Improving outcomes in non-small cell lung cancer; population analysis of radical radiotherapy

M Brada[1,3], C Ball[2], S Mitchell[2], H Forbes[1,2] & S Ashley[1]

[1]Department of Radiation Oncology, Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, Wirral, CH63 4JY

[2]National Clinical Analysis and Specialised Applications Team (NATCANSAT), Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, Wirral, CH63 4JY

[3]Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Sherrington Building, Ashton Street, Liverpool L69 3GE

Abstract

Aim

Regional utilisation of radical radiotherapy (RT) in non-small cell lung cancer (NSCLC) was used to define optimal utilisation to improve outcome and as a surrogate for evidence of RT efficacy.

Patients & Methods

65,412 NSCLC cases diagnosed in England 2012-13 were linked to comprehensive national radiotherapy dataset, hospital admissions and the Office of National Statistics. Geographical variation in utilisation was determined using a multivariate binary logistic regression analysis after adjusting for age, stage, deprivation, comorbidity and other radical treatment and the effect of radical RT utilisation on survival was investigated. Survival was adjusted for dependent and independent variables and the effect of differing levels of utilisation was assessed by the log likelihood test.

Results

17.6% cases potentially eligible for radical RT (stages 0-III) received radiotherapy with radical intent. Utilisation of radical RT had an impact on survival ($p<0.00001$). Adjusting for age, stage, deprivation index and comorbidity, counties with lowest utilisation (≤15%) had the worst survival (HR=1.13). The highest utilisation quintile counties (≥25%) had worse survival compared to counties with lower utilisation (≈20%)($p<0.0001$). Analysis of stages II&III showed the same pattern; increase in utilisation from 20% to ≥25% resulting in a 3% drop in 2-year population survival ($p=0.001$).

Conclusion

The utilisation of radical RT has a significant impact on NSCLC population survival. Improvement in survival of NSCLC population can be achieved by offering radical RT to a larger proportion of patients while avoiding excessive use. Geographical variation in RT utilisation provides indirect evidence of survival benefit of radical radiotherapy.

Introduction

Radical external beam radiotherapy (RT) is the mainstay of treatment in patients with locally advanced and localised non-small cell lung cancer (NSCLC) not suitable for surgery. While accepted as standard treatment, the magnitude of survival benefit of radical RT is not known as it has not been compared in randomised trials to a policy of no RT (1). It is therefore difficult to promote the use of radical RT as a means of improving survival in NSCLC patient population.

Nevertheless, radical RT has for many decades been accepted as an effective treatment and trials testing to what extent it would prolong survival would be difficult if not impossible to mount and it is unlikely such a randomised study of radical RT would be appropriate. Accepting that radiotherapy is effective in prolonging survival, regional variation in utilisation of radical RT may be associated with different outcomes. It has been noted that regional variation in the use of lung cancer surgery correlates with regional differences in lung cancer survival (2, 3), If an increase in RT utilisation was linked to improved survival this could be considered as a quasi-experiment demonstrating the efficacy of radiotherapy.

If increased radical RT utilisation was indeed associated with improved outcome it would be appropriate to understand its regional and national determinants to develop strategies to encourage optimal RT utilisation to improve survival in the lung cancer population. This is of particular relevance as lung cancer remains a malignancy with the highest mortality.

Public Health England (PHE) and previously the National Clinical Analysis and Specialised Applications Team (NATCANSAT) collected comprehensive radiotherapy data (radiotherapy dataset – RTDS) from 2009 which gives a unique picture of radiotherapy utilisation throughout the country. Linking RTDS with other national data sources provides an opportunity to study the use of radiotherapy for specific disease indications and their impact on population survival.

We report the analysis of the NSCLC national cohort linked to RTDS, Hospital Episode Statistics (HES) and survival data obtained from the Office of National

Statistics (ONS). Identifying potential regional variation in the use of radical radiotherapy resulting in differing outcomes provides the opportunity to improve the survival results in patients with NSCLC. In addition the geographical variation in radical RT utilisation can be considered as a surrogate to a trial of radical RT and its effect on survival.

Methods

Lung cancer cohort & survival

A list of all non-small cell lung cancers (NSCLC) registered in England in 2012 and 2013 was obtained from Public Health England. The selection criteria used were ICD10 codes: C33 - malignant neoplasm of the trachea or C34 - malignant neoplasm of bronchus and lung and morphology code M8046/3– non-small cell lung cancer; 65687 cases were identified.

Data items obtained from the registry data base included NHS number, date of birth, diagnosis codes (ICD-10 topography and morphology codes), tumour laterality, stage of disease and postcode of residence – used to compute strategic cancer network (SCN), commissioning region, geographical area of residence (LSOA codes) and deprivation index (4).

The NHS number was used to link the cancer records with survival data from Office of National Statistics (ONS). Two hundred and sixty seven cases could not be linked as no NHS number was recorded; these were excluded from the analysis. The remaining cases (65420) were followed via ONS records until 31st December 2015. Dates of death were obtained but not cause of death. As statutory death registration is required within 5 days (coroners cases may take longer) the survival data is as near to complete as possible. In the absence of a death registration, the assumption is that the lung cancer patient was alive on 31/12/2015. While deaths occurring abroad would not be known to the NHS and therefore missed, this is likely to represent a very small number of cases. After detailed review a further 8 cases were excluded as the recorded date of death was inconsistent with the date of diagnosis.

A total of 65412 cases diagnosed in England in 2012 and 2013 were subject to analysis.

Geographical location

The LSOA (Lower Layer Super Output Area) codes derived from the postcode of residence were used to allocate cases firstly to one of 348 administrative areas and then to ceremonial counties. To achieve geographical areas of broadly similar population size, London was split into 'Inner London' and 'Outer London' [rather than City of London & Greater London]. Due to small numbers, Rutland was combined with Leicestershire. This gave a total of 48 geographical areas ('counties').

Radiotherapy

The NHS number was used for linkage with the National Radiotherapy Dataset (RTDS), a centralised radiotherapy database to which all facilities providing radiotherapy services in England were required to return all details of prescriptions and treatment. Radiotherapy delivered in a private facility and funded privately is not recorded. All records of radiotherapy prescriptions to the primary (P), the primary & regional nodes (PR), regional nodes (R) or to non-anatomically specified primary site (A) were downloaded from the database and were used to create the treatment summary record (TSR). Data items of the TSR are total dose received (Gy), number of fractions, radiotherapy diagnosis (ICD-10 code) and treatment intent (radical/palliative).

Surgery

The NHS number was used for linkage with the Hospital Episodes Statistics (HES) database. Any lung excision procedures (lobectomy or pneumonectomy) that occurred within the time window of 6 months before to 18 months post diagnosis were recorded.

Comorbidity

Charlson comorbidity score (5) was calculated from diagnosis codes recorded in the HES database (6, 7) identifying the relevant diagnoses associated with admitted patient care episodes in the period from 30 to 3 months prior to diagnosis. The HES data does not include diagnoses of HIV and these were not included in the score. Lung cancer or metastatic cancer codes in this period were also excluded from the co-morbidity score.

Data validation

For the purpose of radical RT utilisation analysis only cases where radical radiotherapy might have been an appropriate treatment option were included. Radical RT is not generally an option for stage IV patients and 29478 cases with stage IV disease were excluded. 10242 cases where the stage was unknown were also excluded as “unknown” stage patients had a similarly poor survival as stage IV cases and the pattern of ‘radical’ RT was similar to the stage IV cases (1.5% of stage IV & 2.9% of unknown stage patients received >45Gy compared to 19% of stage 0-III]. 25692 cases of stage 0 – III NSCLC were evaluated for the analysis of utilisation (Figure 1).

Cases were selected for the cohort on the basis of a NSCLC diagnosis as recorded by the cancer registries. Because of inconsistencies in matching the cancer registry diagnosis and the radiotherapy diagnosis, all radiotherapy records for each patient were downloaded from the radiotherapy database. This included treatment to the primary lung tumour, to metastases and to second primaries. Radiotherapy records where the radiotherapy diagnosis was anything other than ‘neoplasms of respiratory and intrathoracic organs’ were subsequently excluded. After excluding non-lung radiotherapy records, 10376 patients (40.4%) received radiotherapy to the lung. Radiotherapy was classified as palliative, radical or SABR according to criteria in Table 1 checked against the initial coding. A further thirty three cases which could not be classified were excluded from the analysis.

Table 1

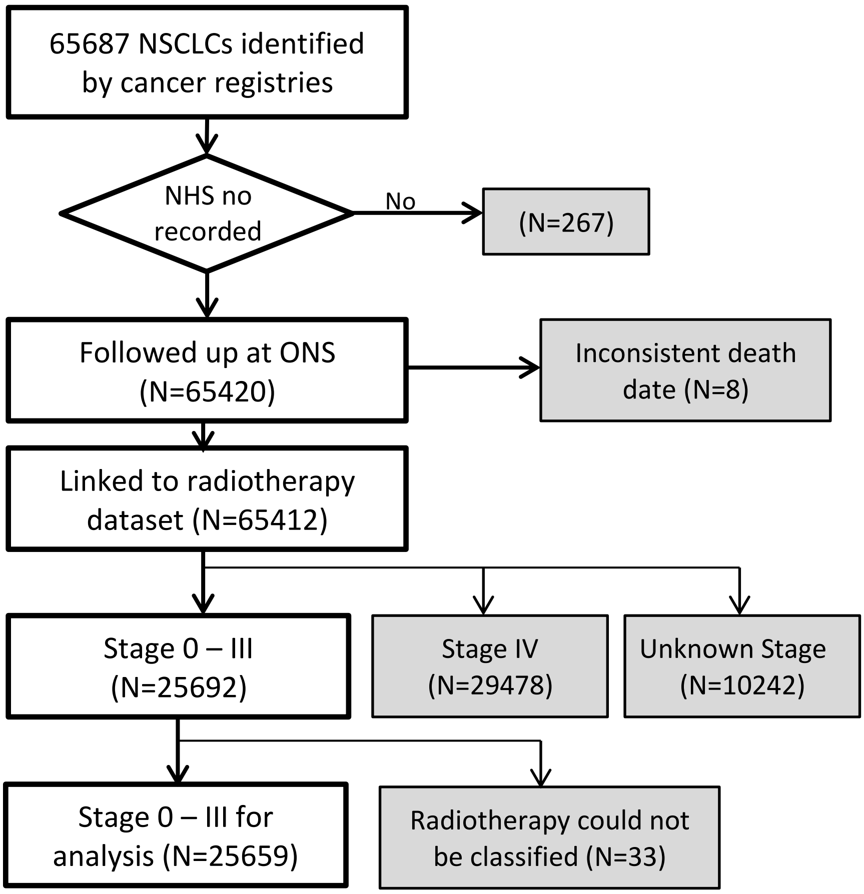
Classification of radiotherapy into radical, palliative and unknown

Dose fractionation	Category	Number of patients
Total Dose > 100Gy	Unknown	2
< 1.5 Gy/#	Unknown	17
≥ 3Gy/# and dose < 40Gy	Palliative	4954
Dose omitted and 1#, 10#, 12#, 13#	Palliative	20
Dose omitted and 5 # and stage ≠ 1	Palliative	22
> 3Gy/# and dose ≥ 40Gy and > 10#	Radical	77
1.5 – 3Gy/#	Radical	4342
Dose omitted and ≥ 20Gy/#	Radical	108
≥ 3 Gy / # and dose ≥ 40Gy and ≤ 10#	SABR	770
Dose omitted and 5 # and stage = 1	Unknown (possibly SABR) analysed as SABR	31
Remainder	Unknown	33

 # - fraction of radiotherapy; radical – fractionated radical radiotherapy; SABR – stereotactic ablative body radiotherapy

Figure 1

Flowchart of cases of NSCLC identified and included in the utilisation analysis



Statistical Methods

The effect of variables on the utilisation of radiotherapy was investigated in a univariate analysis and the significance of differences assessed by the chi-squared test or chi-squared test for trend. A multivariate binary logistic regression analysis was done to determine the utilisation in each of the counties after adjusting for the effect of age, stage, deprivation, comorbidity and other radical treatment (defined as lung excision or SABR). Significance was assessed by the Wald chi-squared test. The adjusted utilisation rates were used to rank the counties in order of increasing radical utilisation rates. Tertiles and quintiles were used to classify the counties as having low, medium or high (very low, low, medium, high and very high) utilisation.

Figure 2

Utilisation of radical radiotherapy by geographical area separated into 3 and 5 utilisation groups

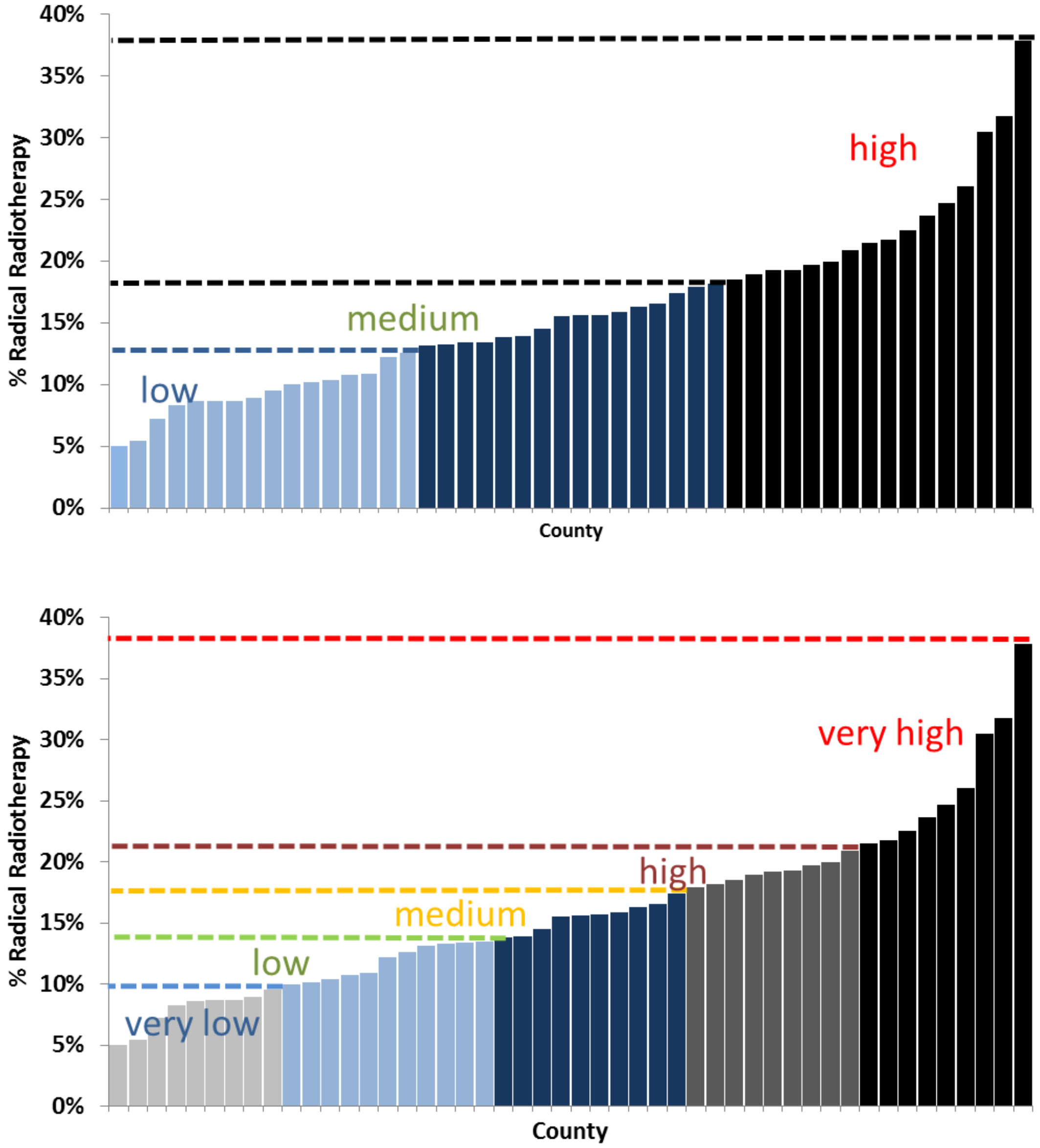


Table 3

**Rates of radical radiotherapy utilisation by County;
Raw data adjusted for age stage and deprivation decile**

		% radical radiotherapy		
County code	No cases	Unadjusted	Adjusted for age, stage, deprivation, comorbidity, other radical treatment	Significance
1	233	12.4%	13.1%	
2	294	9.9%	8.6%	Unadjusted :
3	260	6.2%	5.0%	
4	252	11.5%	10.7%	P << 0.00001
5	385	21.6%	20.9%	χ^2 test
6	799	23.4%	23.7%	
7	457	29.1%	31.7%	
8	243	30.5%	30.5%	Adjusted :
9	288	17.4%	16.5%	
10	476	13.0%	13.8%	P<< 0.00001
11	550	17.3%	16.3%	Wald
12	353	19.8%	18.5%	chi-squared
13	481	22.2%	22.5%	test
14	424	16.7%	17.4%	
15	413	12.1%	10.9%	
16	838	10.6%	10.0%	
17	327	8.3%	7.2%	
18	943	33.7%	37.9%	
19	676	16.7%	14.5%	
20	77	6.5%	5.5%	
21	397	9.3%	8.7%	
22	856	20.9%	20.0%	
23	64	23.4%	19.7%	
24	844	15.5%	13.9%	
25	1572	25.1%	24.7%	
26	368	13.9%	13.4%	
27	474	15.2%	15.9%	
28	1210	16.5%	18.2%	
29	485	21.4%	21.5%	
30	420	24.8%	26.0%	
31	302	9.9%	9.5%	
32	202	17.3%	15.6%	
33	528	15.0%	15.5%	
34	1500	16.5%	15.7%	
35	279	9.7%	10.2%	
36	241	9.5%	8.7%	
37	326	8.6%	8.3%	
38	813	17.7%	17.9%	
39	510	14.3%	13.4%	
40	348	20.4%	19.3%	
41	435	19.1%	19.2%	
42	934	18.7%	18.9%	
43	176	14.2%	12.6%	
44	1350	13.4%	13.3%	
45	340	13.8%	12.2%	
46	1464	19.4%	21.8%	
47	231	10.0%	8.9%	
48	221	11.8%	10.4%	

The effect of differing levels of radical radiotherapy utilisation on survival was investigated in a multivariate Cox regression analysis. The assumption of proportional hazards was confirmed by log minus log plots. Survival was adjusted for age, stage, deprivation, comorbidity and other radical treatment and differences between the county tertiles (quintiles) were assessed by the log likelihood test. Results for each utilisation group were summarised by the hazard ratio relative to the tertile (quintile) with the greatest utilisation.

The primary objective of the study was to look at differences in the utilisation of fractionated radical radiotherapy. Since a low utilisation could be compensated by a higher use of SABR, the analysis adjusted for this factor. As SABR is almost entirely restricted to stage I patients, a further sensitivity analysis was carried out for stage II and III patients alone.

Results

Utilisation of Radical Radiotherapy

Overall 17.6% of patients with NSCLC potentially eligible for radical treatment intent received fractionated radical radiotherapy (Table 2). There was an increase in the rate of radical radiotherapy with the stage of disease from 11.8% for stage 0/I to 21.4% for stage III. There was a gradual decrease in radical radiotherapy utilisation with age from the highest utilisation in the 40-59 age group (Table 2). Utilisation was highest (19.6%) in the most deprived areas and lowest (14.7%) in the least deprived. Patients with comorbidity scores of 2 or more had lower rates of radical radiotherapy utilisation.

Table 2

Rates of radical radiotherapy utilisation in stages 0 – III NSCLC

Characteristic		No. cases	Radical RT	% radical RT	significance
All cases		25659	4527	17.6%	
Stage of disease	0 I II III	117 8717 4878 11947	18 1025 929 2555	15.4% 11.8% 19.0% 21.4%	P<< 0.00001 χ^2 test for trend
Age	< 40 40 – 49 50 – 59 60 – 69 70 – 79 80 – 89 >= 90	50 429 2222 7059 9286 5863 750	10 119 571 1520 1615 665 27	20.0% 27.7% 25.7% 21.5% 17.4% 11.3% 3.6%	P << 0.00001 χ^2 test for trend
Deprivation decile	1 – most deprived 2 3 4 5 6 7 8 9 10-least deprived	3839 3209 2985 2756 2544 2498 2312 2119 1892 1505	751 609 531 452 439 431 388 357 348 221	19.6% 19.0% 17.8% 16.4% 17.3% 17.3% 16.8% 16.8% 18.4% 14.7%	P = 0.0001 χ^2 test for trend
Comorbidity	0 1 2 3 4 5 6 +	16840 3962 2481 1232 619 311 214	3186 687 321 175 88 41 29	18.9% 17.3% 12.9% 14.2% 14.2% 13.2% 13.6%	P << 0.00001 χ^2 test
Other radical treatment	None Surgery / SABR	17045 8614	3824 703	22.4% 8.2%	P << 0.00001 Fishers exact test

The use of fractionated radical radiotherapy varied across the counties (Table 3). As utilisation is likely to be affected by prognostic and treatment variables, the rates for the counties were calculated after adjusting for age, stage, deprivation, comorbidity and other radical treatment (Figure 2 & Table 3).

Radical RT Utilisation and Survival

By Dec 31st 2015, 15956 of the NSCLC patients (62.2%) had died. Age, stage, comorbidity and other radical treatment were all independent significant predictors of survival whilst deprivation was of marginal significance. After adjusting for these factors, the utilisation of radical radiotherapy had an impact on survival ($p<0.00001$). Dividing the counties into 3 groups, those with the highest utilisation had the best overall survival (Table 4) (2 year survival 48.6%) compared to medium (2 year survival 45.4%) and low utilisation (2 year survival 44.3%). Dividing the counties into 5 groups according to radiotherapy utilisation the counties with the highest utilisation had poorer survival (2 year survival 47.5%) than those in the second lower utilisation group (2 year survival 49.1%) (Table 4).

Based on the optimal level of utilisation, the data indicate that the lives of an additional 346 (95% CI: 284 – 406) lung cancer patients per year could have been extended beyond 2 years.

Of the 801 SABR cases, 712 (89%) were stage 0 / I. As a sensitivity test, the analysis was repeated for stage II and III patients alone. In this poorer survival group, differing levels of radical fractionated radiotherapy utilisation showed the same pattern of survival (Table 4). Dividing the cohort into three groups, those counties with the highest utilisation had a 2 year survival of 34.1% compared to 31.6% in the medium and 30.0% in the lowest utilisation groups (Table 4). Dividing the counties into 5 groups according to radiotherapy utilisation the counties with the highest utilisation had a worse survival (2 year survival 32.9%) compared to counties with lower utilisation (2 year survival 36.1%)

Table 4

Hazard ratios (HR) relative to the highest utilisation group divided into 3 groups (tertiles) and 5 groups (quintiles) for stages 0 – III NSCLC cases (n=25659) (A) and for stages II & III (n=16825) (B).

A

tertiles	HR*	95% CI*	Significance	2 yr. survival*
Low utilisation	1.13	1.08 – 1.18	p<0.001	44.3%
Medium	1.09	1.06 – 1.13	p<0.001	45.4%
High utilisation	1.0			48.6%
quintiles				
Very Low utilisation	1.09	1.04 – 1.15	p=0.001	44.1%
Low	1.10	1.05 – 1.16	p<0.001	44%
Medium	1.05	1.00 – 1.09	P=0.05	46%
High	0.95	0.91 – 1.00	P=0.04	49.1%
Very high utilisation	1.0			47.5%

B

tertiles	HR*	95% CI*	Significance	2 yr. survival*
Low utilisation	1.13	1.08 – 1.18	p<0.001	30.0%
Medium	1.08	1.04 – 1.13	p<0.001	31.6%
High utilisation	1.0			34.1%
quintiles				
Very Low utilisation	1.08	1.02 – 1.15	p=0.012	30.1%
Low	1.10	1.04 – 1.17	p=0.001	29.4%
Medium	1.03	0.98 – 1.08	p=0.3	31.7%
High	0.92	0.87 – 0.97	p=0.001	36.1%
Very high utilisation	1.0			32.9%

CI - confidence interval
*** corrected for age, stage, deprivation index & comorbidity**

Discussion

The analysis of the population of patients diagnosed with non-small cell lung cancer (NSCLC) in England in a 2 year period from January 2012 to December 2013 shows marked geographical variation in the use of radical radiotherapy (RT) and increased utilisation of RT is associated with improved NSCLC population survival. It also provides supporting evidence that radical RT in patients with locally advanced NSCLC is likely to be effective in prolonging survival.

The relationship between RT utilisation and survival is not linear. Although not previously demonstrated for surgery (3) or RT (2) it would fit with the hypothesis that only a proportion of patients with locally advanced NSCLC are suitable for radical RT most likely due to a combination of comorbidity, poor performance status, tumour size, age and other potential prognostic factors. This suggests that offering radical treatment to patients with poor predicted outcome is unlikely to overcome some of the determinants of the adverse prognosis and may even be detrimental.

The relationship between utilisation of radical treatment and outcome in patients with NSCLC has been demonstrated for surgery (3) and for other oncological treatments although the study looked at all lung cancer rather than NSCLC alone (2). The potential "optimum" utilisation has been suggested but not previously shown.

The data and the analysis are subject to potential bias. Although the survival endpoint in a population in England is reliable, some of the variables analysed may be affected by inaccuracy inherent in a large population study where data recording is not subject to detailed scrutiny. For example this may be an issue when defining treatment intent particularly when the analysis of outcome should be by treatment intent rather than treatment delivered.

The RT data is part of RT data set (RTDS) collected by NATCANSAT directly from radiotherapy providers using software which extracts data from Oncology Management Systems, and subject to a standard set of quality assurance measures upon receipt. This ensures that the dataset is complete (i.e. includes all patients treated), accurate and of acceptable quality.

To avoid or at least minimise bias inherent in an analysis by "treatment delivered", discrepancies between stated treatment intent and actual treatment delivered were individually analysed and allocated based on an algorithm shown in Table 1. This ensures that patients receiving lower than planned doses who are assumed to have stopped treatment early are correctly allocated to radical rather than palliative treatment intent. Similarly, the results could be skewed by increasing use of stereotactic ablative body radiotherapy (SABR) given to patients with localised disease where the outcome is considered to be equivalent to surgery (8, 9). To avoid bias, SABR patients were grouped with patients treated with attempted curative surgery and not included in the RT utilisation analysis. It is therefore likely that the RT utilisation rate reported here is reasonably accurate and represents the actual delivery of fractionated radical RT to patients with localised and locally advanced NSCLC in England in the study period.

Other factors may determine the outcome in addition to RT utilisation. Known measurable predictors of outcome which vary with RT utilisation including age, comorbidity, stage and the use of surgery were corrected for in the analysis. The missing factors are performance status and the use of systemic anticancer therapy (SACT).

Performance status (PS) information was not nationally recorded. Comorbidity index, particularly derived from HES data, while potentially not fully representative of performance status is a reasonable surrogate used in other studies (10). However an effect of PS on the reported outcomes independent of age and comorbidity cannot be excluded.

In the study period (2012-13) SACT data was not routinely collected on national basis and is not easily accessible particularly for such a large cohort. An expected survival benefit of adjuvant chemotherapy of the order of 5% (11) (12) in the population of patients treated, even if all patients in the high utilisation regions and none in the low utilisation regions received chemotherapy, is unlikely to translate to the reported increase in population survival. As only a proportion of patients treated with radical RT also receive chemotherapy a potential variation in utilisation is unlikely to significantly influence the reported outcome and this was demonstrated in a lung cancer population study where the utilisation of chemotherapy was not associated with an overall survival difference (2). Similarly the use of concomitant compared to sequential chemoradiotherapy (13) even if correlated with utilisation, is unlikely to be responsible for the reported population difference.

The reported results raise the issue of the potential determinants of utilisation that could be altered to improve survival particularly in patients with locally advanced NSCLC. Age and comorbidity are likely to be dependent rather than independent predictors. Deprivation index had only minimal association with utilisation which suggests that the variation in radical RT utilisation is not primarily determined by socio-economic status.

The analysis of differential utilisation was carried out by ceremonial counties and not regions identified by healthcare provider. Such analysis should however be carried out best by healthcare authorities to identify if the differences are provider specific. From the available data there is no significant correlation between the number of cases of NSCLC in the county and RT utilisation (data not shown). While there is no clear geographical distribution of utilisation, assessment such as proximity to RT centres has not been examined and may be of importance as geographical access to cancer services has impact on survival (14).

Conclusion

The utilisation of radical RT is an important and independent determinant of survival in patients with localised and locally advanced NSCLC. On the basis of the available evidence, health authorities should ensure that RT providers offer radical treatment to a larger proportion of patients suitable for radical RT while avoiding excessive use in patients considered unsuitable for radical treatment.

References:

1. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax. 2001 Aug;56(8):628-38. PubMed PMID: 11462066.
2. Moller H, Coupland VH, Tataru D, Peake MD, Mellemgaard A, Round T, et al. Geographical variations in the use of cancer treatments are associated with survival of lung cancer patients. Thorax. 2018 Jun;73(6):530-7. PubMed PMID: 29511056.
3. Riaz SP, Luchtenborg M, Jack RH, Coupland VH, Linklater KM, Peake MD, et al. Variation in surgical resection for lung cancer in relation to survival: population-based study in England 2004-2006. Eur J Cancer. 2012 Jan;48(1):54-60. PubMed PMID: 21871792.
4. Government DoCaL. English indices of deprivation 2015. 2015.
5. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83. PubMed PMID: 3558716.
6. Gildea G MS, Greenberg D, Price G, Francis M, Thomson CS, Poole J. Derivation of a Charlson co-morbidity index from routine HES data.
7. Maringe C, Fowler H, Rachet B, Luque-Fernandez MA. Reproducibility, reliability and validity of population-based administrative health data for the assessment of cancer non-related comorbidities. PloS one. 2017;12(3):e0172814. PubMed PMID: 28263996. Pubmed Central PMCID: 5338773.
8. Solda F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol. 2013 Oct;109(1):1-7. PubMed PMID: 24128806.
9. Zhang B, Zhu F, Ma X, Tian Y, Cao D, Luo S, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. Radiother Oncol. 2014 Aug;112(2):250-5. PubMed PMID: 25236716.
10. Henson KE, Fry A, Lyratzopoulos G, Peake M, Roberts KJ, McPhail S. Sociodemographic variation in the use of chemotherapy and radiotherapy in patients with stage IV lung, oesophageal, stomach and pancreatic cancer: evidence from population-based data in England during 2013-2014. Br J Cancer. 2018 May 10. PubMed PMID: 29743552.
11. Group N-sCLCC. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. Bmj. 1995;311(7010):899-909. PubMed PMID: 7580546.
12. Auperin A, Le Pechoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol. 2006 Mar;17(3):473-83. PubMed PMID: 16500915.
13. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010 May 01;28(13):2181-90. PubMed PMID: 20351327.
14. Murage P, Crawford SM, Bachmann M, Jones A. Geographical disparities in access to cancer management and treatment services in England. Health & place. 2016 Nov;42:11-8. PubMed PMID: 27614062.