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# Treatment of lung cancer in the elderly: Influence of comorbidity on toxicity and survival

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ABSTRACT

*Background:* More than 50% of new cases of lung cancer (LC) are diagnosed in elderly patients. It is necessary to know correct treatment of these patients but there is a lack of evidence-based data regarding this age group, leading to an undertreatment based on a supposed lack of tolerance to radical treatments.

*Aim:* To evaluate the results of radiotherapy (RT) treatment in elderly patients with LC in our institution and the relation between survival, toxicity and comorbidities.

*Materials and methods:* We retrospectively analyzed all patients over 70 years old with LC, treated with RT with or without chemotherapy (CT), in the radiotherapy department of the Instituto Português de Oncologia do Porto Francisco Gentil (IPOPFG), between January 2000 and December 2007.

*Results:* Three-year overall survival (OS) rate was 33.8%. Median progression free survival was 18.1 months. For patients treated with exclusive radical radiotherapy the 3-year OS rate was 51.5% and for patients treated with sequential and concurrent CTRT, 3-year survival rates were 44% and 25.4%, respectively. We did not find a statistical relationship between the presence of comorbidities and survival. Toxicity presented by the patients was not influenced by comorbidities and did not influence survival.

*Conclusion:* Our results allow us to conclude that elderly patients are likely to benefit from radical treatments. Chemo-radiotherapy seems to increase survival but should be used carefully in old patients outside clinical trials. Comorbidities did not seem to influence survival and toxicity of treatments, although larger studies are necessary to prove this.

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## 1. Background

Lung cancer (LC) is the main cause of cancer death in western countries, and more than 50% of new cases are diagnosed in elderly patients. In the last decade, the incidence and mortality from LC have decreased among individuals aged 50 years and younger but have increased among those aged 70 years or older.[1] Between 80% and 85% of LC are non-small-cell lung cancers (NSCLC), and more than 50% of all patients with NSCLC are older than 65 years.[2] Because of the rapid aging of populations, the proportion of LC diagnosed in elderly people will rise, and it is necessary to know correct treatment of these patients.

The main concern about aggressive treatment in the elderly is that therapy results in excessive toxicity and poor

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outcome. However, age itself should not be used as a criterion for the choice of a treatment modality. A comprehensive geriatric assessment is mandatory to evaluate functional status, comorbidities, mental status, psychological state, social support, nutritional status, polypharmacy and geriatric conditions, in order to improve patients' condition before treatment.

There is a lack of evidence-based data regarding the appropriate treatment of the elderly, since they have generally been excluded from prospective trials. This lack of information is especially relevant in the field of radiotherapy (RT), and has led to an undertreatment of patients based on a supposed lack of tolerance to radical treatments.

Age does not appear to have an influence on the frequency and severity of acute and late side-effects, so it is not a sufficient reason to exclude patients from curative radiotherapy when it is indicated, either in NSCLC or small-cell lung cancer (SCLC).[3,4]

Elderly patients who participated in Phase III trials for stage III NSCLC were likely to gain a survival advantage from RT and chemotherapy (CT) compared with RT alone, although, as in the case of younger patients, there was an additional toxicity with this therapy modality.[5]

## 2. Aim

In this study we aimed to evaluate the global survival, progression free survival and acute toxicity of elderly patients treated with RT for LC (both NSCLC and SCLC) in our institution. We also studied the relation between survival and comorbidities presented by the patients, in order to investigate if the prognosis differed in patients with significant comorbidities, to adopt a different attitude towards their management if indicated.

## 3. Materials and methods

Even though the definition of the elderly remains debatable, we chose the age of 70 years as a minimum level. We retrospectively analyzed all patients over 70 years old with LC, treated with RT with or without CT, in the radiotherapy department of the Instituto Português de Oncologia do Porto Francisco Gentil (IPOPFG), between January 2000 and December 2007. Medical records were reviewed and patients' comorbidities were classified according to the Charlson Score (Appendix A). Acute and late toxicities were classified according to the Common Toxicity Criteria, version 2.0. Patients who had been treated with RT for distant metastases were excluded.

Patients were treated with a 3D conformal plan to receive a total dose of 60–70 Gy with 2 Gy daily fractions in the cases with curative intent and a total dose of 40 Gy with 2.5 Gy daily fractions for palliative intent. Energies used were 6 MV or 15 MV, or a combination of both. Chemotherapy schemes consisted of platinum associated with etoposide, gemcitabine or paclitaxel.

Data were analyzed using SPSS software version 17.0, overall survival (OS) and progression free survival (DFS) were calculated using the Kaplan-Meier method, and the log-rank test was used for differences between curves.

**Table 1 – Patients' characteristics.**

| Characteristics | Number of patients |
|---|---|
| Median age | 74.5 (70–84) |
| *Karnofsky performance status* | |
| 50 | 1 (1.1%) |
| 60 | 8 (8.9%) |
| 70 | 8 (8.9%) |
| 80 | 32 (35.6%) |
| 90 | 38 (42.2%) |
| 100 | 3 (3.3%) |
| *Charlson score* | |
| 0 | 45 (50%) |
| 1 | 23 (25.6%) |
| 2 | 15 (16.7%) |
| 3 | 3 (3.3%) |
| 4 | 1 (1.1%) |
| 6 | 3 (3.3%) |
| *Stage (NSCLC–TNM/AJCC)* | |
| IA | 6 (7.2%) |
| IB | 16 (19.3%) |
| IIA | 2 (2.4%) |
| IIB | 6 (7.2%) |
| IIIA | 21 (25.3%) |
| IIIB | 30 (36.2%) |
| IV | 2 (2.4%) |
| *Stage (SCLC)* | |
| Limited | 5 (71.4%) |
| Extensive | 2 (28.6%) |
| *Histology* | |
| Squamous cell | 36 (40%) |
| Adenocarcinoma | 37 (41.1%) |
| Small cell carcinoma | 7 (7.8%) |
| Undifferentiated large cell | 4 (4.4%) |
| Mixed histology | 6 (6.7%) |

## 4. Results

From January 2000 to December 2007, 90 patients over 70 years old received treatment with RT for LC at IPOPFG. Patients' characteristics are summarized in Table 1.

The median age was 74.5 years (range 70–84) and most patients presented a Karnofsky performance status of 80% or more.

Half of the patients had a Charlson score of 0 (no significant comorbidities), 25.6% and 16.7% had a score of 1 and 2, respectively, and 7 patients had a score $\geq$3. Comorbidities presented by the patients are summarized in Tables 1 and 2. The most frequent comorbidities presented by the patients were chronic pulmonary disease (17.8%), diabetes (16.7%), other tumors (12.2%) and ulcer disease (12.2%).

Stages IIIA and IIIB were the most frequent in NSCLC (61.5%), and 71.4% of SCLC were staged as limited disease. Adenocarcinoma and squamous cell carcinoma represented 41.1% and 40% of the NSCLC histologies, respectively.

Forty-eight patients (53.3%) were submitted to sequential chemo-radiotherapy (CTRT) and 10 patients (11.1%) were treated with concurrent CTRT. Exclusive radiotherapy was used in 27 patients, 17 with radical intent (18.9%) and 10 with palliative intent (11.1%). Five patients (5.6%) were submitted to surgery and adjuvant radiotherapy. Two patients were submitted to brachytherapy, one after concurrent CTRT and the

**Table 2 – Patients' comorbidities.**

| Comorbidities | Number of patients (%) |
|---|---|
| Chronic pulmonary disease | 16 (17.8%) |
| Diabetes | 15 (16.7%) |
| Other tumor | 11 (12.2%) |
| Ulcer disease | 4 (4.4%) |
| Congestive heart failure | 3 (3.3%) |
| Myocardial infarct | 3 (3.3%) |
| Cerebrovascular disease | 2 (2.2%) |
| Metastatic solid malignancy | 2 (2.2%) |
| Peripheral vascular disease | 1 (1.1%) |
| Diabetes with end organ damage | 1 (1.1%) |
| Dementia | 1 (1.1%) |
| Moderate renal disease | 1 (1.1%) |
| Leukemia | 1 (1.1%) |
| Moderate liver disease | 1 (1.1%) |

**Table 3 – Patients' treatments.**

| Treatment | Number of patients (%) |
|---|---|
| Sequential chemo-radiotherapy | 48 (53.3%) |
| Concurrent chemo-radiotherapy | 10 (11.1%) |
| Exclusive radical radiotherapy | 17 (18.9%) |
| Post-surgery radiotherapy | 5 (5.6%) |
| Exclusive palliative radiotherapy | 10 (11.1%) |
| Brachytherapy (after CTRT) | 2 (2.2%) |
| Total | 90 |

others after sequential CTRT. Patients' treatments are summarized in Table 3.

The toxicities presented by the patients were mostly grade I and II, and 2 cases of grade III toxicity were registered, one gastro-intestinal (esophageal) and the other hematological toxicity (leukopenia), which means a 2.2% grade III toxicity. The patient that presented with grade III esophageal toxicity had a Charlson score of 2, and the patient with grade III hematological toxicity had a Charlson score of 0; both were submitted to concurrent CTRT.

Results of curative radiotherapy are summarized in Table 4. Median overall survival (OS) for all patients was 29 months and the 3-year OS rate was 33.8%. Median progression free survival for all patients was 18.1 months. For patients treated with exclusive radical radiotherapy, median OS was 38.8 months

**Table 4 – Treatment response after curative radiotherapy.**

| Treatment | Number of patients ($n = 75$) |
|---|---|
| Sequential chemo-radiotherapy | 48 |
| Partial response | 6 (12.5%) |
| Complete response | 2 (4.2%) |
| Stable disease | 25 (52.1%) |
| Progression | 14 (29.2%) |
| Unknown | 1 (2.1%) |
| Concurrent chemo-radiotherapy | 10 |
| Partial response | 2 (20%) |
| Complete response | 1 (10%) |
| Stable disease | 6 (60%) |
| Progression | 1 (10%) |
| Exclusive radical radiotherapy | 17 |
| Partial response | 4 (23.5%) |
| Stable disease | 11 (64.7%) |
| Progression | 2 (11.8%) |

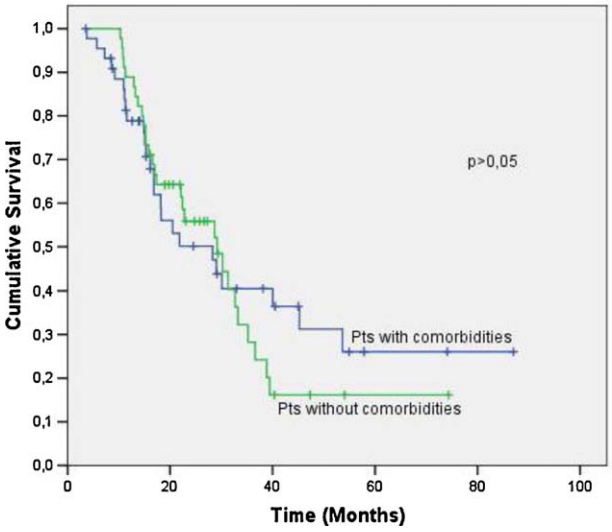


**Fig. 1 – Comorbidities and survival.**

and the 3-year OS rate was 51.5%. For patients treated with sequential and concurrent CTRT, median OS and 3-year survival rates were 28.6 and 15.3 months, and 44% and 25.4%, respectively.

We did not find a statistical relationship between the presence of comorbidities and survival, as shown in Fig. 1 (we divided patients in two groups, one with Charlson score 0 (45 patients) and the other with Charlson score ≥1 (45 patients)). In our analysis, the toxicity presented by the patients was also not influenced by comorbidities, and did not influence survival.

## 5. Discussion

Our study analyses one group of elderly patients who were submitted to thoracic RT with or without CT. As a retrospective study, it presents a selection bias, and it is important to explain the criteria usually considered in our institution when deciding on the treatment strategy for this group of patients. Patients with stage IV or large tumors, significant comorbidities or Karnofsky performance status <70% are submitted to thoracic radiotherapy with palliative intent (10 patients in this study). The remaining cases are individually evaluated for thoracic radiotherapy with radical intent; patients with significant comorbidities that are not suitable for chemotherapy are submitted to RT alone, while the others are submitted to CTRT.

There are few studies about treatment of LC in this age group. Pignon et al. reviewed 1208 patients treated with thoracic RT, comparing the toxicities observed in 6 different age groups and found no difference in the incidence of nausea, dyspnoea, esophagitis, asthenia and performance status, although weight loss was significantly higher in the oldest group ($p = 0.002$).[3]

A prospective study was done by Schild et al. to evaluate the value of combined CTRT in the elderly with stage III NSCLC. They studied 166 patients over 65 years old, and the results showed a better OS in the group treated with CTRT ($p = 0.05$),

**Table 5 – Survival after curative radiotherapy.**

| Treatment | Median progression free survival (months) | Median overall survival (months) | 3-year overall survival |
|---|---|---|---|
| All patients ($n = 75$) | 18.1 | 29 | 33.8% |
| Exclusive radical RT ($n = 17$) | 20.0 | 38.8 | 51.5% |
| Concurrent CTRT ($n = 10$) | 8.0 | 15.3 | 25.4% |
| Sequential CTRT ($n = 48$) | 16.6 | 28.6 | 44% |

in spite of a significantly higher incidence of grade III acute toxicity ($p < 0.01$).[6]

The low toxicity presented by our patients was probably due to the fact that few patients had been submitted to concurrent CTRT as a result of our strict selection criteria.

Lonardi et al. have reviewed 48 patients over 75 years old treated with RT for NSCLC stages IIIA and IIIB, and concluded that there was a significant increase in overall survival for patients treated with doses higher then 50 Gy, when compared with patients treated with lower doses.[7]

In this study, all patients treated with radical intent were submitted to radiation doses higher than 50 Gy.

A phase III study of the North Central Cancer Treatment Group (NCCTG) compared the results of treatment with combined RTCT, conventionally fractionated RT and hyperfractionated RT, and examined the relationship between age and outcome of treatments. The results showed that survival was not significantly worse in older individuals, although toxicity was higher in this group.[8]

The available studies show that combined CTRT is possible in this age group, with better results as compared with RT alone.

In our study, when comparing survival for the different treatment groups (Table 5), we found a better survival in the exclusive radiotherapy group (with radical intent), compared with the two groups treated with CTRT. The number of patients in this study does not allow us to conclude that RT alone is better than CTRT, but we can say that RT in radical doses was well tolerated by our old patients with comorbidities.

## 6. Conclusion

Our results were similar to those described in the literature for younger aged groups, which allows us to conclude that elderly patients are likely to benefit from radical treatments. The sequential or concurrent chemotherapy seems to increase survival but should be carefully used in old patients outside clinical trials. *In this study, concomitant CTRT seemed to deliver worse survival, although it may be due to the small size of the sample.*

## Appendix A. Appendix A – Charlson score

| Condition | Assigned weight |
|---|---|
| Myocardial infarction | 1 |
| Congestive heart failure | 1 |

Appendix A *Continued*

| Condition | Assigned weight |
|---|---|
| Peripheral vascular disease | 1 |
| Cerebrovascular disease | 1 |
| Dementia | 1 |
| Chronic pulmonary disease | 1 |
| Connective tissue disease | 1 |
| Ulcer disease | 1 |
| Liver disease mild | 1 |
| Diabetes | 1 |
| Hemiplegia | 2 |
| Renal disease moderate or severe | 2 |
| Diabetes with end organ damage | 2 |
| Any malignancy | 2 |
| Leukemia | 2 |
| Malignant lymphoma | 2 |
| Liver disease. Moderate or severe | 3 |
| Metastatic solid malignancy | 6 |
| AIDS | 6 |

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