

# Resection rate of lung cancer in Teesside (UK) and Varese (Italy): a comparison after implementation of the National Cancer Plan

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## ABSTRACT

**Background** In a lung cancer survey in 2000 we showed significantly less favourable stage distribution and lower resection rate in Teesside (UK) than in the comparable industrialised area of Varese (Italy). Lung cancer services in Teesside were subsequently reorganised according to National Cancer Plan recommendations.

**Methods** For all new lung cancer cases diagnosed in Teesside (n=324) and Varese (n=260) during the 12 months October 2010 to September 2011 (hereafter 'the 2010 cohort'), demographic, clinico-pathological and disease management data were prospectively recorded using the same database and protocol as the 2000 survey. Findings were analysed focusing on resection rate.

**Results** In the 2010 cohort compared with 2000, both in Teesside and Varese emergency referral decreased ( $p<0.001$ ), performance status improved ( $p<0.001$ ), but cancer stage shift was not seen; resection rate improved in Teesside, from 7% to 11% ( $p=0.054$ ), and was unchanged in Varese (24%). Moreover, in Teesside compared with Varese the stage distribution remained less favourable, stage I–II non-small cell lung cancer (NSCLC) proportion being respectively 12% and 19% ( $p=0.040$ ), and resection rate in all lung cancers remained lower (11% and 24%;  $p<0.001$ ). On multivariate analysis, resection predictors in Teesside were as follows: stage I–II NSCLC (OR 86.14; 95% CI 31.80 to 233.37), performance status 0–1 (OR 5.02; 95% CI 1.48 to 17.07), belonging to 2010 cohort (OR 2.85; 95% CI 1.06 to 7.64).

**Conclusions** In Teesside the main independent predictor of resection was disease stage; in 2010–2011 compared with 2000, lung cancer service improved but stage shift did not occur, and resection rate increased but remained significantly lower than in Varese.

## INTRODUCTION

Observational evidence supports the concept that surgery is the main intervention that may improve long-term survival of patients with lung cancer (LC),<sup>1–4</sup> and surgical resection rate is commonly used as one measure of a region's effectiveness in treating this disease.<sup>5</sup> In 2013 the IQR of resection rates for all LCs (including histologically confirmed and unconfirmed) was a low 11.5–17.4% in the

## Key messages

### What is the key question?

► A decade after the 2000 National Cancer Plan implementation, were lung cancer stage distribution and resection rate still worse in Teesside (UK) than in the comparable industrialised area of Varese (Italy)?

### What is the bottom line?

► In Teesside, lung cancer service improved in 2010–2011 relative to 2000, but early-stage diagnosis was still infrequent. Cancer stage did not shift and resection rate remained significantly lower than in Varese.

### Why read on?

► Findings suggest that in Teesside further efforts should focus on diagnosing lung cancer at an earlier stage, as this is the main predictor of resection.

UK<sup>6</sup> compared with 20–25% resection rates in other high-income European countries and the US.<sup>7–9</sup> This disparity is related to differences in demography, tumour biology and comorbidities; suboptimal management of the disease in the UK, including delayed diagnosis and variable access to thoracic surgeons, may also play a role.<sup>7–10–12</sup> Previous comparisons of international LC resection rates with those in the UK, based on cancer registries, were limited by lack of information on patient clinico-pathological characteristics and stage-specific treatment; thus the impact of these key factors in determining the generally lower resection rate in the UK remains unclear.<sup>13–14</sup>

Aiming to minimise problems in direct comparison of LC management, in 2000 we carried out a 12-month prospective study of LC presentation and treatment modalities in Teesside (UK) and in the comparable industrialised area of the Province of Varese (Italy), using an identical database and data collection protocol for the two populations. We found that patients with LC in Teesside had more comorbidities, were diagnosed at a later stage, had more aggressive subtypes, less frequently



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underwent active oncological treatment and had a markedly lower resection rate in all LCs, relative to Varese (7% vs 24%).<sup>7</sup> After 2000 the Teesside LC service was enhanced with waiting time guidelines and dedicated thoracic surgeons' attendance at multidisciplinary team (MDT) meetings, according to National Health Service Cancer Plan recommendations.<sup>15</sup> In Varese the LC service organisation has remained essentially unchanged. A decade after the 2000 survey, we repeated the comparison of LC presentation and management in these two geographical areas, and in this paper we focus on the evaluation of changes in resection rate.

## METHODS

### Data collection

The LC cases diagnosed during the 12 months from October 2010 to September 2011 in the referral hospitals of Teesside and Varese (hereafter 'the 2010 cohort') were prospectively collected using an identical data collection protocol as in the year 2000. The characteristics of the referral hospitals in Teesside (University Hospital of North Tees, Stockton-on-Tees, and University Hospital of Hartlepool) and in Varese (University Hospital Azienda Ospedale di Circolo di Varese and Hospital S. Antonio Abate di Gallarate) have not substantially changed since 2000.<sup>7</sup> At both sites, during the study period all new clinical or pathological diagnoses of LC (ICD-10 C33–C34) were included; we excluded cases of mesothelioma, carcinoid, adenocystic carcinoma, and adenosquamous carcinoma of the lung. Patients presenting with suspected LC in Teesside and Varese were investigated using similar protocols, as specified below. During the 2000 and 2010–2011 surveys a voluntary programme of chest radiography screening for LC at the population level was active in the Varese area, covering about 10% of high-risk smokers.<sup>7</sup>

Collected data were analysed and compared with those obtained in the year 2000 survey. Research Ethics Committee approval was obtained in Varese; in Teesside the study was approved by the Trust's Research and Development Department as part of a service improvement programme.

### Diagnosis and management

Conventional diagnostic and staging procedures were performed as indicated by British Thoracic Society (BTS) guidelines,<sup>16</sup> using chest X-rays (CXRs), CT, positron emission tomography (PET), sputum cytology, fiberoptic bronchoscopy, fine needle aspiration cytology, endobronchial ultrasound-transbronchial needle aspiration and video-assisted thoracoscopic surgery. Treatment was carried out according to BTS recommendations,<sup>16</sup> namely, surgical resection for eligible patients with early stage (stages I and II) non-small cell LC (NSCLC) and for a selected group with low-risk NSCLC stage IIIA disease; radical radiotherapy ( $\geq 50$  Gy) for patients with early stage NSCLC not suitable for surgery; chemotherapy and/or radiotherapy for patients with good performance status and inoperable NSCLC (stages III and IV); chemotherapy with/without radiotherapy for patients with small cell LC (SCLC). Palliation in advanced or inoperable cases was effected by chemotherapy, radiotherapy, pain control and nutritional support. In the two UK hospitals chemotherapy was administered, while radiotherapy and surgery were performed after referral to the Middlesbrough subregional centre, where the volume of lung resections was approximately 80 procedures/year. In Varese, chemotherapy was administered at both hospitals, while radiotherapy and surgery for all patients were carried out at the University Hospital Azienda Ospedale di Circolo di Varese (lung resections volume, approximately 70

procedures/year). In Teesside and Varese, management decisions were based on discussions at MDT meetings. Notably, after 2000 in Teesside the lung cancer service organisation was implemented with at least one thoracic surgeon attending MDT meetings and with cancer waiting time guidelines and targets introduced by the Cancer Plan in England; specifically, 31 days from diagnosis to treatment, and 62 days from urgent referral to treatment.<sup>15</sup> In Varese these basic features of LC service organisation, with minor differences of waiting times, were already present in 2000 and remained unchanged in 2010–2011.

### Data recorded

The following data were gathered from LC case records: age at diagnosis; gender; LC risk factors (smoking habit, occupational risk); comorbidities and Adult Comorbidity Evaluation-27 (ACE-27) score;<sup>17</sup> percentage of predicted FEV<sub>1</sub>; WHO Eastern Cooperative Oncology Group performance status; source of patient referral to LC specialist; mode of presentation (symptomatic/asymptomatic); clinical diagnosis or histological subtype; clinical stage according to Mountain;<sup>18</sup> management (radiotherapy, chemotherapy, surgical resection, no active cancer treatment). Causes of non-operability (advanced stage; comorbidity; SCLC histology) were recorded.

### Definitions used in the study

For 'date of diagnosis', 'occupational risk', 'comorbidity', 'source of referral', 'urgent/emergency admission', 'lung cancer specialist', 'active treatment' we used the same definitions as in the year 2000 study.<sup>7</sup> To facilitate comparison of tumour stage distribution between the 2010–2011 and 2000 survey, only the clinical stage assessed according to Mountain<sup>18</sup> was reported. Resection rate, expressed as the proportion of cases for which an operation was performed to eradicate the cancer, was calculated against the three main denominators: all LCs, NSCLCs, stage I–II NSCLCs.

### Analysis of results and statistical methods

Continuous variables were reported as mean with SD, or median with range. Categorical data were presented as numbers and percentages, and were compared by  $\chi^2$  test or Fischer's exact test. Comparison between groups was made using Student's *t* test or the Mann–Whitney *U* test for continuous variables. *p* Values  $<0.05$  were considered statistically significant.

Extracted database variables were tabulated using Microsoft Excel (Microsoft Corp, Redmond, Washington, USA). Factors affecting the probability of use of surgery in LC treatment were examined using logistic regression models. The multivariable model included all factors with a *p* value  $<15\%$  from the univariate model that considered all recorded data for LC cases. We excluded histology from the multivariable model because of collinearity with NSCLC stage. Sensitivity analysis was performed by backwards selection methods, to test potentially significant predictors of resection among those available. Statistical analysis was made with MedCalc Statistical Software V.13.3.3 (MedCalc Software bvba, Ostend, Belgium).

## RESULTS

From 1 October 2010 to 30 September 2011, 324 patients in Teesside and 265 in Varese presented with LC (annual crude incidence respectively of 98 and 71 per 100 000 population). After case record review, five patients in Varese were excluded from analysis due to non-adherence to histological subtype criteria. The final totals were 324 patients with LC in Teesside and

260 in Varese. The data of cases diagnosed in 2010–2011 were compared with the 2000 survey data,<sup>7</sup> focusing on resection rate.

### Demographics and clinical presentation

Table 1 summarises the characteristics of patients with LC. The crude number of newly diagnosed cases increased in the 2010 cohort relative to 2000, by 21% in Teesside and by 7% in Varese. Also the patient mean age at diagnosis significantly increased in Teesside ( $p=0.018$ ) and in Varese ( $p=0.003$ ). The smoking history of patients with LC fell to 40.0 median pack-years in both geographical locations. The prevalence of patients with occupational risk significantly decreased in Teesside ( $p<0.001$ ) and approached that of Varese, where it did not significantly vary. The prevalence of patients with comorbidities and the pulmonary function measured as percent of predicted FEV<sub>1</sub> were unchanged at both sites. Recording of FEV<sub>1</sub> remained poor (65% in Teesside, 54% in Varese). The ACE-27 score distribution was similar in the 2010 cohorts ( $p=0.184$ ) and patient performance status at diagnosis improved in Teesside ( $p<0.001$ ) and in Varese ( $p<0.001$ ), remaining significantly better in Varese. In Teesside the urgent/emergency referrals decreased significantly ( $p<0.001$ ), and general practitioners were still the main source of referral to LC specialists; in Varese, urgent/emergency referral of patients with LC was also less frequent than in the year 2000 ( $p<0.001$ ). In the 2010 cohorts

the vast majority of patients with LC still were diagnosed with symptoms, significantly more frequently so in Teesside than in Varese (93% and 75%;  $p<0.001$ ); analysis of symptomatic patients only still showed that, comparing Teesside to Varese, a greater proportion of patients had performance status 2–4 (46% vs 19%;  $p<0.001$ ) and poorer lung function (predicted FEV<sub>1</sub> %:  $66\pm24$  vs  $80\pm17$ ;  $p<0.001$ ).

### Histology and staging

As summarised in table 2, in the 2010 cohort the rates of histologically confirmed LC in Teesside (72%) and in Varese (83%) were stable compared with a decade earlier. The frequency of histological subtypes varied: adenocarcinoma increased in Teesside ( $p=0.044$ ) and in Varese ( $p<0.001$ ); SCLC decreased in Teesside ( $p=0.021$ ), while in Varese it did not change. The proportion of LCs that were diagnosed as stage I–II NSCLC did not significantly vary over time, thus remaining significantly lower in Teesside than in Varese (12% vs 19%;  $p=0.040$ ). In both locations there was no shift towards a more favourable stage distribution (figures 1 and 2). The frequency of advanced (stage III–IV) NSCLC diagnosis was higher in the later survey than in 2000; this increase was more marked in Teesside.

### Treatment and resection rate

In the 2010 cohort compared with 2000 the proportion of patients receiving active oncological treatment increased

**Table 1** Comparison of demographic and clinical data at presentation in the Teesside and Varese 2000 cohort<sup>7</sup> and 2010 cohort

	Teesside			Varese		
	2000 Cohort	2010 Cohort	p Value	2000 Cohort	2010 Cohort	p Value
Patients with LC, n	268	324		243	260	
Age, mean (SD)	69 (10)	71 (10)	0.018	67 (10)	70 (10)	0.003
Male/female (ratio)	153/115 (1.33)	169/155 (1.09)	0.265	200/43 (4.65)	198/62 (3.19)	0.090
Risk factors						
Smoker (%)	142/257 (55%) <sup>a</sup>	161/319 (50%) <sup>b</sup>		111/243 (46%)	122/258 (47%) <sup>c</sup>	
Former smoker (%)	105/257 (41%) <sup>a</sup>	134/319 (42%) <sup>b</sup>		99/243 (41%)	102/258 (40%) <sup>c</sup>	
Never smoker (%)	10/257 (4%) <sup>a</sup>	24/319 (8%) <sup>b</sup>		33/243 (13%)	34/258 (13%) <sup>c</sup>	
Median pack/years*	45.5 <sup>d</sup>	40.0 <sup>e</sup>	0.001	45.0 <sup>f</sup>	40.0 <sup>g</sup>	<0.001
Occupational risk (%)†	93/185 (50%) <sup>h</sup>	96/284 (34%) <sup>i</sup>	<0.001	69/226 (31%) <sup>j</sup>	69/256 (27%) <sup>k</sup>	0.386
Comorbidity, n patients (%)	193/263 (73%) <sup>l</sup>	238/320 (74%) <sup>m</sup>	0.860	156/243 (64%)	177/260 (68%)	0.358
Adult Comorbidity Evaluation-27 score‡						
0 (none)	–	78 (18%) <sup>m</sup>		–	57 (22%)	
1 (mild)	–	44 (20%) <sup>m</sup>		–	53 (20%)	
2 (moderate)	–	75 (23%) <sup>m</sup>		–	61 (23%)	
3 (severe)	–	123 (38%) <sup>m</sup>		–	89 (34%)	
FEV <sub>1</sub> as % of predicted (SD)	63% (22) <sup>n</sup>	67% (23) <sup>o</sup>	0.204	78% (23) <sup>p</sup>	82% (19) <sup>q</sup>	0.334
Performance status 0–1	38%	57%	<0.001	62%	84%	<0.001
Performance status 2–4	62%	43%		38%	16%	
Source of referral to LC specialist						
General practitioner, urgent/emergency	171/268 (64%)	122/324 (38%)	<0.001	148/243 (61%)	103/260 (40%)	<0.001
General practitioner, 2-week rule/routine	53/268 (20%)	163/324 (50%)	<0.001	35/243 (14%)	44/260 (17%)	0.438
Other consultant	44/268 (16%)	39/324 (12%)	0.126	55/243 (23%)	111/260 (43%)	<0.001
Chest X-ray screening	0/268 (0%)	0/324 (0%)	–	5/243 (2%)	2/260 (1%)	0.218
Mode of presentation						
Asymptomatic diagnosis, by incidental imaging	17/253 (7%) <sup>r</sup>	24/324 (7%)	0.876	47/223 (21%) <sup>s</sup>	64/260 (25%)	0.357
Diagnosis by symptoms	236/253 (93%) <sup>r</sup>	300/324 (93%)		176/223 (79%) <sup>s</sup>	196/260 (75%)	

The referral hospitals in Teesside served a population of about 330 000, in Varese about 375 000.

Number of missing cases: <sup>a</sup> 11; <sup>b</sup> 5; <sup>c</sup> 2; <sup>d</sup> 43; <sup>e</sup> 46; <sup>f</sup> 82; <sup>g</sup> 37; <sup>h</sup> 83; <sup>i</sup> 40; <sup>j</sup> 17; <sup>k</sup> 4; <sup>l</sup> 5; <sup>m</sup> 4; <sup>n</sup> 128; <sup>o</sup> 114; <sup>p</sup> 142; <sup>q</sup> 120; <sup>r</sup> 15; <sup>s</sup> 20.

\*Pack/years in smokers and former smokers.

†Occupations and industries that are known or suspected to be associated with LC.

‡ACE-27 score distribution between Teesside and Varese was not statistically different ( $p=0.184$ ).

LC, lung cancer

**Table 2** Histology and staging of lung cancers diagnosed in the Teesside and Varese 2000 cohort<sup>7</sup> and 2010 cohort

	Teesside			Varese		
	2000 Cohort	2010 Cohort	p Value	2000 Cohort	2010 Cohort	p Value
Total of lung cancer cases, n	268	324		243	260	
Histologically unconfirmed cases*, n (%)	75 (28%)	91 (28%)	0.948	44 (18%)	44 (17%)	0.727
Histologically confirmed cases, n (%)	193 (72%)	233 (72%)		199 (82%)	216 (83%)	
Adenocarcinoma	42 (22%)†	72 (31%)†	0.044	60 (30%)†	109 (50%)†	<0.001
Squamous cell carcinoma	68 (35%)†	67 (29%)†	0.185	84 (42%)†	72 (33%)†	0.062
Large cell carcinoma	21 (11%)†	20 (9%)†	0.525	4 (2%)†	5 (2%)†	0.832
Unspecif. non-small cell carcinoma	16 (8%)†	40 (17%)†	0.011	21 (11%)†	3 (1%)†	<0.001
SCLC	46 (24%)†	34 (15%)†	0.021	30 (15%)†	27 (13%)†	0.446
Total of NSCLC	147 (55%)	199 (61%)		169 (70%)	189 (73%)	
NSCLC by stage‡						
Stage I–II	37 (14%)	40 (12%)	0.687	53 (22%)	49 (19%)	0.421
Stage III–IV	104 (39%)	159 (49%)	0.015	116 (48%)	138 (53%)	0.231
NSCLC not staged	6 (2%)	0 (0%)	0.022	0 (0%)	0 (0%)	–

\*Histologically unconfirmed cases are those with lung cancer clinical diagnosis only.

†% of all staged, histologically confirmed cases only.

‡Not available: two patients in Varese 2010 cohort.

NSCLC, non-small cell lung cancers (including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and unspecified NSCLC); SCLC, small cell lung cancer.

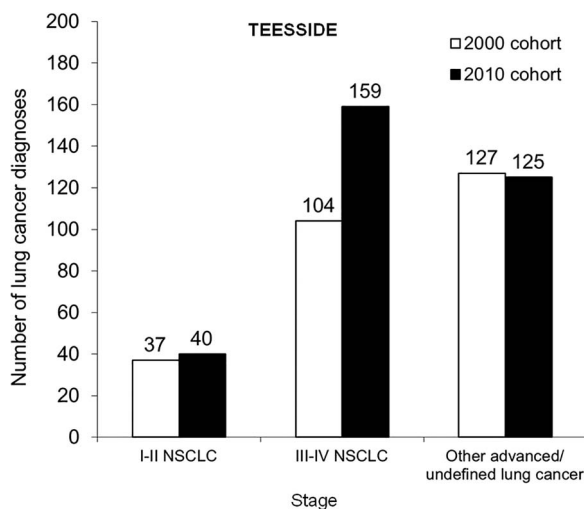
significantly in Teesside from 50% to 66%; it remained stable at 75% in Varese (table 3). The overall use of radiotherapy increased in Teesside, while it decreased in Varese; the proportion of cases treated with chemotherapy as the sole therapy, or in combination with other treatments, rose at both sites. Details of surgical resection rates in Teesside and in Varese are shown in table 3. The resection rates increased in Teesside, reaching 11% in all LCs ( $p=0.054$ ), 18% in NSCLC ( $p=0.096$ ), 67% in stage I–II NSCLC ( $p=0.056$ ). In Varese the corresponding resection rates were stable over the considered decade (24% in all LCs, 33% in NSCLC, 88% in stage I–II NSCLC), and in the 2010 cohort they remained significantly higher than in Teesside. The 30-day postoperative mortality in the 2010 cohort was nil at both sites. Most resections at both locations were lobectomies. The pneumonectomy rate fell in Teesside from 41% of all resections in 2000 to 17% a decade later. Mean age of resected patients increased in both populations: from  $64\pm 9$  to  $68\pm 7$  years in Teesside ( $p=0.080$ ) and from  $65\pm 9$  to  $69\pm 8$  years

in Varese ( $p=0.022$ ). Notably, if the patients with incidental findings were excluded from the analysis, resection rates in all LCs were not significantly different in the two cities' 2010 cohorts (10% and 14%,  $p=0.205$ ) (table 4).

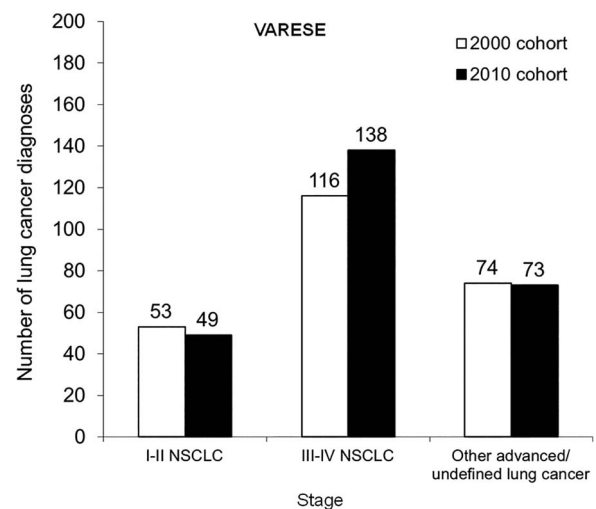
In both locations, over the decade no significant changes were seen in the distribution of causes of non-operability; however a trend of more frequent inoperable advanced stage NSCLC was recorded in Teesside (table 5).

### Predictors of resection

To investigate the predictors of surgical treatment in Teesside, logistic regression analysis was performed considering age, gender, symptoms, referral, performance status, cancer stage and period of LC diagnosis. At univariate analysis the unadjusted OR of undergoing surgery significantly increased for NSCLC stage I–II ( $p<0.001$ ), performance status 0–1 ( $p<0.001$ ), non-emergency referral ( $p<0.001$ ), asymptomatic at diagnosis ( $p<0.001$ ), belonging to 2010 cohort ( $p=0.055$ )



**Figure 1** Stage and histology distribution in patients with lung cancer at diagnosis in Teesside in the 2000 cohort<sup>7</sup> and in the 2010 cohort. NSCLC, non-small cell lung cancer.



**Figure 2** Stage and histology distribution in patients with lung cancer at diagnosis in Varese in the 2000 cohort<sup>7</sup> and in the 2010 cohort. NSCLC, non-small cell lung cancer.



**Table 3** Treatment modalities of lung cancers diagnosed in the Teesside and Varese 2000 cohort<sup>7</sup> and 2010 cohort

	Teesside			Varese		
	2000 Cohort	2010 Cohort	p Value	2000 Cohort	2010 Cohort	p Value
Total lung cancer cases, n	261*	324		243	260	
Treatment						
No active cancer treatment	130 (50%)	110 (34%)	<0.001	60 (25%)	64 (25%)	1
Radical radiotherapy (≥50 Gy)	1 (0.4%)	24 (7%)	<0.001	2 (1%)	1 (0.5%)	0.523
Palliative radiotherapy	66 (25%)	48 (15%)	0.001	54 (22%)	27 (10%)	<0.001
Chemotherapy	35 (13%)	51 (16%)	0.429	45 (19%)	81 (31%)	0.001
Radiotherapy+chemotherapy	12 (5%)	54 (17%)	<0.001	23 (9%)	23 (9%)	0.810
Other active treatment	0 (0%)	1 (0%)	0.369	0 (0%)	1 (0.5%)	0.333
Surgical resection†						
In all lung cancers	17/261 (7%)	36/324 (11%)‡	0.054	59/243 (24%)	63/260 (24%)‡	1
Lobectomy	8/17 (47%)	27/36 (75%)		42/59 (71%)	49/63 (78%)	
Pneumonectomy	7/17 (41%)	6/36 (17%)		9/59 (15%)	8/63 (13%)	
Wedge resection	2/17 (12%)	3/36 (8%)		8/59 (14%)	6/63 (9%)	
In NSCLC	17/147 (12%)	36§/199 (18%)¶	0.096	59/169 (35%)	63**/189 (33%)¶	0.753
In stage I–II NSCLC	17/37 (46%)	27/40 (67%)††	0.056	44/53 (83%)	43/49 (88%)††	0.500
In stage IIIA NSCLC	0/22 (0%)	5/47 (11%)‡‡	0.276§§	8/20 (40%)	13/39 (33%)‡‡	0.613
In symptomatic lung cancers	13/253 (5%)	29/300 (10%)¶¶	0.045	31/176 (18%)	27/196 (14%)¶¶	0.308

Data are presented as number of patients with percentage of total valid cases.

\*Treatment data not available in seven untraceable patients.

†All surgeries performed with curative intent, including cases undergoing induction chemotherapy or adjuvant chemo/radiotherapy.

‡Resection rate in all lung cancers in Varese versus Teesside:  $p < 0.001$ .

§Including 27 NSCLC stage I–II; 5 NSCLC stage IIIA; 2 NSCLC stage IIIB; 2 NSCLC stage IV.

¶Resection rate in all NSCLC cases in Varese versus Teesside:  $p < 0.001$ .

\*\*Including 43 NSCLC stage I–II; 13 NSCLC stage IIIA; 4 NSCLC stage IIIB; 1 NSCLC stage IV. Stage not available for two patients.

††Resection rate in NSCLC stage I–II in Varese versus Teesside:  $p = 0.020$ .

‡‡Resection rate in NSCLC stage IIIA in Teesside versus Varese:  $p = 0.010$ .

§§Yates'  $p$  value.

¶¶Resection rate in symptomatic lung cancers in Teesside versus Varese:  $p = 0.205$ .

NSCLC, non-small cell lung cancer.

(table 6). As shown in table 6, independent predictors of LC resection were stage I–II NSCLC (OR 86.14), performance status 0–1 (OR 5.02), age +1 year (OR 0.95), belonging to 2010 cohort (OR 2.85).

The analysis of predictors of resection in Varese showed that independent predictors of resection were (in order of importance): stage, age, performance status, asymptomatic diagnosis (table 7).

## DISCUSSION

By repeating in 2010–2011 the comparison of LC management in Teesside and in Varese, we aimed to analyse the magnitude and possible causes of persisting disparity in LC resection rate between these two locations. Acknowledging concerns about data completeness and comparability, efforts were made to capture all new LC cases diagnosed at both sites during the study period, under the principal investigators' supervision (AI and RNH), using the same database and protocol as in the 2000 survey.<sup>7</sup> We found that LC crude annual incidence in the 2010 cohort relative to 2000 rose by 21% in Teesside and by 7% in Varese. Such an increase, almost exclusively due to more diagnoses of advanced stage NSCLC, has several possible explanations. These include higher quality of preoperative staging processes and stage migration, population growth (+3% in Teesside;<sup>19</sup> +7% in Varese<sup>20</sup>) and ageing over the considered decade. The more robust LC incidence rise in the UK site likely reflects improved local LC service organisation and markedly increased case ascertainment rate in the UK over the study period, as documented by the National Lung Cancer Audit.<sup>21</sup>

Our study shows that important demographic differences persisted between patients diagnosed with LC in the two locations. In

the 2010 cohort the male/female ratio in Varese was three times that in Teesside, however the ratio decreased in both cities over a decade; this decrease was more pronounced in Varese, reflecting the trend of more frequent LC diagnosis in female patients in recent years in Italy.<sup>22</sup> Moreover, after a decade, significant differences between cities persisted in lung function, performance status, source of referral, and rates of incidental diagnosis, histological confirmation, adenocarcinoma, total NSCLC, stage I–II NSCLC, active treatment, and surgical resection (table 4).

In Teesside, the earlier referral of symptomatic patients and application of waiting time guidelines recommended by the National Cancer Plan did not lead to a more favourable LC stage distribution; the proportion of cancers diagnosed as stage I–II NSCLC did not significantly change in the 2010 cohort relative to 2000 and remained significantly lower in Teesside than in Varese (12% vs 19%). Moreover, in Teesside after a decade the rate of histologically unconfirmed LC remained stable above European standards, and significantly higher than in Varese. Our findings mirror the outcome of LC awareness and early referral campaigns conducted in 2008 and 2011 in other UK areas, which resulted in higher incidence of advanced LC diagnoses, without stage shift.<sup>23–24</sup> A recent study, however, showed a 3.1% increase in proportion of NSCLC diagnosed in stage I and 2.3% increase in resections for patients seen during a national campaign in the UK to raise public awareness of persistent cough as a LC symptom.<sup>25</sup>

It should be underscored that the proportion of asymptomatic LC diagnoses following incidental imaging was nearly three times greater in Varese compared with Teesside, suggesting a more conservative use of radiologic imaging exams in general in the UK setting. Overall, the proportion of screening detected

**Table 4** Comparison of demographics, pathology and treatment of lung cancer in Teesside and Varese in the 2010 cohort

	Teesside 2010 Cohort	Varese 2010 Cohort	p Value
Patients with LC, n	324	260	
Age, mean (SD)	71 (10)	70 (10)	0.175
Male/female (ratio)	169/155 (1.09)	198/62 (3.19)	<0.001
Risk factors			
Median pack/years	40 <sup>a</sup>	40 <sup>b</sup>	0.175
Occupational risk (%) <sup>*</sup>	96/284 (34%)	69/256 (27%)	0.084
Comorbidity, n patients (%)	238/320 (74%)	177/260 (68%)	0.095
FEV <sub>1</sub> as % of predicted (SD)	67% (23) <sup>c</sup>	82% (19) <sup>d</sup>	<0.001
Performance status 0–1	57%	84%	<0.001
Performance status 2–4	43%	16%	
Source of referral to LC specialist			
General practitioner, urgent/emergency	122/324 (38%)	103/260 (40%)	0.629
General practitioner, 2-week rule/routine	163/324 (50%)	44/260 (17%)	<0.001
Other consultant	39/324 (12%)	111/260 (43%)	<0.001
Chest X-ray screening	0/324 (0%)	2/260 (1%)	0.385†
Mode of presentation			
Asymptomatic diagnosis, by incidental imaging	24/324 (7%)	64/260 (25%)	<0.001
Diagnosis by symptoms	300/324 (93%)	196/260 (75%)	
Histologically confirmed cases, n (%)	233 (72%)	216 (83%)	0.001
Adenocarcinoma, n (%)	72 (31%)‡	109 (50%)‡	<0.001
Squamous cell carcinoma, n (%)	67 (29%)‡	72 (33%)‡	0.294
Large cell carcinoma, n (%)	20 (9%)‡	5 (2%)‡	0.004
Unspecif. non-small cell carcinoma, n (%)	40 (17%)‡	3 (1%)‡	<0.001
SCLC, n (%)	34 (15%)‡	27 (13%)‡	0.518
Total of NSCLC	199 (61%)	189 (73%)	0.004
NSCLC by stage**§			
Stage I–II	40 (12%)	49 (19%)	0.030
Stage III–IV	159 (49%)	138 (53%)	0.336
Treatment			
No active cancer treatment	110 (34%)	64 (25%)	0.014
Radical radiotherapy (≥50 Gy)	24 (7%)	1 (0.5%)	<0.001
Palliative radiotherapy	48 (15%)	27 (10%)	0.112
Chemotherapy	51 (16%)	81 (31%)	<0.001
Radiotherapy+chemotherapy	54 (17%)	23 (9%)	0.005
Other active treatment	1 (0%)	1 (0.5%)	0.560†
Surgical resection¶			
All lung cancers	36/324 (11%)	63/260 (24%)	<0.001
NSCLC	36/199 (18%)	63/189 (33%)	<0.001
Stage I–II NSCLC	27/40 (67%)	43/49 (88%)	0.020
Stage IIIA NSCLC	5/47 (11%)	13/39 (33%)	0.010
Symptomatic LCs	29/300 (10%)	27/196 (14%)	0.205

Number of missing cases: <sup>a</sup> 46; <sup>b</sup> 37; <sup>c</sup> 114; <sup>d</sup> 120.

<sup>\*</sup>Occupations and industries that are known or suspected to be associated with LC.

†Yates' p value.

‡% of all staged, histologically confirmed cases only.

§Not available: two patients in Varese.

¶All surgeries performed with curative intent, including cases undergoing induction chemotherapy or adjuvant chemo/radiotherapy.

LC, lung cancer; NSCLC, non-small cell lung cancers (including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and unspecified NSCLC); SCLC, small cell lung cancer.

LCs in the Varese 2010 cohort was minimal, likely due to scarce adherence to the screening programme.<sup>26</sup> Therefore, we hypothesise that more frequent early-stage disease diagnosis by incidental imaging observed in Varese may reflect a greater LC awareness at population level and among general practitioners,<sup>27</sup> and a more liberal use of CXR and chest CT for follow up in a variety of diseases. If LC screening by low-dose chest CT were implemented in the UK, as proposed by an expert panel<sup>11</sup> in the wake of the National Lung Screening Trial results showing 20% LC mortality reduction,<sup>28</sup> the number of asymptomatic LC diagnoses could rise. The results of the NELSON study, the Dutch

large trial of CT screening for LC, will be announced by the end of 2015<sup>29</sup> and will likely affect the decision by health policy makers in European countries to promote LC screening at the population level.

Focusing on LC resection rate in our study, we found that the use of surgery in Teesside grew to 11% in the 2010 cohort (with all registered LCs used as denominator), reflecting the UK trend in recent years.<sup>10–30</sup> The resection rate in NSCLC and in stage I–II NSCLC, that have been proposed as benchmark audit indicators for LC services,<sup>21–31</sup> also rose in the Teesside 2010 cohort, but remained significantly lower than in Varese. We

**Table 5** Causes of non-operability in unresected cases in the Teesside and Varese 2000 cohort<sup>7</sup> and 2010 cohort

	Teesside			Varese		
	2000 Cohort	2010 Cohort	p Value	2000 Cohort	2010 Cohort	p Value
Total lung cancer cases, n	261*	324		243	260	
Advanced NSCLC: stage III–IV, n (%)	103 (39%)	150 (46%)†	0.097	103 (42%)‡	120 (46%)§	0.395
Comorbidity in						
NSCLC stage I–II, n (%)	17 (7%)	13 (4%)	0.173	9 (4%)	6 (2%)	0.358
NSCLC not staged, n (%)	4 (2%)	0 (0%)	0.083¶	0 (0%)	0 (0%)	–
Lung cancer not histologically confirmed, n (%)	74 (28%)	91 (28%)	0.944	44 (18%)	44 (17%)	0.727
Histology: SCLC, n (%)	46 (18%)	34 (10%)	0.013	28 (12%)*	27 (10%)	0.683
Total unresected cases, n (%)	244 (93%)	288 (89%)	0.054	184 (76%)	197 (76%)	1

Data are presented as number of patients with percentage of total valid cases.

\*Total valid cases in Teesside=261/268; seven patients moved to other districts and their treatment could not be traced.

†Nine of the 159 patients with NSCLC stage III–IV diagnosed in the Teesside 2010 cohort had resection.

‡Thirteen of the 116 patients with NSCLC stage III–IV diagnosed in Varese in 2000 had resection.

§Eighteen of the 138 patients with NSCLC stage III–IV diagnosed in the Varese 2010 cohort had resection.

¶Yates' p value.

\*\*Two of the 30 patients with SCLC diagnosed in Varese had resection.

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

hypothesise that this difference in resection rate may be contributed to by higher incidence of asymptomatic LC findings in Varese; notably, if patients with incidental diagnosis were excluded, resection rates in all LCs are not significantly different in the two cities' 2010 cohorts (10% and 14%,  $p=0.205$ ).

The pneumonectomy rate fell in Teesside over a 10-year period. We think that better preoperative staging, closer adherence to surgical guidelines and the presence of a dedicated thoracic surgeon willing to take on difficult lobectomies played a role in reducing the pneumonectomy rate.

At both sites the causes of non-operability did not substantially change. However, among all inoperable cases the

proportion of advanced stage NSCLC increased in 2010–2011, as the frequency of these advanced cancers grew. The increased use of surgery in Teesside is likely attributable in part to overall improvement of LC service, documented by earlier case referral, better patient performance status at diagnosis and >97% of new LC cases discussed at MDT meetings in 2010 and 2011.<sup>21 32</sup> Routine participation of a specialist thoracic surgeon in lung MDT meetings in Teesside was likely a major contribution to LC resection rate rise, as suggested by others.<sup>12 33</sup> Whether the improved LC resection rate in Teesside will translate into increased long-term survival needs to be evaluated by prolonged follow-up. Nevertheless, in the 2010 cohort the LC resection rate using all registered LCs as the denominator

**Table 6** Univariate and multivariate analysis by logistic regression of predictors of radical resection in 585 patients with lung cancer diagnosed in Teesside (UK) in the 2000 cohort<sup>7</sup> and 2010 cohort

Univariate			
Risk factor	Unadjusted OR	95% CI	p Value
Age (+1 year)	0.97	0.95 to 0.99	0.015
Gender (male vs female)	0.75	0.42 to 1.34	0.337
Symptoms at diagnosis (yes vs no)	4.29	2.01 to 9.16	<0.001
Source of referral (emergency vs other)	2.95	1.56 to 5.55	<0.001
Performance status (2–4 vs 0–1)	15.04	5.35 to 42.31	<0.001
Stage (others vs NSCLC stage I–II)	78.54	35.16 to 175.42	<0.001
2000 cohort vs 2010 cohort	1.80	0.99 to 3.29	0.055
Multivariate			
Risk factor	Adjusted OR	95% CI	p Value
Age (+1 year)	0.95	0.91 to 0.99	0.012
Symptoms at diagnosis (yes vs no)	0.81	0.26 to 2.53	0.714
Source of referral (emergency vs other)	2.09	0.80 to 5.42	0.131
Performance status (2–4 vs 0–1)	5.02	1.48 to 17.07	0.010
Stage (others vs NSCLC stage I–II)	86.14	31.80 to 233.37	<0.001
2000 cohort vs 2010 cohort	2.85	1.06 to 7.64	0.037

Histology was removed because of collinearity with NSCLC stage.  
NSCLC, non-small cell lung cancer.

**Table 7** Univariate and multivariate analysis by logistic regression of predictors of radical resection in 503 patients with lung cancer diagnosed in Varese (Italy) in the 2000 cohort<sup>7</sup> and 2010 cohort

Univariate			
Risk factor	Unadjusted OR	95% CI	p Value
Age (+1 year)	0.98	0.96 to 1.00	0.043
Gender (male vs female)	1.33	0.82 to 2.16	0.247
Symptoms at diagnosis (yes vs no)	7.37	4.61 to 11.79	<0.001
Source of referral (emergency vs other)	2.43	1.58 to 3.72	<0.001
Performance status (2–4 vs 0–1)	3.54	1.90 to 6.59	<0.001
Stage (others vs NSCLC stage I–II)	64.33	33.46 to 123.66	<0.001
2000 cohort vs 2010 cohort	1.00	0.66 to 1.50	0.990
Multivariate			
Risk factor	Adjusted OR	95% CI	p Value
Age (+1 year)	0.95	0.91 to 0.98	0.004
Symptoms at diagnosis (yes vs no)	2.54	1.17 to 5.53	0.018
Source of referral (emergency vs other)	1.66	0.82 to 3.37	0.159
Performance status (2–4 vs 0–1)	3.37	1.31 to 8.64	0.012
Stage (others vs NSCLC stage I–II)	62.40	27.78 to 140.15	<0.001

Histology was removed because of collinearity with NSCLC stage.  
NSCLC, non-small cell lung cancer.

remained significantly lower in Teesside (11%) than in Varese (24%). Of note, comparison of four cancer registries in northern Italy in 2003–2005 showed that in the two Italian areas where >80% of LCs were histologically verified and a thoracic surgery unit was present, the resection rate in all LCs was 23.9% and 25.3% respectively, similar to that in Varese; it was 9.2% in the area lacking a thoracic surgery facility.<sup>3</sup>

The strengths of this study are the prospective design and use of the same database and protocol for data collection in 2000 and a decade later, both in Teesside and in Varese. The limitations are the lack of information on patient factors influencing the willingness to undergo surgery, and on surgeon factors such as degree of specialisation and propensity to take on high-risk surgical cases.

Multivariate analysis showed that in Teesside the most powerful predictor of surgical treatment, among the clinico-pathological factors considered, was stage I–II NSCLC (OR 86.14). Accordingly, in the 2010 cohort the low proportion of stage I–II NSCLC at diagnosis in Teesside was probably the dominant cause of the persistently low resection rate compared with Varese. However, the lower resection rates in Teesside remained heavily influenced by poorer performance status (OR 5.02). The increase in surgery and other anticancer treatments in Teesside after a decade reflect better performance status and the service change, with increased early referrals and fewer emergency presentations.

In conclusion, the main result of this study is that in Teesside the LC service improved in the 2010 cohort relative to 2000, but disease stage, the main predictor of resection, did not shift and the use of surgery remained significantly lower than in Varese.

Based on our findings it is unlikely that in Teesside the resection rate in LC will reach the 20% rate observed in other high-income countries unless LC is diagnosed at an earlier stage. Patients with LC need to be diagnosed before they become symptomatic.

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## REFERENCES

- Wright G, Manser RL, Byrnes G, *et al.* Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. *Thorax* 2006;61:597–603.
- Riaz SP, Lichtenborg M, Jack RH, *et al.* Variation in surgical resection for lung cancer in relation to survival: population-based study in England 2004–2006. *Eur J Cancer* 2012;48:54–60.
- Mangone L, Minicozzi P, Vicentini M, *et al.* Key factors influencing lung cancer survival in northern Italy. *Cancer Epidemiol* 2013;37:226–32.
- Treasure T, Russell C, Morton D, *et al.* Surgical resection of lung cancer England: more operations but no trials to test their effectiveness. *Thorax* 2012;67:759–61.
- Beattie G, Bannon F, McGuigan J. Lung cancer resection rates have increased significantly in females during a 15-year period. *Eur J Cardiothorac Surg* 2010;38:484–90.
- National Lung Cancer Audit Report 2014. <http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2014-15/HSCICNLCA-2014finalinteractivereport.pdf> (accessed 16 Apr 2015).
- Imperatori A, Harrison RN, Leitch DN, *et al.* Lung cancer in Teesside (UK) and Varese (Italy): a comparison of management and survival. *Thorax* 2006;61:232–9.
- Damhuis RA, Schütte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. *Eur Respir J* 1996;9:7–10.
- Dransfield MT, Lock BJ, Garver RI. Improving the lung cancer resection rate in the US Department of Veterans Affairs Health System. *Clin Lung Cancer* 2006;7:268–72.
- Lim E, Popat S. What exactly are we doing to improve low lung cancer survival in the United Kingdom? *Thorax* 2013;68:504–5.
- Sethi T, Lim E, Peake M, *et al.* Improving care for patients with lung cancer in the UK. *Thorax* 2013;68:1181–5.
- Lau KKW, Rathinam S, Waller DA, *et al.* The effects of increased provision of thoracic surgical specialists on the variation in lung cancer resection rate in England. *J Thorac Oncol* 2013;8:68–72.
- Walters S, Maringe C, Coleman MP, *et al.* Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax* 2013;68:551–64.
- Strand TE. More emphasis on resection rates! *J Thorac Oncol* 2012;7:1067–8.
- NHS Executive: The National Cancer Plan. *A plan for investment, a plan for reform.* London: Department of Health, 2000.
- Lim E, Baldwin D, Beckles M, *et al.* Guidelines on the radical management of patients with lung cancer. *Thorax* 2010;65(Suppl 3):iii1–27.
- Piccirillo JF, Tierney RM, Costas I, *et al.* Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004;291:2441–7.
- Mountain CF. Revision in the International System for Staging Lung Cancer. *Chest* 1997;111:17010–17.
- Office for National Statistics (ONS). Census result shows increase in population of the North East. <http://www.ons.gov.uk/ons/rel/mro/news-release/census-result-shows-increase-in-population-of-the-north-east/censusnortheastn0712.html> (accessed 16 Apr 2015).
- 2011 Census in the Province of Varese (Italy). [http://www.istat.it/it/lombardia/dati?q=gettableterr&dataset=DCIS\\_POPRES1&dim=21,1,0,182,8,0&lang=2&tr=0&te=1](http://www.istat.it/it/lombardia/dati?q=gettableterr&dataset=DCIS_POPRES1&dim=21,1,0,182,8,0&lang=2&tr=0&te=1) (accessed 16 Apr 2015).
- National Lung Cancer Audit Report 2012. <http://www.hqip.org.uk/assets/NCAPOP-Library/NCAPOP-2012-13/Lung-Cancer-National-Audit-Report-pub-2012.pdf> (accessed 16 Apr 2015).
- Ministry of Health Report 2014. I numeri del cancro in Italia. [http://www.registri-tumori.it/PDF/AIOM2014/I\\_numeri\\_del\\_cancro\\_2014.pdf](http://www.registri-tumori.it/PDF/AIOM2014/I_numeri_del_cancro_2014.pdf) (accessed 2 Oct 2015).
- Cheyne L, Foster C, Lovatt V, *et al.* Improved lung cancer survival and reduced emergency diagnoses resulting from an early diagnosis campaign in Leeds 2011. *Thorax* 2012;67(Suppl 2):A44–5.
- Athey VL, Suckling RJ, Tod AM, *et al.* Early diagnosis of lung cancer: evaluation of a community-based social marketing intervention. *Thorax* 2012;67:412–17.
- Ironmonger L, Ohuma E, Ormiston-Smith N, *et al.* An evaluation of the impact of large-scale interventions to raise public awareness of a lung cancer symptom. *Br J Cancer* 2015;112:207–16.
- Dominioni L, Rotolo N, Poli A, *et al.* Self-selection effects in smokers attending lung cancer screening: a 9.5-year population-based cohort study in Varese, Italy. *J Thorac Oncol* 2010;5:428–35.
- Dominioni L, Poli A, Mantovani W, *et al.* Assessment of lung cancer mortality reduction after chest X-ray screening in smokers: a population-based cohort study in Varese, Italy. *Lung Cancer* 2013;80:50–4.
- Aberle DR, Adams AM, Berg CD, *et al.* National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
- Kauczor HU, Bonomo L, Gaga M, *et al.* European Society of Radiology (ESR) and the European Respiratory Society (ERS). ESR/ERS white paper on lung cancer screening. *Eur Radiol* 2015;25:2519–31.
- Riaz SP, Linklater KM, Page R, *et al.* Recent trends in resection rates among non-small cell lung cancer patients in England. *Thorax* 2012;67:811–14.
- Laroche CM, Wells F, Coulden R, *et al.* Improving surgical resection rate in lung cancer. *Thorax* 1998;53:445–9.
- National Lung Cancer Audit Report 2011. <http://hqip.org.uk/assets/NCAPOP-Library/Lung-Cancer-NHS-IC-AUDIT-2011.pdf> (accessed 16 Apr 2015).
- Rich AL, Tata LJ, Free CM, *et al.* Inequalities in outcomes for non-small cell lung cancer: the influence of clinical characteristics and features of the local lung cancer service. *Thorax* 2011;66:1078–84.