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Original Article

Stage III Non-small Cell Lung Cancer Management in England

J.B. Adizie [*], A. Khakwani [†], P. Beckett [‡], N. Navani [‡], D. West [‡], I. Woolhouse [*], S.V. Harden [‡]

[*] University Hospitals Birmingham, Birmingham, UK
[†] Department of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
[‡] Care Quality Improvement Department, Royal College of Physicians, London, UK

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Abstract

Aims: We present the first analysis of the management and outcomes of stage III non-small cell lung cancer (NSCLC) conducted in England using National Lung Cancer Audit data.

Materials and methods: Patients diagnosed with stage III NSCLC in 2016 were identified. Linked datasets (including Hospital Episode Statistics, the National Radiotherapy Dataset, the Systemic Anti-Cancer Dataset, pathology reports and death certificate data) were used to categorise the treatment received. Kaplan–Meier survival curves were obtained, with survival defined from the date of diagnosis to the date of death.

Results: In total, 6276 cases of stage III NSCLC were analysed: 3827 stage IIIA and 2449 stage IIIB; 1047 (17%) patients were treated with radical radiotherapy with 676 (11%) of these also receiving chemotherapy. Twenty per cent of patients with stage IIIA disease underwent surgery, with half of these also receiving chemotherapy, predominantly delivered in the adjuvant setting. Of note, 2148 (34%) patients received palliative-intent treatment and 2265 (36%) received no active anti-cancer treatment. The 1-year survival was 32.9% (37.4% for stage IIIA), with the highest survival seen for those patients receiving chemotherapy and surgery.

Conclusions: We highlight important gaps in the optimal care of patients with stage III NSCLC in England. Multimodality treatment with either surgery or radical radiotherapy combined with chemotherapy was delivered to less than one-fifth of patients, even though these regimens are considered optimal. Timely access to specialist resources and staff, the practice of effective shared decision making and challenging preconceptions have the potential to optimise management.

Key words: Concurrent chemoradiotherapy; multimodality treatment; population-based study; stage III NSCLC

Introduction

The overall survival for patients diagnosed with lung cancer in England is poor compared with other countries [1]. The National Lung Cancer Audit (NLCA) was established in 2004 to identify variation in practice and patient outcomes across the country and to drive improvement in lung cancer care [2]. Since then, there has been an increase in surgical resection of early lung cancers, correlating with improved survival for early stage disease [3].

In 2014, the NLCA moved from using a bespoke standalone database (LUCADA) to using datasets collected and quality assured by the National Cancer Registration and Analysis Service (NCRAS), Public Health England. This enabled detailed information on non-surgical treatments for lung cancer to be reported in the measured outcomes, including the use of radical radiotherapy from the National Radiotherapy Dataset (RTDS) and systemic anti-cancer treatment from the Systemic Anti-Cancer Dataset (SACT).

The recently updated National Institute for Health and Care Excellence (NICE) lung cancer guidance (March 2019) recommends trimodality treatment as the standard of care for patients with stage III (N2) disease and good performance status, in keeping with international guidance [4,5]. Whereas for patients with a good performance status and unresectable stage III non-small cell lung cancer (NSCLC), treatment with platinum-based doublet chemotherapy concurrent with radiotherapy (chemoradiotherapy) is advocated [6]. However, the newly published NICE technology appraisal recommending the use of adjuvant durvalumab after concurrent chemoradiation represents a treatment paradigm shift for this stage [7]. Finally, for less

Author for correspondence: J.B. Adizie, University Hospitals Birmingham, Birmingham, UK.

E-mail address: j.adizie@nhs.net (J.B. Adizie).

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fit patients, guidelines recommend the use of palliative-intent chemotherapy or radiotherapy [4,5].

For the first time, the NLCA presents treatment patterns and outcomes for stage III NSCLC patients that are benchmarked against results from international population-based studies.

Materials and Methods

Databases

The NLCA is a validated database using data collated, maintained and quality assured by NCRAS at Public Health England [8]. Information on lung cancer patients submitted by 142 English National Health Service (NHS) Trusts through the Cancer Outcome and Services Dataset are linked to other NCRAS datasets, including Hospital Episode Statistics (HES), RTDS, SACT and the Office of National Statistics. All participating NHS Trusts had the opportunity to validate their submitted Cancer Outcome and Services Dataset data and are responsible for submitting their SACT and RTDS data. NCRAS also carry out internal validation of their datasets.

Study Population and Covariates

The study population included patients diagnosed with lung cancer (International Classification of Diseases code C34) with pathologically confirmed NSCLC (based on the recorded Systematised Nomenclature of Medicine codes) and clinically confirmed NSCLC cases in England between 1 January 2016 and 31 December 2016. Patients identified only by death certification were excluded. Analyses were restricted to those with stage III using TNM version 7 [9]. The following variables were also identified: age at diagnosis, gender, socioeconomic status (derived from the postcode and linked with the Index of Multiple Deprivation) and Eastern Co-operative Oncology Group performance status according to the World Health Organization definition recorded at the time of diagnosis. The HES database was used to calculate the Charlson Co-morbidity Index (a composite score that has been validated for use in this dataset) preceding the date of lung cancer diagnosis [10].

Treatment Definitions

Treatment variables are defined as:

(i) Surgical resection from HES data using Office of Population Census and Survey Classification of Intervention version 4 (OPCS-4) codes and methods reported previously [8];
(ii) Lung cancer-specific systemic anti-cancer therapy identified from the SACT database;
(iii) Radical radiotherapy from RTDS using a combination of data items, including treatment intent, total prescribed dose >50 Gy and prescribed number of fractions (10 or more, but with the vast majority delivered in 20 or more fractions) [11]. Concurrent chemoradiation was categorised as the first fraction of radiotherapy starting between the first and last administration dates of SACT.

Statistical Analysis

All data and statistical management were carried out using STATA version 15 (StataCorp). Multivariate logistic regression analysis was used to estimate the odds of receiving curative-intent treatment and 1-year survival by patient features and clustered for NHS Trust. Adjusted and unadjusted Kaplan–Meier overall survival curves were obtained, with survival defined from the date of diagnosis to the date of death. Only patient factors known at the time of diagnosis were considered in adjusted analyses to minimise bias. The median follow-up time from diagnosis was 313 days (10 months) with an interquartile range of 115 days (4 months) to 627 days (20 months).

Results

Overall

During 2016, 6276 cases of stage III NSCLC were diagnosed in England, of which 3827 were stage IIIA and 2449 were stage IIIB. The demographic details are shown in Table 1;

Table 1
Patient demographics for stage III non-small cell lung cancer patients (n = 6276)

	Patients (n)	%
Gender		
Female	2746	43.8
Male	3530	56.3
Age		
<65 years	1340	21.9
65–80 years	3559	56.7
>80 years	1377	21.4
Stage		
IIIA	3827	61.0
IIIB	2449	39.0
Performance status		
0	1158	18.5
1	2054	32.7
2	1073	17.1
3	951	15.2
4	235	3.7
Missing	805	12.8
Townsend quintile		
1 (most affluent)	790	12.6
2	1079	17.2
3	1229	19.6
4	1501	23.9
5 (least affluent)	1671	26.6
Missing	6	0.1
Charlson index		
0	2511	40.0
1	1442	23.0
2	1549	24.7
3+	774	12.3

56.3% of patients were men and 56.7% were aged 65–80 years. About one-half of patients had a performance status of 0–1.

Treatment

Treatment patterns are shown in Table 2. In total, 2265 (36%) cases had no record of receiving any active treatment for their stage III lung cancer and 2136 (34%) received treatments of palliative intent (either systemic therapy alone or palliative radiotherapy or both).

In total, 1860 (30%) patients received curative-intent treatment (surgery or radical radiotherapy). Seventy per cent (394/565) of patients with stage IIIA, performance status 0–1 and age <65 years received curative-intent treatment and 56% (671/1201) in the 65–80 years age bracket. Thirty per cent (112/390) of patients with stage IIIB, performance status 0–1 and age <65 years received curative-intent treatment and 24% (173/707) in the 65–80 years age bracket. Bimodality treatment with chemotherapy and surgery or radiotherapy with curative intent was delivered to 1123 (18%).

Seven hundred and seventy patients with stage IIIA underwent surgery, 56% (431 patients) also received chemotherapy, predominantly delivered in the adjuvant setting. Forty-three (1%) patients received trimodality therapy in either the adjuvant or neoadjuvant setting.

In total, 1047 (17%) stage III patients were treated with radical radiotherapy, with 676 (65%) also receiving chemotherapy.

For patients receiving chemotherapy and radical radiotherapy where complete treatment dates were available, 34% received concurrent chemoradiation and 66% received sequential chemoradiation.

Where performance status was available, 171 (36%) performance status 0–1 cases received concurrent chemoradiation (115/300 stage IIIA) and 310 (64%) performance status 0–1 received sequential chemoradiation (185/300 stage IIIA).

Regional Variation

The variation in the use of curative-intent treatment for stage IIIA disease with either surgery or radical radiotherapy by NHS Trust (anonymised) is shown in Figure 1. Rates vary from 8 to 80%. Variation rates were not analysed for stage IIIB due to the heterogeneity of this stage and therefore the low likelihood of surgery being offered.

Survival

The 1-year survival for stage III NSCLC was 32.9% (37.4% for stage IIIA). Survival stratified by stage, age and performance status is shown in Table 3. The 1-year survival for patients with stage IIIA, performance status 0–1 and age <65 years was 54.5%. Adjusted and unadjusted Kaplan–Meier survival curves by treatment received for all stage III cases and just for stage IIIA cases are shown in Figures 2–4. Proportions of patients surviving to 1 year are shown in the Supplementary Table S1, with the highest overall survival seen for those patients receiving multimodality treatment. These data highlight three notable points. First, the survival curves for bimodality treatment regimens (chemotherapy and surgery versus chemotherapy and radiotherapy) diverge before 1 year in unadjusted, adjusted and stage IIIA-specific analyses, with the highest survival seen for patients receiving the former regimen. Second, the surgery-alone arm crosses the chemoradiotherapy group at just over 1 year in the adjusted stage III and IIIA analyses. Finally, over this relatively short follow-up timescale, there was no difference in survival identified between patients receiving concurrent or sequential radiotherapy (see Supplementary Figure S1).

The full results of the multivariate logistic regression analyses by patient factors with curative-intent treatment

Table 2
Treatment patterns for patients with stage III non-small cell lung cancer ($n = 6276$)

	Stage IIIA ($n = 3827$)	%	Stage IIIB ($n = 2449$)	%
Group 1: Surgery	770	20.1	43	1.8
Surgery	302	7.9	19	0.8
Surgery and adjuvant chemotherapy	356	9.3	12	0.5
Neoadjuvant chemotherapy and surgery	34	0.9	2	0.1
Surgery and radiotherapy	37	1.0	8	0.3
Trimodality therapy	41	1.1	2	0.1
Group 2: Radical radiotherapy	712	18.6	335	13.7
Radical radiotherapy	291	7.6	80	3.3
Radical radiotherapy and chemotherapy	421	11.0	255	10.4
Group 3: Palliative-intent treatment	1023	26.7	1125	45.9
Palliative radiotherapy and chemotherapy	182	4.8	234	9.6
Palliative radiotherapy	396	10.3	321	13.1
Chemotherapy alone	396	10.3	570	23.3
Group 4: Best supportive care (no treatment)	1322	34.5	946	38.6

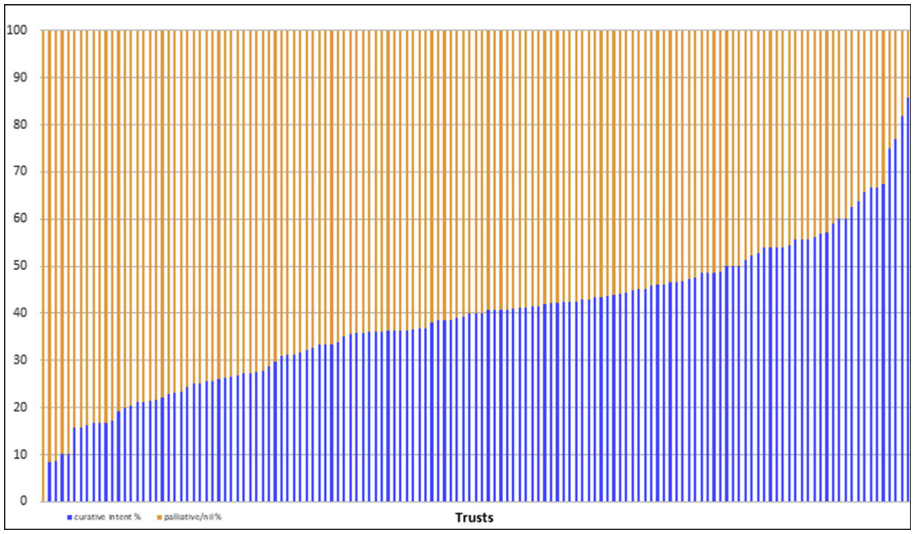

Fig 1. Variation (%) in stage IIIA non-small cell lung cancer curative-intent treatment by National Health Service Trust (anonymised).

Table 3
One-year survival (%) and curative-intent treatment rate by age, stage and performance status

	One-year survival (%)	Curative-intent treatment (%)
Overall stage III	32.9	39.0
Stage IIIA only	37.4	50.8
Performance status		
0–1	44.7	45.4
2	25.4	19.4
3–4	14.6	3.2
Age group (years)		
<65	44.0	44.7
65–80	33.1	31.2
>80	21.6	12.1
Stage IIIA and performance status 0–1 by age (years)		
<65	54.5	69.7
65–80	48.2	55.9
>80	42.7	38.4

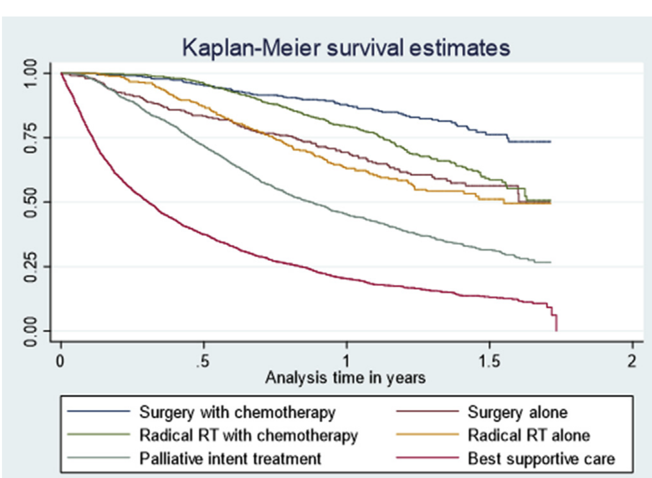

Fig 2. Unadjusted Kaplan–Meier survival estimates by treatment modality for stage III non-small cell lung cancer.

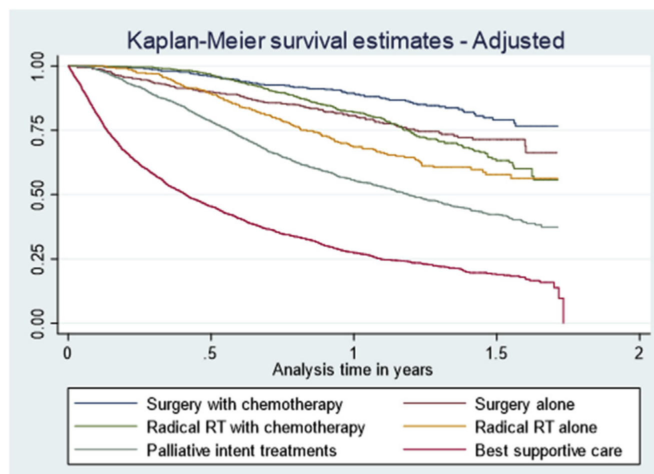

Fig 3. Adjusted Kaplan–Meier survival estimates by treatment modality for stage III non-small cell lung cancer adjusted for age, gender, performance status and socioeconomic status.

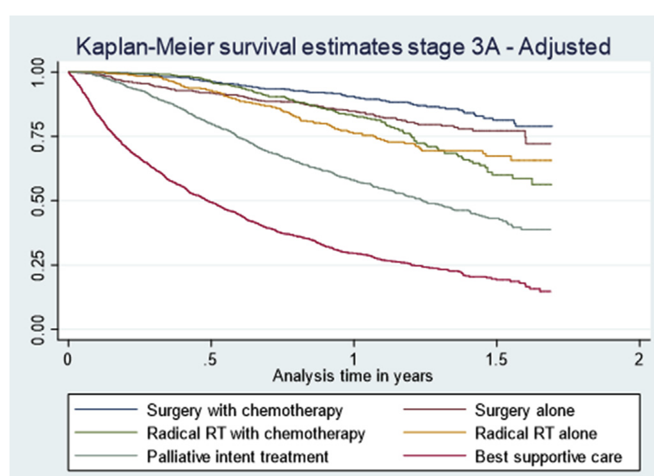

Fig 4. Adjusted Kaplan–Meier survival estimates for stage IIIA non-small cell lung cancer adjusted for age, gender, performance status and socioeconomic status.

and 1-year survival are shown in Supplementary Table S2. Patient factors significantly associated with decreased odds of surviving to 1 year and receiving curative-intent treatment include increasing age and performance status ($P < 0.001$ for both).

Discussion

To our knowledge, this is the first comprehensive analysis of the management of stage III NSCLC conducted in England using population-based data linked with specific radiotherapy and chemotherapy datasets. So far, previous studies have focused on outcomes from specific patient groups, such as patients undergoing surgical resections or receiving radiotherapy [12,13]. Twenty per cent of patients with NSCLC present with stage III disease in the UK, although this figure will probably change with the introduction of screening, as indicated by the NELSON study [14]. However, optimal management is essential to achieve improved overall survival outcomes [2].

We show that about 40% of patients with stage IIIA receive curative-intent treatment, with less than one-fifth receiving multimodality treatment. Tables 4 and 5 show how modality-specific treatment rates compare with published international population-based studies for stage III (Table 4) and stage IIIA (Table 5) with similar inclusion criteria. The overall, and stage IIIA-specific, curative-intent treatment rates reported in the current study are the lowest of all the published studies. Although surgical resection rates are comparable, less than one-fifth of patients receive radical radiotherapy as part of their treatment compared with about a half of patients in Australia, USA, Belgium and the Netherlands [15–18]. Additionally, over one-third of patients at stage IIIA do not receive any active treatment, which compares with 13–18% in other studied countries [17–20].

Additionally, the 1-year survival rate of 33% reported in the current study does not compare favourably with other studies [British Colombia (51%) [21], Belgium (53.1%) [17] and the Netherlands (44.8%; >65 years analysed only) [18]]. The rate of 55% found in the optimised subgroup (<65 years, performance status 0–1 and stage IIIA) is consistent with international data. These figures may be reflective of the high rates of patients not given any active anti-cancer treatment or treated with palliative intent.

The reasons for the comparatively low outcomes reported in the current study are probably multifactorial, including patient, tumour, clinician and organisational factors. The management of this diverse stage is complex, ranging from surgical patients identified with occult pathological N2 disease for whom adjuvant chemotherapy is recommended to patients presenting with bulky mediastinal nodal disease where concurrent chemoradiotherapy is advised. Our data include all lung cancer cases diagnosed in England; therefore, it is important to note that the proportion of all patients whose data are included will probably be larger than in other reported series.

Table 4
Comparative treatment rates by modality for patients with stage III non-small cell lung cancer (%)

	National Lung Cancer Audit, 2019 England ($n = 6276$)	Vinod *et al.*, 2008 [15] Australia ($n = 1812$)	Little *et al.*, 2007 [16] USA ($n = 11\,168$)	Driessen *et al.*, 2018 [18] The Netherlands ($n = 7057$)	Verleye *et al.*, 2018 [45] Belgium ($n = 1987$)
Surgery alone	5.1	4.0	6.6	9.5*	11.7*
Surgery with chemotherapy	7.1	2.0	7.1		
Radical radiotherapy	5.9	31.0	16.5	35.9	6.6
Radical radiotherapy with chemotherapy	10.8	19.0	36.2	14.5	33.9
Curative-intent therapy	28.9	56.0	66.4	59.9	32.8
Multimodality treatment	17.9	21.0	43.3	14.5	52.1
Palliative-intent treatment	34.2	11.0	11.5	13.4	32.8
Best supportive care	36.1	28.0	18.5	26.5	15.4

* Results not reported separately.

Table 5
Comparative treatment rates by modality for patients with stage IIIA non-small cell lung cancer (%)

	National Lung Cancer Audit, 2019 England ($n = 3827$)	Verleye *et al.*, 2018 [45] Belgium ($n = 1197$)	Driessen *et al.*, 2018 [18] The Netherlands ($n = 3960$)*	Dickhoff *et al.*, 2016 [19] The Netherlands ($n = 4816$)	Hancock *et al.*, 2014 [20] USA ($n = 83\ 913$)
Surgery alone	7.9	17.0†	21.0	11.0	14.0†
Surgery with chemotherapy	11.3		47.0	4.0	
Radical radiotherapy	7.6	8.1	8.0	12.0	69.0†
Radical radiotherapy with chemotherapy	11.0	32.8	11.0	45.0	
Curative-intent therapy	37.8	57.9	76.0	72.0	83.0
Multimodality treatment	22.3	†	†	49.0	NR
Palliative-intent treatment	26.7	27.1	11.0	9.0	17.0
Best supportive care	34.5	15.0	13.0	18.0	NR

* Patients >65 years old only included.
† Results not reported separately.

Patient factors cannot wholly explain our findings. The demographics in this cohort are shown to be similar to other lung cancer populations from Western countries in terms of age and performance status [15,16,21,22].

Patients included in the NLCA dataset were found to have a lower co-morbidity burden than in other studied populations. Studies based in Australia and the USA report 80% and 72%, respectively, and have at least one co-morbidity in their stage III cohort [16,21]. This compares with only 60% in the NLCA population. The Charlson Index was used as a proxy for co-morbidity burden. This composite score has been validated in cohorts of men and women with malignant and non-malignant diseases [23]. Studies using NLCA data derive this index from hospital admission data. Therefore, all diagnoses may not be captured if a condition is managed by a general practitioner. This may explain our comparatively low co-morbidity burden and raises the possibility of residual confounding [10]. Despite this, the methodology used to derive the score has been validated for use in the NLCA cohort [10]. Furthermore, the distribution of the index is similar to general practitioner datasets and cohorts of patients with NSCLC [24–26]. Comparative international data on the deprivation index is lacking.

Patient factors that were found to be significantly associated with improved 1-year survival and curative-intent treatment in the current study were a performance status of 0–2, younger age (<65 years) and stage IIIA. However, about one-third of patients in this group did not receive curative-intent treatment, suggesting that treatment decisions are influenced by factors other than patient and tumour variables.

Clinician factors may explain the high proportion of patients receiving palliative-intent treatment or no active treatment. Qualitative work conducted in early stage NSCLC shows that a failure of clinicians to effectively discuss all treatment options with patients influences treatment rates [27]. Additionally, Légaré *et al.* [28] found that the most significant variable determining whether a patient will engage in shared decision making is the clinician's attitude. Hence, it is possible that nihilistic attitudes among health professionals may contribute to our low radical radiotherapy and multimodality treatment rates. Such attitudes among respiratory physicians may contribute to low referral and pathological confirmation rates [29]. Similarly, a fatalistic attitude among treating clinicians may limit receipt of treatment [30,31]. Providing patients with surgical and oncology treatment assessments by the relevant teams (as recommended by the British Thoracic Society on the optimal treatment strategy for clinical N2 NSCLC) is key [32]. Widespread implementation of this approach has the potential for quality improvement interventions to address two findings. First, the low number of patients receiving multimodality treatment, including neoadjuvant or trimodality therapy in surgical patients, which currently sits at just 10%. Second, the high numbers of patients ($n = 321$) receiving surgery alone; a treatment approach not supported by evidence or guidelines. This is pertinent, given that the updated NICE lung cancer guidelines advocate chemoradiotherapy before surgery in multimodality stage

IIIA treatment; a practice that is clearly not currently executed [4]. However, it should be noted that the definition of radical radiotherapy in this study is > 50 Gy, which is higher than may be used in practice in a trimodality regimen. Additionally, factors such as patient preference and a decline in patient performance status after surgery may explain this finding.

The registry-based data reported in the current study include all stage III NSCLC patients diagnosed in England; some will be too unwell or frail for treatment and many will not be surgical candidates. However, the variation across hospital Trusts in the proportion of patients treated with either surgery or radical radiotherapy would suggest that as a country, there is room to increase the amount of radical radiotherapy offered to stage III patients and to critically review how this is given in combination with chemotherapy. This is particularly relevant in light of a recent trial showing significantly improved overall survival with the addition of adjuvant durvalumab after concurrent chemoradiotherapy [33]. Of all patients receiving chemoradiotherapy, only one-third had this in the concurrent setting. This compares with rates of 94% in the USA and 92% in Canada [21,34]. Therefore, a large change in practice is required if adherence to the latest NICE guidance is to be achieved [4]. Understanding barriers to access and re-evaluating preconceptions of what is considered radically encompassable with the use of modern radiotherapy techniques, such as intensity-modulated radiotherapy and image-guided radiotherapy, may improve low radical concurrent radiotherapy rates. Moreover, encompassability can only be adequately assessed with planning attempts to ascertain dose and volume data. Therefore, these attempts require reimbursement, even if patients do not progress to receive a radical dose.

An accurate assessment of performance status is crucial to determining appropriate management plans. However, studies report conflicting data in the reliability of clinician-assessed performance status measurement, with variable levels of interobserver agreement [35–37]. Additionally, the recorded measurement tends to be that assessed on initial presentation rather than that at the time of assessment by a treating clinician. This inconsistency will probably have an impact on results.

There is an increasing body of literature indicating that organisational characteristics and access to specialist care significantly affect patient outcomes and contribute to national variation [17,21,38]. We have previously shown that patients in England and Wales with NSCLC seen in a Trust with a low organisational score (derived from resource and staffing factors from the national lung cancer commissioning guidance) are significantly less likely to survive to 1 year, receive curative-intent treatment or receive timely care after adjusting for patient factors across all disease stages [38].

Access to up to date staging and treatment modalities is key in stage III NSCLC. The concordance between clinical and pathological stage for stage IIIA NSCLC has been reported to be less than 40%, with the majority of incorrectly staged tumours subsequently being downstaged [19,39]. Details of the extent of staging is not available in the NLCA dataset. However, 102 Trusts fall below the 75% target for pathological confirmation. Therefore, patients run the risk of missing out on potentially curative treatment [2].

Another factor is inequity of access to specialist staff, demonstrated by the second NLCA organisational audit [2]. Lung cancer nurse specialists have been shown to be key in enhancing communication and patient decision making, yet less than a fifth of Trusts meet the lung cancer national commissioning guidance requirement of having a minimum of one whole-time equivalent specialist nurse per 80 new lung cancer diagnoses per year [2,40,41].

Finally, timeliness of access to facilities is important, as emphasised by national guidance [4,42]. Lung cancers can progress and the performance status of patients can drop in the waiting time for diagnostics, advice and treatment [43]. This is particularly important for this subgroup of patients who frequently require additional staging investigations and complex treatment planning [29,43,44]. Timely access to specialist facilities is essential if improvements are to be made, which can be achieved through adoption of the National Optimal Lung Cancer Pathway [42].

In summary, improving outcomes for patients with stage III disease in England requires a multifaceted approach. Undertreatment has the potential to be addressed by a specialist multidisciplinary team for complex stage III patients and training on optimal patient selection. However, financial investment in lung cancer services and deficiencies in service structure require urgent attention to enable timely access to essential diagnostic/therapeutic modalities to ultimately change patient outcomes.

Strengths and Limitations

The main strength of this study is the completeness and quality of the NLCA data, providing an accurate picture of patient management in this subgroup. Through the linked datasets, details of treatments received by patients, including drug names, doses, frequency and timing, are available; a deficiency highlighted in similar previous population-based studies. Additionally, data have been validated by Trusts.

Two main limitations should be acknowledged. First, the retrospective nature of the real-world data may be subject to confounding, under-reporting and selection bias. Selection bias may in part explain why the treatment regimens involving surgery are shown to have better survival than the other curative-intent regimens. These patients may represent a fitter group or were more accurately staged intraoperatively.

Second, as previously mentioned, details on the quality of staging or the tumour volume/location are not available in the NLCA dataset. Therefore, eligibility for curative-intent treatment and details of stage designation cannot be verified. Nevertheless, the collected information on treatment patterns provide important data on practice trends to drive improvements in practice.

Conclusions

We highlight important gaps in the optimal care of patients with stage III NSCLC. Establishing current treatment patterns is important in this pivotal era of immunotherapy and updated NICE guidance. Significant improvements in overall survival seen with the addition of durvalumab after concurrent chemoradiotherapy for patients with inoperable stage III disease heralds a treatment paradigm shift. However, without addressing deficiencies in care, only 4% of stage III patients in England would currently benefit from such advancements [33]. Timely access to specialist resources and staff, the practice of effective shared decision making and challenging preconceptions require urgent attention to address regional variation in curative-intent treatment if patients are to have the best chance of surviving this disease.

Conflict of Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.07.020.

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