



## AUDIT, RESEARCH AND GUIDELINE UPDATE

# Clinical management of older people with non-small cell lung cancer in England

Paul Beckett,<sup>1</sup> Matthew Callister,<sup>2</sup> Laila J Tata,<sup>3</sup> Richard Harrison,<sup>4</sup> Michael D Peake,<sup>5</sup> Roz Stanley,<sup>6</sup> Ian Woolhouse,<sup>7</sup> Mark Slade,<sup>8</sup> Richard B Hubbard<sup>9</sup>

► Additional materials are published online only. To view these files please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2011-200994>).

<sup>1</sup>Burton Hospitals NHS Foundation Trust, Burton-on-Trent, UK

<sup>2</sup>Department of Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, UK

<sup>3</sup>Department of Epidemiology, University of Nottingham, Nottingham, UK

<sup>4</sup>Department of Respiratory Medicine, North Tees General Hospital, Stockton-on-Tees, UK

<sup>5</sup>Department of Respiratory Medicine, Glenfield Hospital, Leicester, UK

<sup>6</sup>The Information Centre for Health and Social Care, Leeds, UK

<sup>7</sup>Department of Respiratory Medicine, University Hospitals of Birmingham, Birmingham, UK

<sup>8</sup>Department of Respiratory Medicine, Papworth Hospital, Cambridge, UK

<sup>9</sup>Department of Respiratory Medicine, University of Nottingham, Nottingham, UK

## Correspondence to

Dr Paul Beckett, Burton Hospitals NHS Foundation Trust, Queens Hospital Belvedere Road, Burton-on-Trent DE13 0RB, UK; [emailpaulbeckett@gmail.com](mailto:emailpaulbeckett@gmail.com)

Received 4 September 2011

Accepted 7 June 2012

Published Online First

6 July 2012

## ABSTRACT

Data for 25261 patients with non-small cell lung cancer whose details were submitted to the National Lung Cancer Audit in England were analysed to assess the effect of age at diagnosis on their clinical management, after accounting for sex, stage, performance status and comorbidity. Multivariate logistic regression showed the odds of having histocytological confirmation and anticancer treatment decreased progressively with age, and was also lower in women. It is likely that these results have a multifactorial explanation, and further research into the attitudes of patients, carers and healthcare professionals, and clinical trials of treatment in older populations, are necessary.

## INTRODUCTION

Approximately 40 000 new cases of lung cancer are diagnosed in England and Wales each year, making it the second commonest cancer in men (after prostate) and women (after breast)<sup>1</sup> and the commonest cause of cancer-related death in both sexes. Treatment and survival rates vary across the UK and do not match those achieved in comparable healthcare systems. Despite recent scrutiny of primary care to try to explain these observations,<sup>2</sup> it is possible that lower levels of investigation and treatment in older patients in secondary care may explain some of the variation observed.

The National Lung Cancer Audit (NLCA) in the UK is commissioned by the Healthcare Quality Improvement Partnership with funds from the Department of Health and maintained jointly by the Health and Social Care Information Centre and the Royal College of Physicians. It has collected data of progressively improving completeness since 2005. These are now of sufficient quality to permit analysis of factors relating to treatment and outcome.<sup>3</sup> We have used NLCA data to quantify the association between age and the presence of histocytological confirmation of diagnosis and/or receipt of anticancer treatment (surgery, chemotherapy or radiotherapy) in people with non-small cell lung cancer (NSCLC).

## METHODS

We obtained data for the 30 098 people with lung cancer first seen in England in 2009 submitted to the NLCA. A comparison of these cases with published lung cancer registrations from the Office of National Statistics for England<sup>1</sup> shows that the

NLCA ascertained the vast majority of lung cancers and case distribution by age at diagnosis was representative of national registry data (see online supplementary figure 1). Of all cases, we excluded those with pathologically confirmed small cell lung cancer or confirmed/suspected mesothelioma, leaving 25 261 people with histocytologically confirmed or clinically diagnosed NSCLC.

The clinical management measures were patients' receipt of histocytological confirmation of NSCLC and receipt of any anticancer treatment (recorded treatment with surgery, radiotherapy or chemotherapy). We assessed these by age at diagnosis grouped into 10-year age bands (60–69 year olds were used as the reference group in analyses), sex, stage (as classified by the American Joint Committee on Cancer and Union Internationale Contre le Cancer V.6), performance status (as classified by the Eastern Cooperative Oncology Group) and recording of a significant diagnosed comorbidity.

We used multivariate logistic regression to quantify the association of age with our clinical management outcomes, adjusting for sex and the other important clinical features. Receipt of presence of histocytological confirmation was also included as a covariate in the multivariable model for anticancer treatment. Finally we looked for evidence of interaction between age and sex by fitting a multiplicative interaction term.

All statistical analyses were carried out using Stata V. SE11.

## RESULTS

The 25 261 patients with NSCLC analysed had a median age of 72 years (interquartile range 64–80). Demographics and clinical features of the patients according to age and the clinical management outcomes are shown in online supplementary tables 1 and 2. Overall, 68% of patients had histocytological confirmation of the diagnosis and 57% received anticancer treatment.

Table 1 shows the ORs for histocytological confirmation by age and sex adjusted for clinical features. Other than for patients in the youngest age group (<40 years), the multivariable model showed the odds of histocytological confirmation decreased progressively with age. For example, compared with patients aged 60–69 years, the OR was 1.4 for patients aged 40–49 and 0.36 for those aged 80–89. Female sex (OR 0.81 compared with men) and having at least one recorded comorbidity (OR 0.75) were associated with reduced odds of

histocytological confirmation, which also decreased markedly with worsening performance status, whereas the relationship with stage was n-shaped with the largest odds being in those with stage IIIB cancer.

We found a statistically significant interaction between age and sex in our multivariate model (likelihood ratio test  $p=0.0009$ ) which showed that, although similar between men and women under 60 years of age, women were less likely than men to receive histocytological confirmation as they became older. For example, the OR was 1.03 (95% CI 0.66 to 1.60) for women compared with men aged 40–49 and the OR was 0.72 (95% CI 0.65 to 0.81) for patients aged 80–89 (figure 1).

For anticancer treatment, the results were very similar to those for histocytological confirmation (table 1) with the odds of anticancer treatment decreasing progressively with age. For example, compared with patients aged 60–69 years, the OR was 1.97 for patients aged 40–49 and 0.24 for those aged 80–89. Female sex (OR 0.91 compared with men) and having at least one recorded comorbidity (OR 0.75) were associated with reduced odds of anticancer treatment, which also decreased markedly with worsening performance status and disease stage. Again there was evidence of an interaction between age and sex (likelihood ratio test  $p=0.007$ ), for example, the OR was 0.97 (95% CI 0.62 to 1.51) for women compared with men aged 40–49 and the OR was 0.78 (95% CI 0.69 to 0.89) for patients aged 80–89 (figure 1).

## CONCLUSIONS

Our results suggest that age has an important impact on the investigation and treatment of people with lung cancer in England. After adjusting for the effects of sex, stage, perfor-

mance status and comorbidity there was a progressive decline in patients' receipt of histocytological confirmation and anticancer treatment from age 50 years onwards. We also found that women with lung cancer were 19% less likely to have histocytological confirmation of their cancer than men and 9% less likely to have anticancer treatment after adjusting for important clinical features. These sex differences were mostly in patients aged 60–89 years, despite very similar proportions of lung cancers in men and women across these age groups.

The main strengths of our study are the large size of the NLCA datasets, which has been shown to be representative of people with lung cancer in the UK.<sup>3</sup> NLCA data completeness has progressively improved since its inception in 2005, with the result that the 30 098 patients analysed for this study represent almost 100% of the cases managed in secondary care that would be expected from population incidence figures. Furthermore comparison between our dataset and the most recently published data on cancer registrations for England does not suggest that older patients are under-represented in the audit dataset, a finding that supports more detailed previously published research.<sup>3</sup> The main weakness of our study is the lack of robust data on comorbidity routinely available in the NLCA, although information on stage and performance status are robust and more complete than other routine sources.

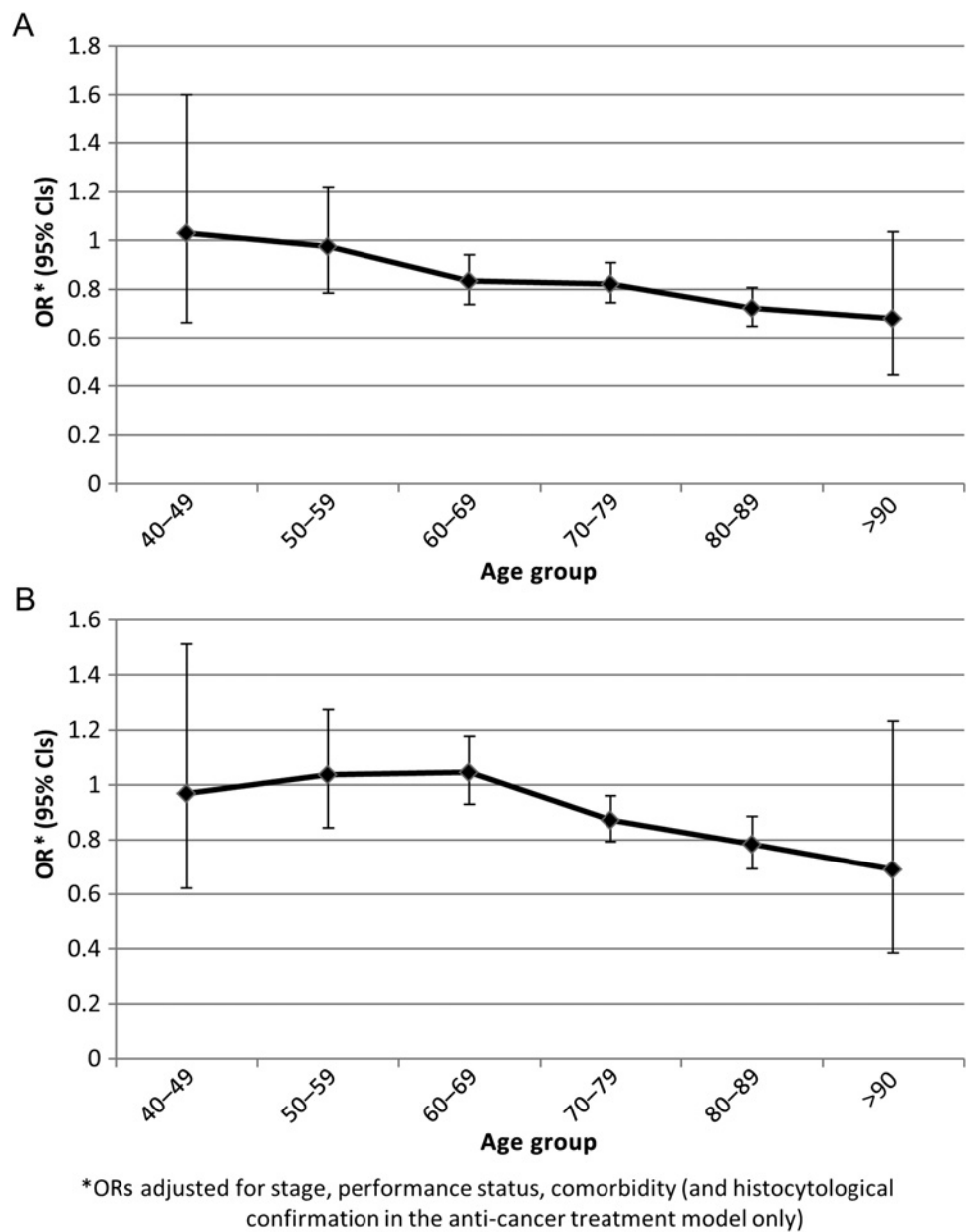
Our results are in line with earlier pilot research on a smaller cohort of 1652 patients from 48 English hospitals with all types of lung cancer which found significant inverse correlations between age and histocytological diagnosis, anticancer treatment and survival.<sup>4</sup> Histocytological confirmation was obtained in 89% of their patients under age 65 years and 80% in those over 75 years and anticancer treatment was given in 78%

**Table 1** ORs for histocytological confirmation and anticancer treatment

|                              | Histocytological confirmation |              |         | Anticancer treatment |              |         |
|------------------------------|-------------------------------|--------------|---------|----------------------|--------------|---------|
|                              | OR*                           | 95% CI       | p Value | OR*                  | 95% CI       | p Value |
| Male                         | 1                             | —            | —       | 1                    | —            | —       |
| Female                       | 0.81                          | 0.77 to 0.86 | <0.001  | 0.91                 | 0.86 to 0.96 | 0.002   |
| Age (years)                  |                               |              |         |                      |              |         |
| <40                          | 0.85                          | 0.55 to 1.31 | 0.451   | 1.10                 | 0.70 to 1.72 | 0.671   |
| 40–49                        | 1.40                          | 1.12 to 1.76 | 0.004   | 1.97                 | 1.57 to 2.47 | <0.001  |
| 50–59                        | 1.34                          | 1.19 to 1.52 | <0.001  | 1.40                 | 1.25 to 1.58 | <0.001  |
| 60–69                        | 1                             | —            | —       | 1                    | —            | —       |
| 70–79                        | 0.71                          | 0.65 to 0.76 | <0.001  | 0.59                 | 0.55 to 0.63 | <0.001  |
| 80–89                        | 0.36                          | 0.33 to 0.39 | <0.001  | 0.24                 | 0.22 to 0.26 | <0.001  |
| >90                          | 0.12                          | 0.10 to 0.15 | <0.001  | 0.07                 | 0.05 to 0.10 | <0.001  |
| Cancer stage                 |                               |              |         |                      |              |         |
| IA                           | 1                             | —            | —       | 1                    | —            | —       |
| IB                           | 1.47                          | 1.23 to 1.75 | <0.001  | 1.29                 | 1.07 to 1.56 | 0.007   |
| IIA                          | 1.07                          | 0.72 to 1.58 | 0.735   | 0.99                 | 0.65 to 1.49 | 0.946   |
| IIB                          | 1.65                          | 1.34 to 2.02 | <0.001  | 1.06                 | 0.86 to 1.30 | 0.585   |
| IIIA                         | 1.66                          | 1.40 to 1.98 | <0.001  | 1.01                 | 0.85 to 1.22 | 0.876   |
| IIIB                         | 1.92                          | 1.65 to 2.25 | <0.001  | 0.85                 | 0.72 to 1.00 | 0.049   |
| IV                           | 1.38                          | 1.20 to 1.59 | <0.001  | 0.59                 | 0.51 to 0.68 | <0.001  |
| Unknown                      | 0.87                          | 0.75 to 1.00 | 0.055   | 0.52                 | 0.44 to 0.60 | <0.001  |
| Performance status           |                               |              |         |                      |              |         |
| 0                            | 1                             | —            | —       | 1                    | —            | —       |
| 1                            | 0.93                          | 0.83 to 1.04 | 0.205   | 0.84                 | 0.76 to 0.94 | 0.002   |
| 2                            | 0.47                          | 0.42 to 0.53 | <0.001  | 0.34                 | 0.30 to 0.38 | <0.001  |
| 3                            | 0.20                          | 0.18 to 0.23 | <0.001  | 0.10                 | 0.09 to 0.11 | <0.001  |
| 4                            | 0.10                          | 0.09 to 0.12 | <0.001  | 0.03                 | 0.02 to 0.04 | <0.001  |
| Unknown                      | 0.43                          | 0.38 to 0.48 | <0.001  | 0.31                 | 0.28 to 0.34 | <0.001  |
| Diagnosed comorbidity        | 0.75                          | 0.69 to 0.82 | <0.001  | 0.75                 | 0.69 to 0.82 | <0.001  |
| Histocytologically confirmed | —                             | —            | —       | 4.02                 | 3.75 to 4.30 | <0.001  |

\*Fully adjusted for all variables in the table.

**Figure 1** Odds ratios for histocytological confirmation (A) and anti-cancer treatment (B) in women compared with men (reference group), stratified by age group.



and 49% respectively. These are slightly higher confirmation and treatment proportions than in NLCA cases overall, however these 1652 patients were a more selected population by virtue of all undergoing bronchoscopy. Similar results have been obtained from studies carried out in the USA, Canada and Europe.

Although there is considerable evidence that tumours behave differently, and outcomes differ, in men and women, there is very little published research on the effect of gender on disease management in patients with lung cancer, since most research has adjusted for sex rather than examining its effect. It is difficult to find a satisfactory explanation for the results observed in our analyses. It is possible that men and women perceive the benefits of a histocytological diagnosis and anticancer treatment differently or that healthcare professionals have a different attitude to a more aggressive management approach in women.

There is good evidence that older patients with comparable clinical features to younger patients can tolerate and benefit equally from investigation and treatment. A recent European

Organisation for Research and Treatment of Cancer statement on treatment in older people, based on a detailed literature review and expert consensus, acknowledges the lack of research evidence to guide clinical decisions about treatment but also clearly states that suitability for treatment should not be defined upon chronological age alone.<sup>5</sup>

How are patients and lung cancer multidisciplinary teams to interpret these results? It is likely that the less active approach to management of lung cancer observed in older people has a multifactorial explanation. Difficulty of access to services, therapeutic nihilism in primary and secondary care, over-estimation of the risks of treatment-related toxicity, and ill-informed patient choice, based perhaps upon the experiences of friends or relatives undergoing different treatment for different cancers, may all play a part. However, it is the multidisciplinary teams who provide key decisions and it is incumbent upon them to examine more closely their own results through local audit and to consider whether their investigation and treatment protocols may inadvertently discriminate against older patients. Further research into attitudes of patients, carers and healthcare

professionals, and clinical trials of treatment in older populations are vital if we are to ensure that all patients receive the very best care, regardless of their age.

**Contributors** PB, RS, MDP and IW lead the team responsible for audit data. RH provided the initial idea for the analysis. PB analysed the data under the supervision of RBH and LJT. PB wrote the paper with substantial input from all authors on content, style and presentation.

**Funding** The National Lung Cancer Audit in the UK is commissioned by the Healthcare Quality Improvement Partnership (HQIP) with funds from the Department of Health and maintained jointly by the Health and Social Care Information Centre (HSCIC) and the Royal College of Physicians.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

1. **Office for National Statistics.** *Cancer Statistics Registration, England, Series MB1.* 2009. <http://www.ons.gov.uk/ons/re/vsob1/cancer-statistics-registrations—england—series-mb1-no—40—2009/cancer-registrations-2009.xls> (accessed 21 Feb 2012).
2. **Holmberg L, Sandin F, Bray F, et al.** National comparisons of lung cancer survival in England, Norway and Sweden 2001–2004: differences occur early in follow-up. *Thorax* 2010;**65**:436–41.
3. **Rich AL, Tata LJ, Stanley RA, et al.** Lung cancer in England: information from the National Lung Cancer Audit (LUCADA). *Lung cancer* 2011;**72**:16–22.
4. **Peake MD, Thompson S, Lowe D, et al.** Ageism in the management of lung cancer. *Age and Ageing* 2003;**32**:171–7.
5. **Pallis AG, Gridelli C, van Meerbeeck JP, et al.** EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. *Ann Oncol* 2010;**21**:692–706.

## Journal club

### CPAP may reduce cardiovascular mortality in patients with OSA

This double-blind randomised crossover study of patients with moderate-to-severe obstructive sleep apnoea (OSA) compared 3 months of therapeutic continuous positive airway pressure (CPAP) with 3 months of sham CPAP with a 1 month wash-out period in between. Markers of the metabolic syndrome were measured before and after each CPAP treatment.

The study population comprised 86 CPAP naïve patients aged 30–65 who were recruited from a sleep laboratory in New Delhi, India. Exclusion criteria were previous or current treatment for hypertension, diabetes, dyslipidemia or any evidence of end-organ damage due to these conditions.

There were modest, statistically significant, reductions in systolic and diastolic blood pressure, glycated haemoglobin, triglycerides, low-density lipoprotein, non-high-density lipoprotein and total cholesterol after CPAP therapy as compared with sham therapy. Additionally, there were significant decreases in body mass index and visceral and subcutaneous fat. Carotid intimal thickness and insulin resistance did not differ significantly. Applying the authors' criteria for the metabolic syndrome, there was a net reduction in the number of patients affected.

Predefined subgroup analysis of patients whose mean adherence with CPAP was five or more hours per night (n=51) revealed, compared with the whole population, significantly greater reductions in systolic and diastolic blood pressure, glycated haemoglobin, triglyceride, LDH and total cholesterol.

The study uses surrogate end points for cardiovascular mortality. CPAP reduces cardiovascular mortality in patients with OSA and CPAP is the recommended treatment for patients with moderate-to-severe OSA.

Further research is needed before we can conclude that additional cardiovascular mortality reduction benefit accrues to this subset of patients with moderate OSA who have the metabolic syndrome.

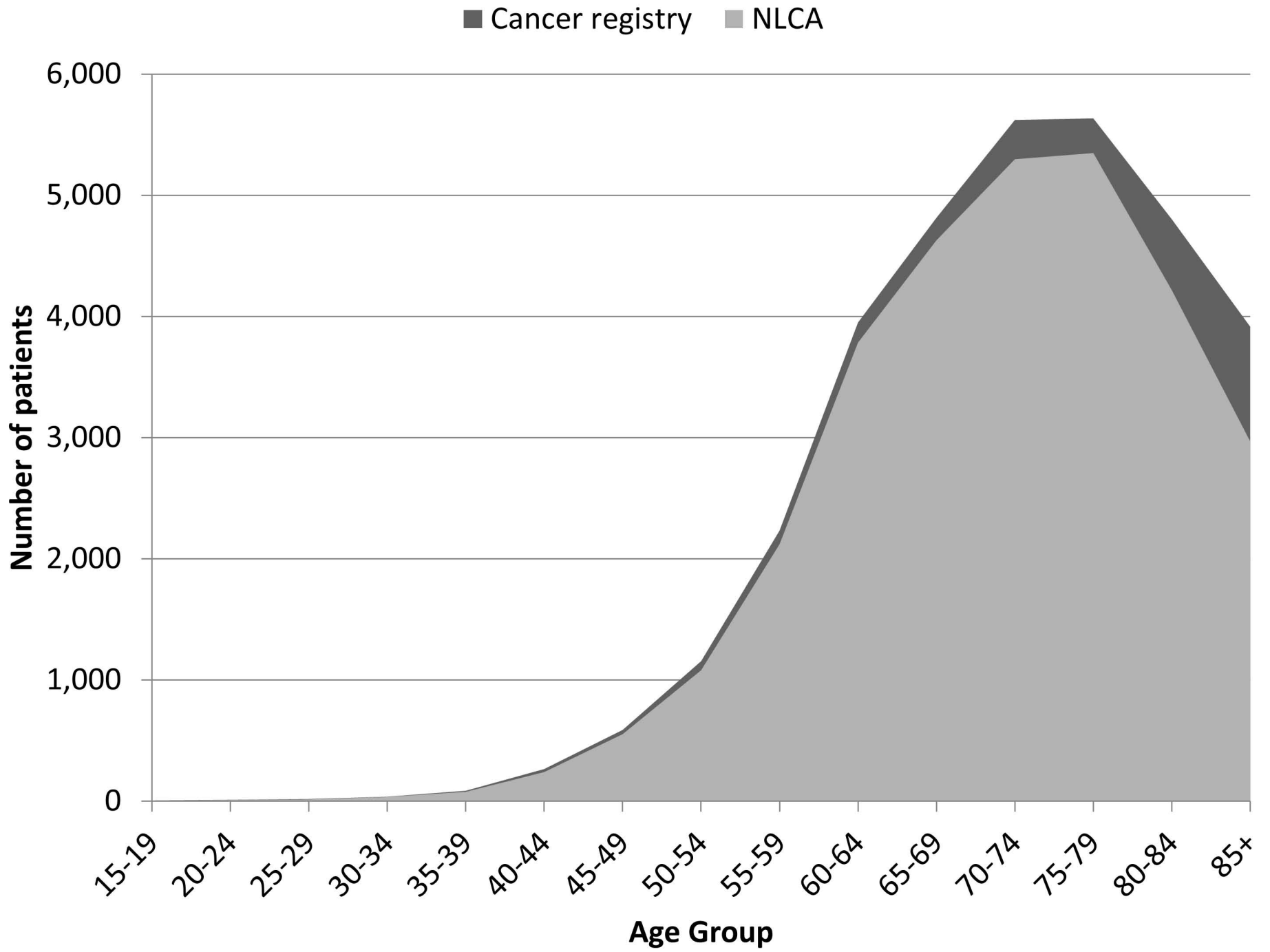
► **Sharma SK, Agrawal S, Damodaran D, et al.** CPAP for the metabolic syndrome in patients with obstructive sleep apnoea. *N Engl J Med* 2011;**365**:2277–86.

#### Carl J Reynolds

**Correspondence to** Dr Carl J Reynolds, CT1, Chelsea and Westminster NHS Trust, Department of Acute Medicine, 369 Fulham Road, London SW10 9NH, UK; [carl.reynolds@nhs.net](mailto:carl.reynolds@nhs.net)

Published Online First 10 February 2012

*Thorax* 2012;**67**:839. doi:10.1136/thoraxjnl-2012-201669



## Further References

1. Austin PC, Tu JV, Daly PA, Alter DA. The use of quantile regression in health care research: a case study examining gender differences in the timeliness of thrombolytic therapy. *Statistics in medicine*. 2005 Mar 15;24(5):791–816. doi: 10.1002/sim.1851.
2. Brown J, Eraut D, Trask C, Davison A. Age and the treatment of lung cancer. *Thorax*. 1996;51(6):564.
3. Cancer Research UK. UK Lung Cancer incidence statistics. 2009 <http://info.cancerresearchuk.org/cancerstats/types/lung/incidence/>.
4. Carreca I, Balducci L, Extermann M. Cancer in the older person. *Cancer Treatment Reviews*. 2005 Aug;31(5):380–402. doi: 10.1016/j.ctrv.2005.04.012.
5. Gridelli C, Maione P, Illiano A, Piantedosi FV, Favaretto A, Bearz A, et al. Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non small-cell lung cancer: the MILES-2P studies. *Journal of Clinical Oncology*. 2007 Oct;25(29):4663–9. doi: 10.1200/JCO.2007.12.5708.
6. Guadagnoli E, Weitburg A, Mor V, Silliman R, Glicksman A, Cummings F. The Influence of Patient Age on the Diagnosis and Treatment of Lung and Colorectal Cancer. *Arch Intern Med*. 1990;150(7):1485–90.
7. Imperatori A, Harrison RN, Leitch DN, Rovera F, Lepore G, Dionigi G, et al. Lung cancer in Teesside (UK) and Varese (Italy): a comparison of management and survival. *Thorax*. 2006;61(3):232–9. doi: 10.1136/thx.2005.040477.
8. Janssen-Heijnen MLG. Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer. *Thorax*. 2004 Jul;59(7):602–7. doi: 10.1136/thx.2003.018044.
9. Møller H, Linklater KM, Robinson D. A visual summary of the EURO CARE-4 results: a UK perspective. *British Journal of Cancer*. 2009 Dec;101 Suppl:S110–4. doi: 10.1038/sj.bjc.6605400.
10. Mor V, Masterson-Allen S, Goldberg R, Cummings F, Glicksman A, Fretwell M. Relationship between age at diagnosis and treatments received by cancer patients. *J Am Geriatr Soc*.

1985;33(9):585–9.

11. National Lung Cancer Audit Report for the audit period 2008. 2009  
[http://www.ic.nhs.uk/webfiles/Services/NCASP/audits and reports/NHS IC Lung Cancer AUDIT 2009 FINAL.pdf](http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS%20IC%20Lung%20Cancer%20AUDIT%202009%20FINAL.pdf).
12. Palma DA, Tyldesley S, Sheehan F, Mohamed IG, Smith S, Wai E, et al. Stage I Non-small Cell Lung Cancer (NSCLC) in Patients Aged 75 Years and Older. *Journal of Thoracic Oncology*. 2010
13. Schüppel R, Büchele G, Batz L, Koenig W. Sex differences in selection of pacemakers: retrospective observational study. *BMJ (Clinical research ed.)*. 1998 May 16;316(7143):1492–5. Jun;5(6):818–24. doi: 10.1097/JTO.0b013e3181d6e052.
14. Smith T. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. *Lung Cancer*. 1995 Dec;13(3):235–52. doi: 10.1016/0169-5002(95)00496-3.
15. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. *Journal of the National Cancer Institute*. 1999 Jan;91(1):66–72. doi: 10.1093/jnci/91.1.66.
16. Vinod SK, O’Connell DL, Simonella L, Delaney GP, Boyer M, Peters M, et al. Gaps in optimal care for lung cancer. *Journal of Thoracic Oncology*. 2008 Aug;3(8):871–9. doi: 10.1097/JTO.0b013e31818020c3.
17. Zachariah B, Balducci L, Venkattaramanabalaji GV, Casey L, Greenburg HM, Delregato JA. Radiotherapy for cancer patients aged 80 and older : A study of effectiveness and side effects. *International journal of radiation oncology, biology, physics*. 39(5):1125–9.

**Table 1: Demographics and Clinical Features by Age Group**

|   | <40        | 40-49      | 50-59         | 60-69         | 70-79         | 80-89         | >90        | Total         |
|---|------------|------------|---------------|---------------|---------------|---------------|------------|---------------|
| <b>Number of patients</b>                 | 134 (0.5%) | 674 (2.7%) | 2,570 (10.2%) | 6,770 (26.8%) | 8,779 (34.8%) | 5,774 (22.9%) | 560 (2.2%) | 25,261 (100%) |
| <b>Males (% male)</b>                     | 73 (54%)   | 320 (47%)  | 1,367 (53%)   | 3,920 (58%)   | 5,162 (59%)   | 3,197 (55%)   | 280 (50%)  | 14,319 (57%)  |
| <b>FEV<sub>1</sub> recorded</b>           | 33 (25%)   | 172 (26%)  | 704 (27%)     | 2,102 (31%)   | 2,713 (31%)   | 1,299 (22%)   | 59 (11%)   | 7,082 (28%)   |
| <b>Mean FEV<sub>1</sub> (Litres)</b>      | 2.6        | 2.4        | 2.0           | 1.8           | 1.5           | 1.35          | 1.2        | 1.6           |
| <b>Mean FEV<sub>1</sub> (% predicted)</b> | 81%        | 75%        | 70%           | 68%           | 66%           | 67%           | 67%        | 68%           |
| <b>Cancer stage</b>                       |            |            |               |               |               |               |            |               |
| <b>IA</b>                                 | 9 (7%)     | 26 (4%)    | 115 (4%)      | 355 (5%)      | 460 (5%)      | 261 (5%)      | 23 (4%)    | 1,249 (5%)    |
| <b>IB</b>                                 | 9 (7%)     | 38 (6%)    | 118 (5%)      | 440 (6%)      | 642 (7%)      | 428 (7%)      | 28 (5%)    | 1,703 (7%)    |
| <b>IIA</b>                                | 1 (1%)     | 1 (0%)     | 16 (1%)       | 46 (1%)       | 65 (1%)       | 25 (0%)       | 3 (1%)     | 157 (1%)      |
| <b>IIB</b>                                | 2 (1%)     | 25 (4%)    | 112 (4%)      | 280 (4%)      | 388 (4%)      | 237 (4%)      | 17 (3%)    | 1,061 (4%)    |
| <b>IIIA</b>                               | 6 (4%)     | 33 (5%)    | 200 (8%)      | 523 (8%)      | 682 (8%)      | 392 (7%)      | 32 (6%)    | 1,868 (7%)    |
| <b>IIIB</b>                               | 12 (9%)    | 93 (14%)   | 359 (14%)     | 964 (14%)     | 1,289 (15%)   | 835 (14%)     | 74 (13%)   | 3,626 (14%)   |
| <b>IV</b>                                 | 52 (39%)   | 282 (42%)  | 1,078 (42%)   | 2,604 (38%)   | 3,232 (37%)   | 2,034 (35%)   | 191 (34%)  | 9,473 (38%)   |
| <b>Unknown</b>                            | 43 (32%)   | 176 (26%)  | 572 (22%)     | 1,558 (23%)   | 2,021 (23%)   | 1,562 (27%)   | 192 (34%)  | 6,124 (24%)   |
| <b>Total</b>                              | 100%       | 100%       | 100%          | 100%          | 100%          | 100%          | 100%       | 100%          |
| <b>Performance status</b>                 |            |            |               |               |               |               |            |               |
| <b>0</b>                                  | 66 (49%)   | 208 (31%)  | 699 (27%)     | 1395 (21%)    | 1130 (13%)    | 408 (7%)      | 19 (3%)    | 3925 (16%)    |
| <b>1</b>                                  | 28 (21%)   | 191 (28%)  | 739 (29%)     | 1962 (29%)    | 2340 (27%)    | 1081 (19%)    | 45 (8%)    | 6386 (25%)    |
| <b>2</b>                                  | 5 (4%)     | 75 (11%)   | 323 (13%)     | 985 (15%)     | 1538 (18%)    | 1163 (20%)    | 92 (16%)   | 4181 (17%)    |
| <b>3</b>                                  | 5 (4%)     | 42 (6%)    | 165 (6%)      | 685 (10%)     | 1419 (16%)    | 1368 (24%)    | 184 (33%)  | 3868(15%)     |
| <b>4</b>                                  | 2 (1%)     | 7 (1%)     | 59 (2%)       | 211 (3%)      | 468 (5%)      | 473 (8%)      | 88 (16%)   | 1308 (5%)     |
| <b>Unknown</b>                            | 28 (21%)   | 151 (22%)  | 585 (23%)     | 1532 (23%)    | 1884 (21%)    | 1281 (22%)    | 132 (24%)  | 5593 (22%)    |
| <b>Total</b>                              | 100%       | 100%       | 100%          | 100%          | 100%          | 100%          | 100%       | 100%          |
| <b>Diagnosed co-morbidity</b>             | 6%         | 6%         | 9%            | 12%           | 16%           | 18%           | 18%        | 14%           |



**Table 2: Demographics and Clinical Features by Outcome Measure**

| Covariate                 | Histocytologically-confirmed<br>(n=17,219) |       | Not histocytologically-confirmed<br>(n=8,042) |       | Anti-cancer treatment<br>(n=14,339) |       | No anti-cancer treatment<br>(n=10,922) |       |
|---------------------------|--|-------|---|-------|-------------------------------------|-------|--|-------|
|                           | n  | %     | n   | %     | n                                   | %     | n                                      | %     |
| <b>Sex</b>                |  |       |   |       |                                     |       |  |       |
| Male                      | 10,038                                     | 58.3% | 4,281   | 53.2% | 8,263                               | 57.6% | 6,056                                  | 55.4% |
| Female                    | 7,181                                      | 41.7% | 3,761   | 46.8% | 6,076                               | 42.4% | 4,866                                  | 44.6% |
| <b>Age</b>                |  |       |   |       |                                     |       |  |       |
| <40                       | 106  | 0.6%  | 28  | 0.3%  | 105                                 | 0.7%  | 29                                     | 0.3%  |
| 40-49                     | 573  | 3.3%  | 101   | 1.3%  | 566                                 | 3.9%  | 108                                    | 1.0%  |
| 50-59                     | 2,161                                      | 12.6% | 409   | 5.1%  | 2,018                               | 14.1% | 552                                    | 5.1%  |
| 60-69                     | 5,311                                      | 30.8% | 1,459   | 18.1% | 4,800                               | 33.5% | 1,970                                  | 18.0% |
| 70-79                     | 6,077                                      | 35.3% | 2,702   | 33.6% | 4,939                               | 34.4% | 3,840                                  | 35.2% |
| 80-89                     | 2,871                                      | 16.7% | 2,903   | 36.1% | 1,855                               | 12.9% | 3,919                                  | 35.9% |
| >90                       | 120  | 0.7%  | 440   | 5.5%  | 56                                  | 0.4%  | 504                                    | 4.6%  |
| <b>Stage</b>              |  |       |   |       |                                     |       |  |       |
| Stage IA                  | 870  | 5.1%  | 379   | 4.7%  | 895                                 | 6.2%  | 354                                    | 3.2%  |
| Stage IB                  | 1,272                                      | 7.4%  | 431   | 5.4%  | 1,246                               | 8.7%  | 457                                    | 4.2%  |
| Stage IIA                 | 110  | 0.6%  | 47  | 0.6%  | 110                                 | 0.8%  | 47                                     | 0.4%  |
| Stage IIB                 | 813  | 4.7%  | 248   | 3.1%  | 746                                 | 5.2%  | 315                                    | 2.9%  |
| Stage IIIA                | 1,425                                      | 8.3%  | 443   | 5.5%  | 1,283                               | 8.9%  | 585                                    | 5.4%  |
| Stage IIIB                | 2,752                                      | 16.0% | 874   | 10.9% | 2,245                               | 15.7% | 1,381                                  | 12.6% |
| Stage IV                  | 6,387                                      | 37.1% | 3,086   | 38.4% | 4,853                               | 33.8% | 4,620                                  | 42.3% |
| Stage Unknown             | 3,590                                      | 20.8% | 2,534   | 31.5% | 2,961                               | 20.6% | 3,163                                  | 29.0% |
| <b>Performance Status</b> |  |       |   |       |                                     |       |  |       |
| PS 0                      | 3,355                                      | 19.5% | 570   | 7.1%  | 3,277                               | 22.9% | 648                                    | 5.9%  |
| PS 1                      | 5,299                                      | 30.8% | 1,087   | 13.5% | 4,941                               | 34.5% | 1,445                                  | 13.2% |
| PS 2                      | 2,850                                      | 16.6% | 1,331   | 16.6% | 2,232                               | 15.6% | 1,949                                  | 17.8% |
| PS 3                      | 1,760                                      | 10.2% | 2,108   | 26.2% | 909                                 | 6.3%  | 2,959                                  | 27.1% |
| PS 4                      | 382  | 2.2%  | 926   | 11.5% | 105                                 | 0.7%  | 1,203                                  | 11.0% |
| PS Unknown                | 3,573                                      | 20.8% | 2,020   | 25.1% | 2,875                               | 20.1% | 2,718                                  | 24.9% |
| <b>Co-morbidity</b>       |  |       |   |       |                                     |       |  |       |
| Yes                       | 2,192                                      | 12.7% | 1,444   | 18.0% | 1731                                | 12.1% | 1905                                   | 17.4% |
| No                        | 15,027                                     | 87.3% | 6,598   | 82.0% | 12608                               | 87.9% | 9017                                   | 82.6% |

