherapy and radiotherapy in patients with unresectable stage III lung cancer, with 2- and 5-year survival rates of 36% and 15%, respectively, with concomitant treatment and 30% and 11% with sequential treatment. Nonetheless, there are other treatment options for patients with a poorer general condition, including sequential chemotherapy and radiotherapy6 or radiation therapy alone.7–9
Several studies indicated that the proportion of patients who receive active treatment for lung cancer decreases with advancing age.\textsuperscript{10,11} Furthermore, in clinical trials, the evidence for the use of different treatment regimens is generally gathered from fit younger patients. Notably, in the meta-analysis of Auperin et al,\textsuperscript{5} most patients included had a good performance status (0–1) and \textless 20\% were aged \textgreater 70 years. It is therefore difficult to extrapolate the findings to all patients with non-small-cell lung cancer (NSCLC) who are elderly and have comorbidities.\textsuperscript{12–14} Although there have been small studies in elderly patients,\textsuperscript{5,15} there is no solid evidence regarding tolerance or the importance of patient clinical characteristics to guide us in deciding which is the best treatment option in this population.

Due to ageing is a vague concept, several tools have been designed to predict toxicity and identify which patients would be good candidates to undergo radical treatment or adapted therapy\textsuperscript{16}.

In this study, we sought to assess patterns of commonly used treatment modalities with curative intent in elderly patients with locally advanced NSCLC and clinical factors predictive of overall survival in the context of daily clinical practice. By combining these clinical findings, we would be able to identify the best treatment for each patient.

**METHODS AND MATERIALS**

**Patient population**

This multicentre prospective observational study included all consecutive patients aged\textgreater 65 years old diagnosed with NSCLC between February 2014 and January 2018. The study was approved by the Ethics Committees of the participating hospitals (xx) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients who participated in the study gave written informed consent prior to inclusion.

**Inclusion criteria:** age\textgreater 65 years, a histological diagnosis of NSCLC, locally advanced disease (stages IIIA or IIIB according to the seventh edition of the American Joint Committee on Cancer Staging TNM classification),\textsuperscript{17} receiving radiotherapy with radical intent, with a total prescribed dose of 50 Gy (undergoing previous surgery) or 60 Gy without a history of surgery, and with or without chemotherapy (concomitant/sequential).

**Exclusion criteria:** previous radiotherapy, recurrence, or previous history of cancer.

**Assessment, treatment and follow-up of patients**

Patients were assessed at their first visit through obtaining a clinical history and performing a physical examination. All treatment decisions for these patients were taken by a multidisciplinary committee in each of the participating centres. The treatment options planned were classified as follows: surgery and postoperative radiotherapy (sequentially after postoperative chemotherapy), concomitant radiochemotherapy, sequential chemotheraphy and radiotherapy, or radiotherapy alone. Data were collected on the following patient characteristics, categorised as indicated (in parentheses): age (65–75 years vs \textgreater 75 years old); the Karnofsky Performance Scale (KPS) (<70 vs\textgreater 70); smoking habit (into three categories,\textsuperscript{18} smoker, ex-smoker and non-smoker; and also into three categories by smoking history\textsuperscript{19} \textless 30 pack-years vs 31–75 pack-years, vs \textgreater 75 pack-years); baseline haemoglobin levels (\textless 12 vs\textgreater 12 g dl\textsuperscript{1–1}); pretreatment weight loss (yes vs no); alcohol abuse (yes vs no); chronic obstructive pulmonary disease (yes vs no)\textsuperscript{21}; pretreatment thromboembolic event (yes vs no), heart disease (yes vs no), diabetes mellitus (yes vs no), type of treatment received (surgery vs concomitant treatment vs sequential treatment vs radiotherapy alone), stage (IIIA vs IIIB), radiation dose (\textless 60 Gy vs \textgreater 60 Gy), radiotherapy technique (3D conformal radiotherapy vs volumetric-modulated arc therapy [VMAT]/intensity modulated radiotherapy [IMRT]).

As it has been suggested that pretreatment quality of life (QOL) has prognostic value,\textsuperscript{22,23} in this study, QOL questionnaire (consisting of the EORTC QOL-C30 and lung cancer module QLQ-LC13) was administered to all patients at baseline. The aim was to assess the effect on survival of patients’ subjective assessment of their own baseline status before treatment.\textsuperscript{24} The EORTC QOL-C30 evaluates QOL in relation to physical, emotional and social factors, considering general level of functioning in oncology patients. The questionnaire is divided into five functional scales (physical functioning, activities of daily living, emotional functioning, cognitive functioning and social functioning), three symptom scales (fatigue, pain and nausea and vomiting), one global health status domain, and finally six independent items (dyspnoea, insomnia, anorexia, constipation, diarrhoea and economic impact).\textsuperscript{25}

The QLQ-LC-13 includes\textsuperscript{26} measures of the symptoms associated with lung cancer (cough, haemoptysis, dyspnoea and pain) and the adverse effects of conventional chemotherapy and radiotherapy (hair loss, neuropathy, sore mouth and dysphagia).

High scores in the symptom scales indicate the presence of symptoms associated with cancer that negatively affect the quality of life. On the other hand, High scores on the global health and functional status scales indicate a better QOL.

For this study, we categorised each of the functional and symptom scores from the questionnaires (EORTC QOL-C30 and module LC13) by the pretreatment score (0–100) into the following categories\textsuperscript{27} \textless 33.3 vs 33.3–66.6 vs \textgreater 66.6 points.

**Treatment**

Regarding radiotherapy, immobilisation and treatment planning were performed with patients in the supine position. A vacuum-locked cradle was used for patient immobilisation when deemed necessary. In all patients, a contrast computed tomography (CT) scan was performed with a 0.5 cm thickness, from the atlas bone (C1) to the second lumbar vertebra, approximately, to include the entire neck and the lungs.

Radiation was administered with 3D conformal radiotherapy or VMAT/IMRT using radiological imaging to delineate the gross target volume of the primary tumour (GTV-P) and/or macroscopic lymph node involvement (GTV-N). Any regions of the tumour visible by endoscopy but not seen in the CT images were...
also included in the GTV-P. The GTV was extended by 6 to 8 mm around the primary tumour and selected lymph nodes to obtain the clinical target volume (CTV), which was, in turn, extended 10 mm laterally and vertically to obtain the planning target volume (PTV). The radical radiotherapy was conventionally fractionated and, in some cases, was preceded by induction or concomitant chemotherapy (doublet therapy with cisplatin or carboplatin) at the discretion of the medical oncologist. Surgery was considered in patients with operable tumours. Thereafter, postoperative radiotherapy was performed in patients found after surgery to have pN2 disease, sequentially after chemotherapy.28–30

In designing the treatment, the aim was to use to the minimum dose possible in neighbouring organs at risk: healthy lung tissue, heart, oesophagus, and spinal cord, following the QUANTEC guidelines.31

Follow-up

After treatment, check-ups were performed first at 1 month after the radiotherapy and then every 3 months (including a CT scan of the neck and chest every 3–6 months) by each of the specialists who participated in their treatment (thoracic surgeons, medical and radiation oncologists). Any acute (up to 3 months after treatment) and chronic (from then until after the end of the radiotherapy) toxicity was recorded, using the Common Terminology Criteria for Adverse Events (vs 4.0.).

Statistical analysis

Continuous variables were expressed as medians and range and categorical variables as frequencies and percentages. To compare categorical variables Chi-square test was used or Fisher exact test when expected frequency less than five.

The primary outcome was the overall survival of the population, analysed using Kaplan-Meier curves. To calculate survival, the time interval considered was from the end of radiotherapy to the date of death (all-cause) or the last follow-up.

Analysis was performed to assess the influence of clinical characteristics (age, sex, TNM stage, KPS score, history of heart disease and diabetes, pretreatment weight loss, diagnosed chronic obstructive pulmonary disease, baseline haemoglobin levels, smoking and drinking habits, history of thromboembolism, pretreatment QOL considering EORTC QLQ-C30 and LC-13 scores) and treatment (modality, radiotherapy technique, and radiation dose) on patient survival.

Table 1. Clinical and treatment characteristics of the population included in the study

| Characteristics                                      | Patients, n = 139 |
|------------------------------------------------------|------------------|
| Age (median and range)                               | 71 years old (65-88) |
| Karnofsky Performance Scale score ≥70                | 135 (97.1%) |
| Karnofsky Performance Scale score <70                | 4 (2.9%) |
| Sex: Male/Female, n (%)                              | 123 (88.5%)/16 (11.5%) |
| Histological diagnosis, n (%)                        |                   |
| Adenocarcinoma                                       | 44 (31.7%) |
| Giant cell carcinoma                                 | 5 (3.6%) |
| Epidermoid/squamous cell carcinoma                   | 90 (64.7%) |
| Comorbidities, n (%)                                  |                   |
| Chronic obstructive pulmonary disease                | Yes 70 (50.4%) |
| Diabetes mellitus                                    | Yes 46 (33.1%) |
| History of heart disease                             |                   |
| • Arrhythmia                                          | 50 (36%) |
| • Hypertensive heart disease                         | 13 (9.4%) |
| • Heart failure                                       | 3 (2.2%) |
| • Ischaemic heart disease                             | 2 (1.4%) |
| • Others                                              | 16 (11.5%) |
| History of thromboembolic event (yes), n (%)         | 16 (11.5%) |
| Smoking habits, n (%)                                |                   |
| Smoker                                               | 52 (37.4%) |
| Ex-smoker                                            | 80 (57.6%) |
| Non-smoker                                           | 7 (5%) |
| Pack/years                                           | 67 (0–162) |
| Alcohol abuse, n (%)                                 |                   |
| No                                                   | 86 (61.9%) |
| Yes                                                  | 53 (38.1%) |
| Weight loss, n (%)                                   |                   |
| No                                                   | 91 (65.5%) |
| Yes                                                  | 48 (34.5%) |
| a) Baseline haemoglobin                               | 11.6 gr/dl (range: 6.8–16.4) |
| Stage, n (%)                                          |                   |
| III A                                                 | 72 (51.8%) |
| III B                                                 | 67 (48.2%) |
| Previous surgery, n (%)                              |                   |
| No                                                    | 115 (82.7%) |
| Yes                                                   | 24 (17.3%) |
| Radiotherapy technique, n (%)                         |                   |
| 3D                                                    | 117 (84.2%) |

Table 1. (Continued)

| Characteristics                                      | Patients, n = 139 |
|------------------------------------------------------|------------------|
| Intensity-modulated radiation therapy                 | 1 (0.7%) |
| Volumetric modulated arc therapy                      | 21 (15.1%) |
| Radiotherapy dose received (median; Gy)               | 66 Gy (50–66 Gy) |

aData on baseline haemoglobin was not available for four patients

(Continued)
Kaplan-Meier curves and log-rank test was used to identify which clinical or treatment-associated variables were predictive of overall patient survival. Subsequently, variables with a \( p < 0.2 \) in the univariate analysis were included in the Cox multivariate regression analysis (using a non-automatic stepwise procedure), to assess whether they were statistically significant independent predictors (\( p \) value < 0.05). Cox proportional hazards analysis was performed to calculate hazard ratios (HRs) and confidence intervals (CIs).

The analysis was performed using the IBM SPSS (version 23.0).

**RESULTS**

We recruited a total of 139 consecutive patients between February 2014 and January 2017, with a median age of 71 years old (65-88), of whom 123 (88.5%) were males and 16 (11.5%) women. Clinical and treatment characteristics of the population included in the study are described in Table 1. In addition, we described characteristics of our study population according to the age (\( \leq 75 \) vs \( >75 \) years). See Supplementary Table 6.

Based on treatment modality, we classified all 139 patients into one of four groups: 24 patients received surgery and postoperative radiotherapy (17.3%), 38 concomitant radiochemotherapy (27.3%), 67 sequential chemotherapy and radiotherapy (48.2%), and 10 radiotherapy alone (7.2%). We then broke these treatment groups down as a function of age (65–75 vs >75 years old; Table 2): in the >75-year-old patients, the multidisciplinary committee mostly recommended chemotherapy and sequential radiotherapy (\( n = 15, 55.6\% \)) or radiotherapy alone (\( n = 6, 22.2\% \)), rather than surgery (\( n = 1, 3.7\% \)) or concomitant radiochemotherapy and (\( n = 5, 16.5\% \)). In contrast, in 65- to 75-year-old patients, surgery and concomitant radiochemotherapy and were recommended by the committee in approximately half of cases. The differences between these groups were significant (\( p = 0.003 \)) (Table 2).

It should be noted that the multidisciplinary committee recommended surgical treatment based on multiple clinical parameters such as performance status, clinical staging, and the presence of comorbidities such as history of heart disease or pulmonary function. Patients undergoing surgery had less chronic obstructive pulmonary disease (\( p = 0.04 \)) and lower T stage (\( p = 0.01 \)).

In addition, (although not statistically significant) patients with previous history of heart disease underwent surgery less frequently (29.2% vs 70.8%). These data are fully described in Supplementary Table 7.

The median radiation dose was 66 Gy (50-66). The median follow-up was 9.9 months (1.18–57.36 months). The median survival was 14 months (range 11–17 months), and the overall survival rates at 6, 12 and 24 months were 82.7%, 60.9 and 32.3%, respectively (Figure 1).

Analyzing factors with a potential influence on overall survival, the following variables were found to be significant in the Kaplan Meier analysis (Table 3): pack-year history (\( p = 0.049 \)); heart disease (\( p = 0.0001 \)); thromboembolic events (\( p = 0.012 \)); physical, role, cognitive and social functioning (\( p = 0.001, p = 0.0001, p = 0.0001 \), and \( p = 0.003 \) respectively); fatigue (\( p = 0.017 \)); pain (\( p = 0.029 \)); loss of appetite (\( p = 0.001 \)); dyspnoea (\( p = 0.001 \));
Table 3. Univariate analysis

| Variables                               | n*  | Median survival | Lower limit | Upper limit | \( P \) value |
|-----------------------------------------|-----|-----------------|-------------|-------------|---------------|
| Patient age                             |     |                 |             |             |               |
| 65–75 years                             | 112 | 14.09           | 11.09       | 17.09       | 0.275         |
| >75 years                               | 27  | 14.42           | 8.42        | 20.42       |               |
| Sex                                     |     |                 |             |             |               |
| Female                                  | 12.2| 0               | 26.3        |             | 0.989         |
| Male                                    | 14.4| 11.6            | 27.2        |             |               |
| Karnofsky Performance Scale score      |     |                 |             |             |               |
| <70                                     | 4   | 4.27            | 21.27       |             | 0.396         |
| ≥70                                     | 135 | 14.42           | 11.28       | 17.56       |               |
| Smoking habits                          |     |                 |             |             |               |
| Smoker                                  | 52  | 20.04           | 12.75       | 27.32       | 0.270         |
| Ex-smoker                               | 80  | 13.20           | 11.18       | 15.23       |               |
| Non-smoker                              | 7   | 33.84           | 0           | 0           |               |
| Pack-years                              |     |                 |             |             |               |
| ≤30                                     | 16  | 33.84           | 2.89        | 64.78       | 0.049         |
| 31–75                                   | 62  | 13.76           | 11.54       | 15.98       |               |
| >75                                     | 61  | 16.92           | 8.59        | 25.24       |               |
| Haemoglobin (g/dl)                      |     |                 |             |             |               |
| <12                                     | 78  | 14.09           | 11.56       | 16.62       | 0.947         |
| ≥12                                     | 57  | 16.06           | 10.91       | 21.21       |               |
| Weight loss                             |     |                 |             |             |               |
| No                                      | 91  | 12.61           | 8.15        | 17.07       | 0.178         |
| Yes                                     | 48  | 20.46           | 12.56       | 28.37       |               |
| Alcohol abuse                           |     |                 |             |             |               |
| No                                      | 86  | 13.76           | 10.17       | 17.35       | 0.492         |
| Yes                                     | 53  | 14.42           | 10.36       | 18.48       |               |
| Chronic obstructive pulmonary disease   |     |                 |             |             |               |
| No                                      | 69  | 16.92           | 9.59        | 24.25       | 0.050         |
| Yes                                     | 70  | 13.07           | 10.37       | 15.77       |               |
| Diabetes Mellitus                       |     |                 |             |             |               |
| No                                      | 93  | 13.20           | 10.69       | 15.71       | 0.928         |
| Yes                                     | 46  | 16.06           | 14.31       | 17.81       |               |
| Heart disease                           |     |                 |             |             |               |
| No                                      | 89  | 23.49           | 13.02       | 33.95       | 0.0001        |
| Yes                                     | 50  | 9.98            | 6.42        | 13.55       |               |
| Thromboembolic event                    |     |                 |             |             |               |
| No                                      | 123 | 16.62           | 11.03       | 22.21       | 0.012         |
| Yes                                     | 16  | 12.35           | 7.27        | 17.43       |               |
| Treatment modality                      |     |                 |             |             |               |

(Continued)
Table 3. (Continued)

|                          | 95% confidence interval |
|--------------------------|-------------------------|
|                          |                         |                         |
| Surgery (yes)            | 24                      | 33.84                   | 0.69                     | 66.99                   | 0.07                     |
| Concomitant chemotherapy | 38                      | 14.09                   | 7.79                     | 20.39                   |
| Sequential chemotherapy  | 67                      | 12.61                   | 8.52                     | 16.70                   |
| Radiotherapy alone       | 10                      | 13.37                   | 4.92                     | 21.81                   |
| Physical functioning, C30|                         |                         |                         |                         |
| ≤33.3                    | 5                       | 4.27                    | 0.81                     | 7.72                    | 0.0001                   |
| 33.3–66.6                | 23                      | 9.56                    | 1.76                     | 17.35                   |
| >66.6                    | 99                      | 20.07                   | 15.05                    | 25.09                   |
| Fatigue, C30             |                         |                         |                         |                         |
| ≤33.3                    | 56                      | 21.06                   | 14.22                    | 27.89                   | 0.017                    |
| 33.3–66.6                | 48                      | 12.61                   | 11.35                    | 13.88                   |
| >66.6                    | 25                      | 8.90                    | 0                        | 19.70                   |
| Nausea and vomiting, C30 |                         |                         |                         |                         |
| ≤33.3                    | 120                     | 14.88                   | 11.62                    | 18.14                   | 0.111                    |
| 33.3–66.6                | 6                       | 14.09                   | 1.28                     | 26.90                   |
| >66.6                    | 3                       | 5.48                    | 0                        | 11.53                   |
| Pain, C30                |                         |                         |                         |                         |
| ≤33.3                    | 91                      | 16.92                   | 10.70                    | 23.13                   | 0.029                    |
| 33.3–66.6                | 22                      | 9.26                    | 4.45                     | 14.07                   |
| >66.6                    | 13                      | 9.56                    | 2.14                     | 16.97                   |
| Dyspnoea, C30            |                         |                         |                         |                         |
| ≤33.3                    | 69                      | 14.42                   | 10.61                    | 18.23                   | 0.407                    |
| 33.3–66.6                | 42                      | 15.40                   | 6.44                     | 24.37                   |
| >66.6                    | 18                      | 9.56                    | 0                        | 22.01                   |
| Loss of appetite, C30    |                         |                         |                         |                         |
| ≤33.3                    | 78                      | 20.99                   | 13.38                    | 28.60                   | 0.001                    |
| 33.3–66.6                | 27                      | 9.26                    | 1.18                     | 17.34                   |
| >66.6                    | 25                      | 10.64                   | 6.31                     | 14.97                   |
| Constipation, C30        |                         |                         |                         |                         |
| ≤33.3                    | 69                      | 20.46                   | 15.29                    | 25.64                   | 0.055                    |
| 33.3–66.6                | 39                      | 13.20                   | 10.74                    | 15.67                   |
| >66.6                    | 22                      | 10.64                   | 4.82                     | 16.46                   |
| Diarrhoea, C30           |                         |                         |                         |                         |
| ≤33.3                    | 110                     | 13.37                   | 10.28                    | 16.46                   | 0.450                    |
| 33.3–66.6                | 17                      | 34.82                   | 13.38                    | 56.26                   |
| >66.6                    | 3                       | 27.72                   | 0                        | 0                       |

(Continued)
Table 3. (Continued)

| Financial impact, C30 | 95% confidence interval |          |
|-----------------------|-------------------------|----------|
| ≤33.3                 | 98                      | 16.06    | 10.40   | 21.72   | 0.143    |
| 33.3–66.6             | 22                      | 12.22    | 4.25    | 20.18   |          |
| >66.6                 | 10                      | 0        | 0       | 0       |          |

**Dyspnoea, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 104                     | 16.92    | 11.15   | 22.68   | 0.001    |
| 33.3–66.6| 18                      | 8.90     | 5.41    | 12.39   |          |
| >66.6    | 4                       | 4.56     | 0       | 13.66   |          |

**Cough, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 31                      | 13.37    | 3.81    | 22.93   | 0.300    |
| 33.3–66.6| 67                      | 16.06    | 12.10   | 20.02   |          |
| >66.6    | 30                      | 12.22    | 4.53    | 19.91   |          |

**Haemoptysis, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 108                     | 15.40    | 8.25    | 22.55   | 0.103    |
| 33.3–66.6| 16                      | 13.37    | 6.16    | 20.57   |          |
| >66.6    | 5                       | 12.32    | 0       | 29.53   |          |

**Sore mouth, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 112                     | 14.42    | 10.92   | 17.92   | 0.689    |
| 33.3–66.6| 14                      | 9.75     | 0       | 0       |          |
| >66.6    | 3                       | 16.06    | 0       | 39.04   |          |

**Dysphagia, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 106                     | 16.06    | 10.28   | 21.84   | 0.003    |
| 33.3–66.6| 17                      | 12.38    | 6.49    | 18.28   |          |
| >66.6    | 6                       | 3.02     | 0       | 8.76    |          |

**Peripheral neuropathy, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 80                      | 13.37    | 10.07   | 16.66   | 0.601    |
| 33.3–66.6| 31                      | 14.42    | 9.22    | 19.61   |          |
| >66.6    | 17                      | 27.07    | 2.31    | 51.82   |          |

**Hair loss, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 83                      | 13.07    | 9.80    | 16.34   | 0.084    |
| 33.3–66.6| 19                      | 13.20    | 10.06   | 16.34   |          |
| >66.6    | 26                      | 34.82    | 0       | 70.93   |          |

**Pain in chest, LC-13**

|          | 95% confidence interval |          |
|----------|-------------------------|----------|
| ≤33.3    | 90                      | 16.06    | 9.77    | 22.36   | 0.0001   |
| 33.3–66.6| 27                      | 16.92    | 9.40    | 24.43   |          |
| >66.6    | 12                      | 4.30     | 2.03    | 6.57    |          |

(Continued)
dysphagia ($p = 0.003$); pain in chest ($p = 0.0001$); and previous surgery ($p = 0.044$) (Figure 2).

No differences in overall survival by treatment modality reached significance ($p = 0.073$), although there was a clinical trend towards higher survival in patients who underwent surgery (see Figure 1). Given this, to assess the role of surgery in the study population, the treatment modalities were grouped into two categories (surgery vs other treatment modalities) for the multivariate analysis (Table 3).

According to the multivariate analysis, the risk of death was higher in patients with pre-existing heart disease, a low score for physical functioning, or symptoms of dysphagia and/or chest pain, as well as those who did not receive surgical treatment. These variables are considered significant independent predictors. The results of multivariate analysis are shown in full in Table 4.

Data on acute and chronic toxicity are summarised in Table 5. We performed subanalysis to assess whether acute and/or chronic toxicity (oesophagitis, pneumonitis, heart toxicity) experienced by the patients was influenced by age (65–75 vs >75 years), dose ($\leq 60$ vs $>60$ Gy), treatment modality, or baseline KPS ($<70$ vs $\geq 70$).

Table 3. (Continued)

| Variable                        | ≤33.3  | 33.3–66.6 | >66.6  | 95% confidence interval | 95% confidence interval |
|---------------------------------|--------|-----------|--------|-------------------------|-------------------------|
| Pain in other parts, LC-13      |        |           |        |                         |                         |
| ≤33.3                           | 54     | 14.09     | 11.28  | 16.90                   | 0.390                   |
| 33.3–66.6                       | 20     | 24.54     | 15.58  | 33.50                   |                         |
| >66.6                           | 16     | 13.37     | 0      | 28.33                   |                         |
| Total dose (Gy)                 |        |           |        |                         |                         |
| ≤60                             | 36     | 14.88     | 12.02  | 17.74                   | 0.720                   |
| >60                             | 103    | 14.42     | 9.91   | 18.93                   |                         |
| Previous surgery                |        |           |        |                         |                         |
| No                              | 115    | 14.09     | 10.85  | 17.33                   | 0.044                   |
| Yes                             | 24     | 33.84     | 0.69   | 66.99                   |                         |
| Technique                       |        |           |        |                         |                         |
| Others                          | 22     | 7.32      | 3.01   | 11.64                   | 0.166                   |
| 3D                              | 117    | 14.88     | 11.77  | 17.99                   |                         |
| Stage                           |        |           |        |                         |                         |
| IIIa                            | 67     | 12.32     | 8.77   | 15.87                   | 0.083                   |
| Others                          | 72     | 16.92     | 10.80  | 23.03                   |                         |

Figure 2. Overall survival regarding treatment modality
By treatment modality, Grade three acute oesophageal toxicity was observed in 2 patients out of 16 treated with surgery and postoperative radiotherapy (after adjuvant chemotherapy), 5/16 treated with concomitant radiochemotherapy, and 1/16 treated with sequential radiotherapy and chemotherapy, while there were no cases in the group given radiotherapy alone; the rate of Grade three oesophagitis being significantly higher among the patients treated with concomitant chemotherapy ($p = 0.022$).

In addition, we have analysed the influence of treatment technique (3D conventional RT vs IMRT/VMAT) in toxicity (including oesophagitis, pneumonitis, heart toxicity). We did not find statistically significant differences. Full data are described in Supplementary Table 8. We did not find any other significant associations between acute or chronic oesophageal, lung or heart toxicity and the aforementioned variables.

**DISCUSSION**

The aim of this study was to assess survival and the patterns of treatment among unselected elderly patients with locally advanced NSCLC. The median survival was 14 months (11–17 months), while the 1- and 2-year overall survival rates were 60.9 and 32.3% respectively. These data are similar to those of other studies that have analysed the survival in elderly patients, and even to those found in younger patients with locally advanced NSCLC.

In our study, 27.3% (38/139) of patients received concomitant radiochemotherapy compared to 48.2% (67/139) who received sequential radiotherapy and chemotherapy (48.2%), in line with other specific studies in elderly patients.

Regarding the treatment modality used, as expected, the least common approaches were surgery and concomitant radiochemotherapy, especially among the oldest patients (>75 years old). In this latter group, the most common treatment modalities were sequential radiotherapy and chemotherapy or radiotherapy alone. Such a trend towards more interventional approaches involving surgery and concomitant radiotherapy and chemotherapy in patients aged 65 to 75 years, while more conservative treatments (sequential radiotherapy and chemotherapy or radiotherapy alone) are indicated in elderly patients (>75 years old), has been described previously by other authors.

In our study, we have not observed significant differences in survival as a function whether patients received concomitant or sequential chemotherapy, in line with the recent study by Driessen et al. The survival rate was even similar in patients who received radiotherapy alone and those who received sequential chemotherapy. This finding contrasts with the results of a meta-analysis which indicated higher survival rates in patients given concomitant radiotherapy and chemotherapy than those given sequential radiotherapy and chemotherapy. Although this might be due to the lack of statistical power in our study, it could also be explained by the trials studied only having included young and fit elderly patients, who are not representative of the patients treated in daily clinical practice.

On the other hand, according to our results, it seems important that, regardless of patient age, a clinical committee carefully selects candidates for surgery, as our multivariate analysis indicates that surgical treatment may influence survival.

Performance status is a well known factor influencing survival in patients with lung cancer. Indeed, in our sample, patients with KPS <70 had a notable tendency towards a shorter survival (median 4.2 vs 14.4 months) than those with KPS ≥70, although these differences were not statistically significant (Table 3). In our opinion this is probably due to the low number of patients (4 out of 139) included in the study with KPS<70. Moreover, considering that only patients undergoing treatment with radical intent were included in this study, it is reasonable in our consideration, including a majority of patients presenting good performance status.
On the other hand, according to our results, general clinical condition as assessed by measuring baseline QOL (in particular, physical functioning, dysphagia and chest pain) was a significant predictor of survival. This is consistent with the results of various other studies.\textsuperscript{23,37,38} We believe that this is important since QOL parameters can easily be assessed in daily clinical practice before treatment using the EORTC questionnaires (QLQc-30 and LC-13) to facilitate decision making and inform patients about their prognosis. We believe that this is particularly important since our study has produced similar results to those of previous studies in lung cancer,\textsuperscript{23,37,38} but with a focus on a specific sample of patients (elderly patients with locally advanced NSCLC) who are often clinically frail and regarding whom decision making may be a challenge. This finding supports the view that QOL data should be collected in daily clinical practice.

Additionally, it was found that a history of specific comorbidities such as heart disease, which is relatively common in this type of patients, was a significant independent predictor of survival. Grose et al\textsuperscript{39} also noted the importance of comorbidities as an independent prognostic factor in early and advanced stages of lung carcinoma. Therefore, the level of comorbidity should be taken into account to stratify patients and interpret the results of clinical trials, especially in elderly patients.\textsuperscript{40}

Regarding toxicity, a direct relationship was not found with age (65–75 vs >75 years old), but was found with the treatment modality, especially in patients who received concomitant chemotherapy, having this group a higher rate of acute oesophagitis. Therefore, when making a treatment recommendation in these patients, we should consider the risk-benefit ratio,\textsuperscript{41} preferences of the patient regarding survival and treatment tolerance, given that in this unselected population of elderly patients the administration of concomitant chemotherapy did not significantly improve survival.\textsuperscript{32}

Regarding smoking, our univariate analysis revealed an association between a higher level of smoking (packs/year) and shorter survival, as was reported by other authors.\textsuperscript{19} Nonetheless, this result was not statistically significant in the multivariate analysis. We did not find associations between survival and anaemia, or other clinical parameters related to the treatment such as the technique or radiation dose (Table 3).

Notably, we did not find differences in survival between the oldest patients in the cohort (>75 years old) and those aged 65 to 75 years, age by itself not being found to be determinant in patient survival.

While age itself did not prove prognostic on the multivariate analyses, surgery instead, was a significant factor. This result should be interpreted with caution since only one patient >75 years underwent surgery. Indeed, in the group >75 years of age, only 16 patients could be truly evaluated for surgery (without considering cases with stage IIIb where surgery is clearly not indicated), regarding PS and comorbidities (see Supplementary Table 6). It is, therefore, a small number of patients that could have influenced our results. Future research should focus on predictive patient characteristics to distinguish patients within the heterogeneous older population who can benefit from curative-intent treatment.

### Table 5. Acute and Chronic toxicity

| Toxicity                        | Patients, n = 139 |
|---------------------------------|-------------------|
| Acute esophagitis n (%)         |                   |
| Yes                             | 69 (49.6)         |
| No                              | 70 (50.4)         |
| Acute esophagitis, grade n (%)  |                   |
| Grade I                         | 13 (9.4)          |
| Grade II                        | 48 (34.5)         |
| Grade III                       | 8 (5.8)           |
| Chronic esophagitis* n (%)      |                   |
| Yes                             | 18 (12.9)         |
| No                              | 118 (84.9)        |
| Acute pneumonitis n (%)         |                   |
| Yes                             | 62 (44.6)         |
| No                              | 77 (55.4)         |
| Acute pneumonitis, grade n (%)  |                   |
| Grade I                         | 12 (8.6)          |
| Grade II                        | 33 (23.7)         |
| Grade III                       | 17 (12.2)         |
| Chronic pneumonitis n (%)       |                   |
| Yes                             | 62 (44.6)         |
| No                              | 75 (54)           |
| Chronic pneumonitis, grade n (%)|                   |
| Grade I                         | 10 (7.2)          |
| Grade II                        | 27 (19.4)         |
| Grade III                       | 21 (15.1)         |
| Grade IV                        | 0                 |
| Grade V                         | 4 (2.9)           |
| Chronic cardiac toxicity        |                   |
| Yes                             | 3 (2.2)           |
| No                              | 136 (97.8)        |
| Type of cardiopathy due to chronic toxicity n (%)|         |
| Heart failure                   | 1 (0.7)           |
| Ischaemic heart disease         | 2 (1.4)           |
After an analysis of overall survival, in line with other studies in younger patients, we affirm that there is no reason to rule out combined treatment for patients based on their age alone.34,36,42

However, we should recognise that this study has some limitations. It should be noted that this study was not designed to explore the benefit of a specific treatment approach as it not a randomised trial.

Indeed, the clinical decision may be difficult in elderly patients with lung cancer (usually fragile population) in the absence of high quality data. Considering the risks of surgery and toxicity of chemo-radiotherapy are often increased in the elderly compared with younger patients, patients in this study were therefore, closely scrutinized. Our management recommendations were generally similar to those of general guidelines for the NSCLC population. Careful evaluation was performed to ensure that treatment was guided by patient characteristics, stage, and not by age. All the treatment decisions were based on patient performance status, tumour resectability including T and N stage (see Supplementary Table 7), pulmonary function and presence of comorbidities. The best radical treatment approach was indicated for each patient in a multidisciplinary board. Whenever possible surgery was indicated (±postop-radiotherapy, regarding TNM stage, resectability and comorbidities), followed by concomitant radiochemotherapy or radiotherapy alone.

We also acknowledge that we did not perform a comprehensive geriatric assessment, that might be necessary to provide the best suitable treatment for each patient, and therefore is increasingly been incorporated in oncologic care demonstrating that it can alter treatment decisions.16

According to the multivariate analysis, the risk of death was higher in patients with pre-existing heart disease, a low score for physical functioning, or symptoms of dysphagia and/or chest pain, as well as those who did not undergo surgical treatment. We recognize several reasons that justify our findings. First, it should be noted that cardiopathy is a frequent comorbidity in elderly patients with lung cancer and one of the major causes of death in the general population. Second, physical functioning is evaluating the patient fitness, considering that a better performance status is generally associated with better survival. Finally, chest pain and dysphagia are symptoms probably related to locoregionally advanced disease in this population and therefore associated with worse prognosis.

Future research on the use of geriatric evaluation in elderly lung cancer patients should be powered to understand how it could potentially contribute to optimal decision making.32,63 On the other hand, it can be difficult to conduct research on elderly patients, given the slow recruitment and strict selection criteria for inclusion of patients in trials.44 In our study, we prospectively assessed an unselected elderly population, an approach which may provide useful insights for daily routine clinical practice.

CONCLUSIONS

Patients over 75 years of age tend to receive more conservative treatments, involving less surgery and less concomitant radiochemotherapy. The surgical modality improved survival and therefore, this treatment modality should be carefully considered on case-by-case basis, regardless of patient age. A history of comorbidities and poor baseline QOL according to the EORTC QLQc30 and LC-13 (low physical functioning, marked dysphagia, and chest pain) are predictive of shorter survival. Therefore, measuring these parameters before treatment may help us to define a population of frail patients with a poorer prognosis to facilitate decision making in clinical practice. Prospective studies in this crucial and understudied area are needed.

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