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Variation in surgical resection for lung cancer in relation to survival: Population-based study in England 2004–2006

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ABSTRACT

Background: Compared with some European countries, England has low lung cancer survival and low use of surgical resection for lung cancer. The use of surgical resection varies within England. We assessed the relationship between surgical resection rate and the survival of lung cancer patients in England.

Methods: We extracted data on 77,349 non-small cell lung cancer (NSCLC) patients diagnosed between 2004 and 2006 from the English National Cancer Repository Dataset. We calculated the frequency of surgical resection by age, socio-economic deprivation and geographical area. We used Cox regression to compute mortality hazard ratios according to quintiles of frequency of surgical resection amongst all 77,349 lung cancer patients, and separately for the 6900 patients who underwent surgical resection.

Results: We found large geographical variation in the surgical resection rate for NSCLC in PCT areas (3–18%). A high frequency of resection was strongly inversely associated with overall mortality (HR 0.88, 95% CI 0.86–0.91 for the highest compared to the lowest resection quintile) and only moderately associated with mortality amongst the resected patients (HR 1.15, 95% CI 0.98–1.36). Compared to the highest resection quintile, 5420 deaths could be delayed in the overall NSCLC group, whereas about 146 more deaths could be expected amongst the resected patients.

Conclusion: The differences in the magnitudes of both the hazard ratios and the absolute excess deaths within resected patients and all NSCLC patients suggests that lung cancer survival in England could plausibly increase if a larger proportion of patients underwent surgical resection. Carefully designed research into the possible benefit of increasing resection rates is indicated.

1. Introduction

Around 40,000 incident cases of lung cancer are diagnosed in the United Kingdom every year, and five-year relative survival is less than 10%.[1] Lung cancer survival is known to be lower in England than in other countries with similar health care systems[2] and the mortality difference is largest early in the period of follow-up.[3] Surgical resection for lung cancer can

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potentially lead to long-term survival and cure, and it is possible that the low survival in England can in part be ascribed to low resection rates.

Non-small cell lung cancer (NSCLC) comprises over 85% of all lung cancers. In patients with early stage NSCLC, pulmonary resection provides the best form of potentially curative treatment.[4] The resection rate in England is reportedly around 10%,[5] whereas elsewhere in Europe and the US resection rates of around 20% to 30% are reported.[6–8] However, most internationally reported resection rates are quoted as a proportion of those patients with a confirmed tissue diagnosis of NSCLC whereas previous UK data has used the total lung cancer population (including those diagnosed on clinic-radiological grounds only) as the denominator. It has been shown that resection rates are variable by region.[9,10] Recent data from the English National Lung Cancer Audit showed that 14% of patients with a confirmed NSCLC diagnosis underwent resection, with some hospital trusts having rates of well over 20%.[11] [http://www.ic.nhs.uk/webfiles/Services/NCASP/] A recent report from one UK hospital reported a resection rate of 25% for NSCLC.[12] The resection rate in NSCLC patients declines above the age of 70 years,[13] although there is strong evidence that they respond equally as well as younger patients.[14] Higher levels of socio-economic deprivation have been associated with the low use of radical resection for lung cancer.[15,16]

The present study was designed to explore the association between lung cancer resection and survival in different parts and subgroups of the English population. The ultimate question is whether it is likely that increasing the use of surgical resection would lead to an increase in lung cancer survival. A priori, we hypothesised that resection and survival would be positively associated in the total lung cancer population (resected patients expectedly living longer than non-resected patients), and negatively associated in the resected patient population (higher surgery rates being associated with surgery being carried out on higher risk patients). The relative magnitudes of these opposing associations could help indicate whether an increase in resection would lead to an increase in the overall lung cancer survival.

2. Methods

2.1. *Lung cancer patients*

We extracted data on 92,952 persons diagnosed with lung cancer (ICD-10 C33-C34) between 2004 and 2006 from the National Cancer Repository Dataset, collated from the regional cancer registries in England and linked with the hospital episode statistics (HES) records.[17] Follow-up for death was until 31st December 2006.

We excluded small cell lung cancer (SCLC) (*n* = 11,428) patients from the analysis of survival in relation to surgical resection because the primary treatment for SCLC is generally chemotherapy. All cancer registrations originating from a death certificate only (DCO) (*n* = 4229) were also excluded. These exclusions left 77,349 patients with NSCLC (47,705) or with unspecified types of lung cancer (29,644) for the analyses.

Patients who had undergone surgical resection were identified from the linked HES data. Radical resections for lung cancer included: lobectomy (66%), total pneumonectomy (13%), partial lobectomy (9%), excision of lung segment (7%), bilobectomy (4%) and seven other, less common procedures (1%).

2.2. *Independent variables*

We computed the proportion of lung cancer patients resident in each Primary Care Trust (PCT) who underwent surgical resection, and derived the quintiles from the resulting distribution. Each lung cancer patient was thereby assigned to a resection quintile, depending on their PCT of residence. There are currently 152 PCT organisations in England with an average population of 339,000 people (inter-quartile range: 214,000–408,000; full range: 91,000–1284,000).

Patients were assigned to a socio-economic deprivation quintile, based on their postcode of residence at the time of lung cancer diagnosis. Quintiles were based on the income domain of the Index of Multiple Deprivation 2004.[18]

Patients were also grouped according to their Government Office Region of residence (East Midlands, East of England, London, North East England, North West England, South East England, South West England, West Midlands and Yorkshire & the Humber).

2.3. *Data analysis*

The proportions of lung cancer patients who underwent surgical resection in the 152 PCT areas in England were displayed in a ranked bar chart, indicating the five quintiles of the distribution. We also mapped the PCTs with indication of the resection quintile of each area.

We used logistic regression models to assess the effects of age, sex, socio-economic deprivation and Government Office Region on the proportion of patients who underwent resection.

Cox proportional hazards regression was used to analyse the survival of lung cancer patients in relation to resection quintile and other covariates. These analyses were carried out amongst all 77,349 lung cancer patients, and separately for the 6900 resected patients. For quality assurance, we repeated the analyses with restriction to the 47,705 patients with a specified morphology diagnosis.

In separate analyses, we used the Government Office Region of residence as an alternative to the resection quintiles. We computed χ^2 values and p-values for trend by fitting a linear categorical variable.

Finally, we computed the excess deaths in each resection quintile amongst all lung cancer patients, and amongst those who had undergone surgical resection. We computed the expected deaths based on the baseline death rate in the reference quintile (lowest resection rate) and the accumulated person-years in the comparison quintiles. Excess deaths were then calculated by subtracting the observed number of deaths from the expected number. Negative values represent the number of deaths postponed.

3. Results

3.1. *Variation in radical resection*

Fig. 1 shows the proportions of lung cancer patients in the 152 PCTs in England who underwent surgical resection. The proportion ranged from 3% to 18% with a median of 9%.

A map of the resection quintiles in PCT areas in England indicated no obvious geographical pattern (data not shown).

3.2. *Predictors of surgical resection*

Initially we analysed the proportions of lung cancer patients who underwent surgical resection in relation to other known characteristics. Resection was highly dependent on age with the proportion of resected patients decreasing from 14% in the youngest patients to less than 1% in the oldest ($p < 0.001$). Resection was more frequent in the most affluent than in the most deprived; the magnitude of this association increased when adjustment was made for the other variables ($p < 0.001$). Resection was slightly more frequent in females than males. There was statistically significant variation between the nine Government Office Regions ($p < 0.001$) (data not shown).

3.3. *Survival analysis; all patients*

We conducted Cox proportional hazard regression analyses for all 77,349 lung cancer patients. The all-cause mortality hazard ratios increased with age and with socio-economic deprivation (data not shown). Female patients had a hazard ratio of 0.93 compared with males.

Table 1 (upper part) shows the unadjusted and adjusted hazard ratios according to cancer resection quintile for the total lung cancer population. Twelve percent of patients underwent surgical resection in the highest quintile compared to 5.6% in quintile 5. The all-cause mortality hazard ratios decreased with increasing resection rates. The quintile with the highest surgical resection rate (quintile 1) had a hazard ratio of 0.88 (95% CI: 0.86–0.91), indicating a 12% decrease in the mortality rate compared to quintile 5. There was a significant trend in the hazard ratios over the five quintiles ($p < 0.001$). Adjusting for the case-mix variables age, sex and socio-economic deprivation led to a very small attenuation of the relationship between surgical resection and mortality.

3.4. *Survival analysis; resected patients only*

A Cox proportional hazards regression analyses of the 6900 resected patients showed that mortality rates increased with age and were lower in female patients than in males. Amongst the resected patients, there was no clear mortality trend with socio-economic deprivation (data not shown).

Table 1 (lower part) shows the survival analysis of the resected patients in relation to the overall proportion of lung cancer patients who had surgical resection. The association between surgical resection and mortality was now reversed and the mortality hazard ratio was highest in quintile 1 where the largest proportion of patients had resections (1.19; 95%CI: 1.01–1.40). The association was not linear and the hazard ratio was lowest in quintile 3 (0.81; 95%CI: 0.67–0.97). There was a statistically significant trend over the five quintiles ($p < 0.001$). This trend was not materially sensitive to adjustment for the case-mix variables, and the hazard ratio in the highest quintile was similar at 1.15 (95%CI: 0.98–1.38).

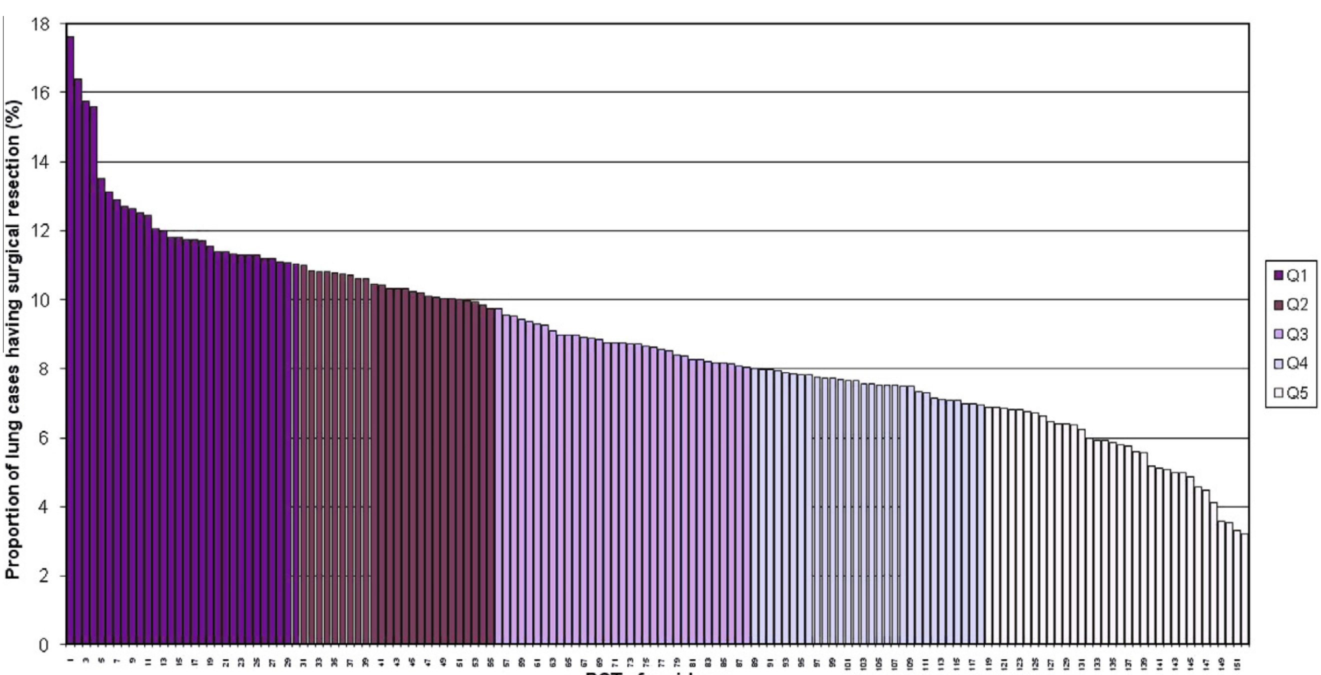

Fig. 1 – The proportions of 77,349 lung cancer patients (excluding SCLC) resident in the 152 PCTs in England, diagnosed between 2004 and 2006, who received surgical resection. The five quintiles of the distribution are indicated.

Table 1 – Mortality hazard ratios (HR) and 95% confidence interval (95% CI) in relation to frequency of surgical resection.

Resection quintile		Number of patients	Proportion of resected patients (%)	Unadjusted		Adjusted*	
				HR	95%CI	HR	95%CI
A: Analysis of all 77,349 lung cancer patients							
1	(11.0–17.6)	15,500	12.3	0.88	(0.86–0.91)	0.88	(0.86–0.91)
2	(9.8–11.0)	15,195	10.4	0.91	(0.89–0.94)	0.92	(0.90–0.94)
3	(8.0–9.7)	15,694	8.8	0.92	(0.90–0.95)	0.93	(0.91–0.95)
4	(7.0–8.0)	15,687	7.5	0.94	(0.92–0.97)	0.95	(0.92–0.97)
5	(3.2–6.9)	15,273	5.6	1.00		1.00	
			χ^2	97.44		86.80	
			p-value for trend	<0.001		<0.001	
B: Analysis of 6900 resected lung cancer patients							
1	(11.0–17.6)	1910	100	1.19	(1.01–1.40)	1.15	(0.98–1.36)
2	(9.8–11.0)	1573	100	1.02	(0.86–1.21)	1.01	(0.85–1.20)
3	(8.0–9.7)	1382	100	0.81	(0.67–0.97)	0.81	(0.67–0.97)
4	(7.0–8.0)	1179	100	0.93	(0.77–1.12)	0.92	(0.76–1.10)
5	(3.2–6.9)	856	100	1.00		1.00	
			χ^2	11.99		9.36	
			p-value for trend	<0.001		0.002	

* Adjusted for age, sex and socio-economic deprivation.

Table 2 – Observed, expected and excess mortality.

Resection quintile		Observed (O)	Expected (E)	Excess mortality (O – E)
A: Analysis of 77,349 lung cancer patients				
1	(11.0–17.6)	11,265	13,226	−1961
2	(9.8–11.0)	11,123	12,442	−1319
3	(8.0–9.7)	11,518	12,735	−1217
4	(7.0–8.0)	11,595	12,519	−924
5	(3.2–6.9)	11,555	11,555	0
Total		57,056	62,476	−5420
B: An analysis of 6900 resected lung cancer patients				
1	(11.0–17.6)	523	441	82
2	(9.8–11.0)	369	361	8
3	(8.0–9.7)	268	332	−64
4	(7.0–8.0)	256	276	−20
5	(3.2–6.9)	197	197	0
Total		1613	1607	6

3.5. *Excess mortality*

Table 2 shows the excess mortality according to resection quintiles amongst all patients (upper part) and resected patients (lower part). When all lung cancer patients were considered, fewer deaths than expected were observed amongst all four resection quintiles, compared to the lowest resection quintile. In the four quintiles with increasing resection rates, an estimated 5420 deaths were postponed in comparison to the lowest resection quintile. Amongst resected patients (Table 2, lower part) the differences between the numbers of observed and expected deaths were much smaller, with the difference between the extreme quintiles 3 and 5 corresponding to 146 deaths.

3.6. *Government Office Region*

Fig. 2 shows the mortality hazard ratios amongst all 77,349 lung cancer patients and the proportions of lung cancer patients who had surgical resection in each Government Office Region in England. Similar to the analysis by PCT resection quintile, there was a decrease in mortality rate with increasing resection. London was outlying with a low mortality rate. The estimates in the figure were not materially changed when

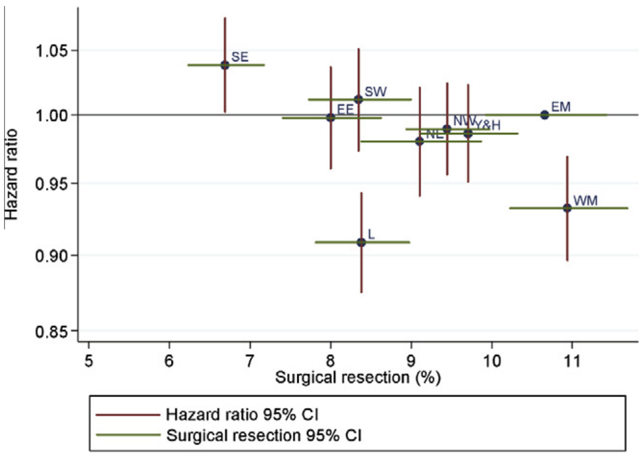

Fig. 2 – Mortality hazard ratios of all 77,349 lung cancer patients diagnosed between 2004 and 2006 in England, against surgical resection (%) in Government Office Region areas, with 95% confidence intervals (CI). The regions are (left to right): South East, East of England, South West, London, North East, North West, Yorkshire & the Humber, East Midlands, West Midlands.

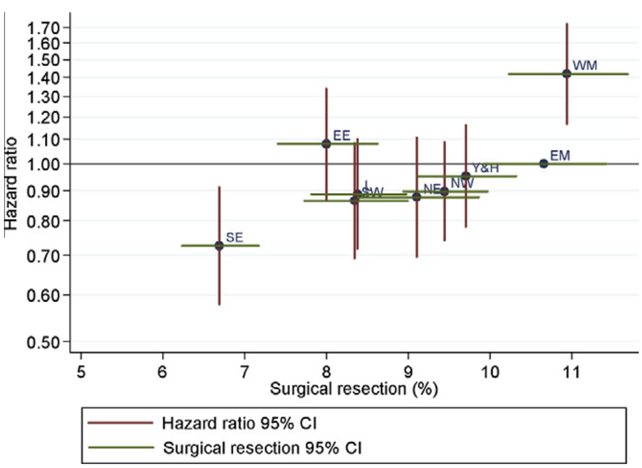

Fig. 3 – Mortality hazard ratios of the 6900 resected lung cancer patients diagnosed between 2004 and 2006 in England, against surgical resection (%) in Government Office Region areas, with 95% confidence intervals (CI). The regions are (left to right): South East, East of England, South West, London, North East, North West, Yorkshire & the Humber, East Midlands, West Midlands.

we adjusted the hazard ratio estimates for age, sex and socio-economic deprivation (data not shown).

Fig. 3 illustrates the corresponding hazard ratios amongst the 6900 resected patients. Consistent with the analysis of PCT resection quintiles, there was an increase in mortality rate amongst the resected patients when overall resection proportion increased. The trend over Government Office Region areas was principally driven by low resection frequency and low mortality amongst the resected in the South East, and a high resection frequency and high mortality amongst the resected patients in the West Midlands. As before, the estimated hazard ratios were not sensitive to statistical adjustment for age, sex and socio-economic deprivation (data not shown).

4. Discussion

Within England, we found variation in the use of surgical resection as a treatment for NSCLC. Higher resection rates were strongly associated with better overall survival and only moderately inversely associated with survival within the resected sub-population. We found these associations both at the level of the 152 PCTs and nine Government Office Regions in England. These associations were independent of age, sex and socio-economic deprivation, but age, sex and socio-economic deprivation were, as expected, associated with the use of surgical resection and with the mortality of lung cancer patients. Other studies have yielded results that are consistent with our findings regarding age[14,19] and socio-economic deprivation.[15,16,20,21]

The resection rate in the linked records of English cancer registrations and Hospital Episode Statistics is low (median: 9%) in comparison with reports from other countries.[20,22–24] The principal strength of our study is the nationwide and very large study population with high completeness of cancer registration and ascertainment of surgical interventions and deaths in the patient cohort. Patients in whom the diagnosis was made only on clinical grounds were thus included in the denominator in this population-based analysis. The limitations of the study are the absence of direct information on co-morbidity[25–28] (other than co-morbidity information provided indirectly through age and socio-economic status), stage and the imaging method to ascertain stage, especially PET-scanning,[29] hospital volumes of resection[10,30] and the degree of clinical specialisation of the surgeons.[31–33]

This population-based, clinical epidemiological analysis explores the variations that occur in the patient population and in the clinical community to address the question 'Would overall lung cancer survival increase if more lung cancer patients had surgical resection of their tumours?' The use of these observational data to address the question entails an extrapolation from the known to the unknown, and is inherently less robust than an imaginary controlled study with a designed contrast of comparing scenarios with for example 10% and 20% resection rates in relation to the survival outcome.

The proportion of lung cancer patients that undergo surgical resection depends on both patient factors (stage of disease; co-morbidity; willingness to be operated), physician factors (propensity to operate on a 'grey-area' patient with, for example, poor lung function, a locally advanced tumour or in an older age group) and institutional factors (availability of specialist thoracic surgical expertise and their presence within the multi-disciplinary team decision making process). If the variation between units and geographical areas is driven mainly by physician and institutional factors, then the observational study may have the same validity as a controlled trial, and would yield similar results. If the variation, however, is mainly brought about by patient-level characteristics, then we will expect that the observational study would over-estimate the association between resection and survival. If the currently non-resected patients are all truly unfit for resection, then they would not benefit from being resected.

Notwithstanding the absence of information on key prognostic variables (e.g. stage, co-morbidity, tobacco smoking) and the inherently observational and partly 'ecological' nature of the data, there are several indications of robustness of our findings. Firstly, it is evident from Table 1 that the hazard ratio estimates and their trends over the resection quintiles are insensitive to statistical adjustment for age and socio-economic deprivation. This makes it very unlikely that patient-level co-morbidity is confounding the observed associations, and makes it rather more likely that the associations are driven by physician- or institution-level factors. This adds weight to the notion that there may be a genuine survival-response to an intervention which facilitates an increase in the resection rate.

Secondly, it was suggested to us in the editorial review of this manuscript that the associations in Table 1 may be confounded by patient-level or tumour-level characteristics manifest by the presence or absence of a specified morphology diagnosis. We, therefore, repeated the analysis in Table 1A with restriction to the 47,705 cases with a specified histology. The results of the restricted analysis were practically identical to those reported in Table 1 (data not shown). This again gives strong evidence that the principal results of this study are not confounded by case-mix valuables relating to poor prognosis and associated with the availability of a specific diagnosis.

Our main results suggest that lung cancer survival could plausibly be increased if a higher proportion of patients were resected. The gradient between resection and survival is steep (Table 1), and in absolute terms (Table 2) there are a large number of lung cancer deaths that could be postponed if more patients were resected.

The survival analysis amongst the resected lung cancer population suggests a scenario of diminishing returns. As more patients are resected, the marginal survival benefit to the individual resected patient reduces. However, the contrast between the analyses of all patients and resected patients suggest that we are a long way from the optimal level of surgical resection. Even the PCT areas and the Government Office Regions with the highest resection rates are plausibly still lower than the desirable level of resection to maximise the survival of lung cancer patients. We note a recent study from Sweden where the resection rates and overall treatment rates in lung cancer are much higher than anywhere in England. The authors concluded that the intensity of active treatment for lung cancer in Sweden was below the desirable level for survival.[24]

If the results of this study, and our interpretations thereof, are accepted by our clinical colleagues, then interventions could be designed to increase the surgical resection rate in lung cancer, such as by striving for universal access to specialist thoracic surgeons in patients who are of borderline fitness or who need more complex surgical procedures. Given the observational nature of the evidence presented and the lack of availability of some key case mix variables such as stage and co-morbidity, we propose that further work needs to be done to assess the relationship between resection rate and overall survival, particularly to try and define if there is an 'optimal' resection rate. Any such study with the intention of increasing the proportion of patients undergoing surgery should be designed carefully so that the effects of the intervention on survival and other end-points can subsequently be evaluated carefully and rigorously. Such activity would need to be supported by accurate and detailed recording of the clinical parameters and an examination of the decision making processes in lung cancer multi-disciplinary teams.

Ethics

Cancer registries in England have approval from the National Information Governance Board to carry out surveillance using the data they collect on all cancer patients under section 251 of the NHS Act 2006. Therefore separate ethical approval was not required for this study.

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Conflict of interest statement

None declared.

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