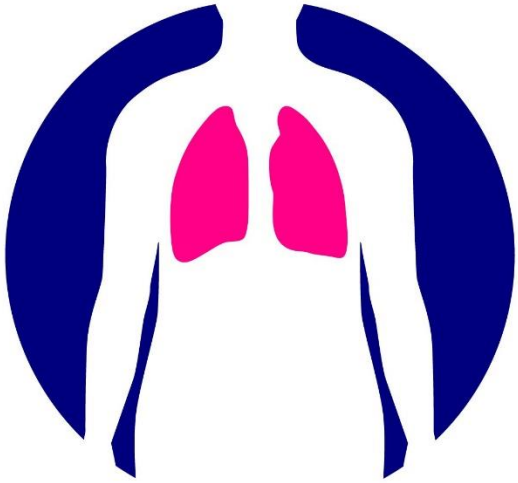

Evaluating concordance with non-small cell lung cancer NICE treatment guideline recommendations

November 2024

CANCER RESEARCH UK

NHS

Together we are beating cancer

Reference

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Authors

Lorna Wills, Jess Fraser, Scarlett Cartwright-Hughes, Rosie Hinchliffe, Shane Johnson, Sophia Lowes, Fahmina Fardus-Reid, Lucy Ironmonger, Jon Shelton, Lyndsy Ambler, Sam Harrison, Sean McPhail, Lizz Paley, Yoryos Lyratzopoulos

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About Cancer Research UK

We're the world's leading cancer charity, dedicated to saving and improving lives through research. We fund research into the prevention, detection and treatment of more than 200 types of cancer through the work of over 4,000 scientists, doctors and nurses. In the last 50 years, we've helped double cancer survival in the UK and our research has played a role in more than half of the world's essential cancer drugs. Our vision is a world where everybody lives longer, better lives, free from the fear of cancer.

Our values

Our values help guide our behaviour and culture in an ever-changing world, building on the best of what we do today and what we aspire to be in the future. They unite and inspire us to achieve our ambitious plans and our mission of beating cancer, together.

Our values are:

Bold

Act with ambition, courage and determination

Credible

Act with rigour and professionalism

Human

Act to have a positive impact on people

Together

Act inclusively and collaboratively

Contents

Executive summary

NICE guidelines for cancer treatment set out recommended treatment for patients. However, the levels of concordance to these guideline recommendations are not known. This project aimed to establish levels of concordance to as many non-small cell lung cancer (NSCLC) NICE treatment guideline recommendations as possible, and to investigate variation in concordance by patient characteristic and Cancer Alliance using cancer registration and treatment datasets.

Concordance was only able to be assessed for a small number of NSCLC treatment recommendations, using currently available routine datasets. Inclusion criteria for these recommendations were largely based on whether a patient was suitable for surgery and their stage at diagnosis. Most of the included recommendations focused on chemotherapy and recommended that eligible groups of patients should receive treatment, but one recommended that neoadjuvant treatment should not be offered.

Concordance to recommended treatment ranged from 18.1% for the recommendation that chemoradiotherapy should be offered to patients diagnosed at stage II or III who are not suitable for or decline surgery to 99.5% for the recommendation that patients should not receive neoadjuvant treatment outside of a clinical trial.

There were no significant associations seen between gender and receiving concordant treatment for any of the recommendations.

Age group was significantly associated with concordance for all the recommendations investigated. Patients aged 45-54 and 55-64 were significantly more likely to have concordant treatment compared to those aged 65-74, while those aged 75+ were less likely. The results for the <45 age group varied with recommendation, with these patients more likely to receive treatment concordant to the recommendation to offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy, but no significant difference seen for the other recommendations.

Comorbidity score was significantly associated with receiving treatment concordant to each of the recommendations investigated. Patients with increasingly high comorbidity score were increasing less likely to receive treatment concordant to the recommendations compared to those with a score of 0.

There were mixed results for the relationship between deprivation quintile and recommendation concordance. A deprivation gradient was present for the recommendation that chemoradiotherapy be offered to patients diagnosed at stage II and III who are not suitable for or decline surgery, with those living in the most deprived quintile of areas significantly less likely to receive concordant treatment compared to those in the least deprived quintile. However, deprivation was not significantly associated with receiving concordant treatment for any of the other recommendations.

There were no significant relationships between ethnicity and receiving recommendation concordant treatment, where ethnicity was known.

Patients diagnosed at a later stage were more likely to receive concordant treatment for three of the four recommendations. However, patients diagnosed at stage 4 were less likely to receive treatment concordant to the recommendation that patients be offered a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy.

Concordance to two of the four recommendations was significantly associated with year of diagnosis, with concordance more likely in later years for the recommendations on chemoradiotherapy and use of cisplatin.

The effect of Cancer Alliance was significant for all recommendations investigated. The recommendation to offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy had the largest standard deviation and coefficient range and the recommendations to offer postoperative chemotherapy to people with good performance status and T1a–4, N1–2, M0 or to consider postoperative chemotherapy for people with good performance status and T2b–4, N0, M0 with tumours greater than 4 cm in diameter had the smallest standard deviation and coefficient range for the effect of Cancer Alliance.

Background

The National Institute for Health and Clinical Excellence (NICE) provides guidelines for promoting good health and preventing and treating ill health in England and Wales (1), including recommendations for the treatment of cancer (2). These guidelines make evidence-based recommendations and, as such, their implementation can be hypothesised to translate to improved outcomes. Investigating the levels of concordance to the treatment guideline recommendations could help to highlight any potential gap between recommended and actual practice and suggest potential areas for improving the delivery of evidence-based treatment.

Yet levels of concordance to NICE guideline recommendations for non-small cell lung cancer (NSCLC) treatment (3) have not been comprehensively investigated in England - although the National Lung Cancer Audit reports the percentage of patients in whom some treatment metrics such as Systemic Anti-Cancer Therapy treatment for advanced and incurable NSCLC were met (4). Recently published evidence indicated that use of chemotherapy and radiotherapy was lower in lung cancer patients in England and the other UK nations compared to many other countries and sub-national jurisdictions participating in the International Cancer Benchmarking Partnership suggesting either lower concordance to guideline recommendations or differing guidelines or inclusion criteria for treatment (5; 6).

There have been several studies of NSCLC treatment guideline concordance in other countries, mostly relating to patient populations in the United States (7; 8; 9; 10; 11; 12; 13; 14; 15), but also Italy (16), the Netherlands (17), Finland (18; 19), Japan (20) and Australia (21; 22). These studies indicate that concordance with NSCLC treatment guidelines is generally lower than those for other cancer sites, such as breast and rectal cancer (17). Treatment guideline adherence generally decreases with increasing age and higher number of comorbidities (7; 8; 11; 12; 18; 19; 20; 21; 22), with several US studies also finding associations between ethnicity and guideline non-concordance (8; 11; 14). Adherence to chemo-radiotherapy guidelines is generally lower than other treatment modalities such as chemotherapy alone (16). Non-concordance due to over-treatment also occurs and is more likely in younger patients. (9).

Other studies have identified reasons for non-concordance with treatment guidelines, including a higher burden of comorbidities, decreased lung function, decision by clinicians to reduce treatment intensity or recommend best supportive care, patient choice, and decline in performance status between diagnosis and intended timing of treatment initiation (18; 23), alongside institutional factors such as treatment in hospitals treating lower than average number of cases and non-teaching hospitals (24).

A number of these studies investigated the relationship between guideline concordance and survival, generally reporting improved outcomes in patients with guideline concordant versus guideline non-concordant care. (7; 18; 11; 14; 15), although one study found that this was only seen for patients with early-stage disease (21).

Methods

Determining which NICE guideline recommendations were suitable for analysis within this project

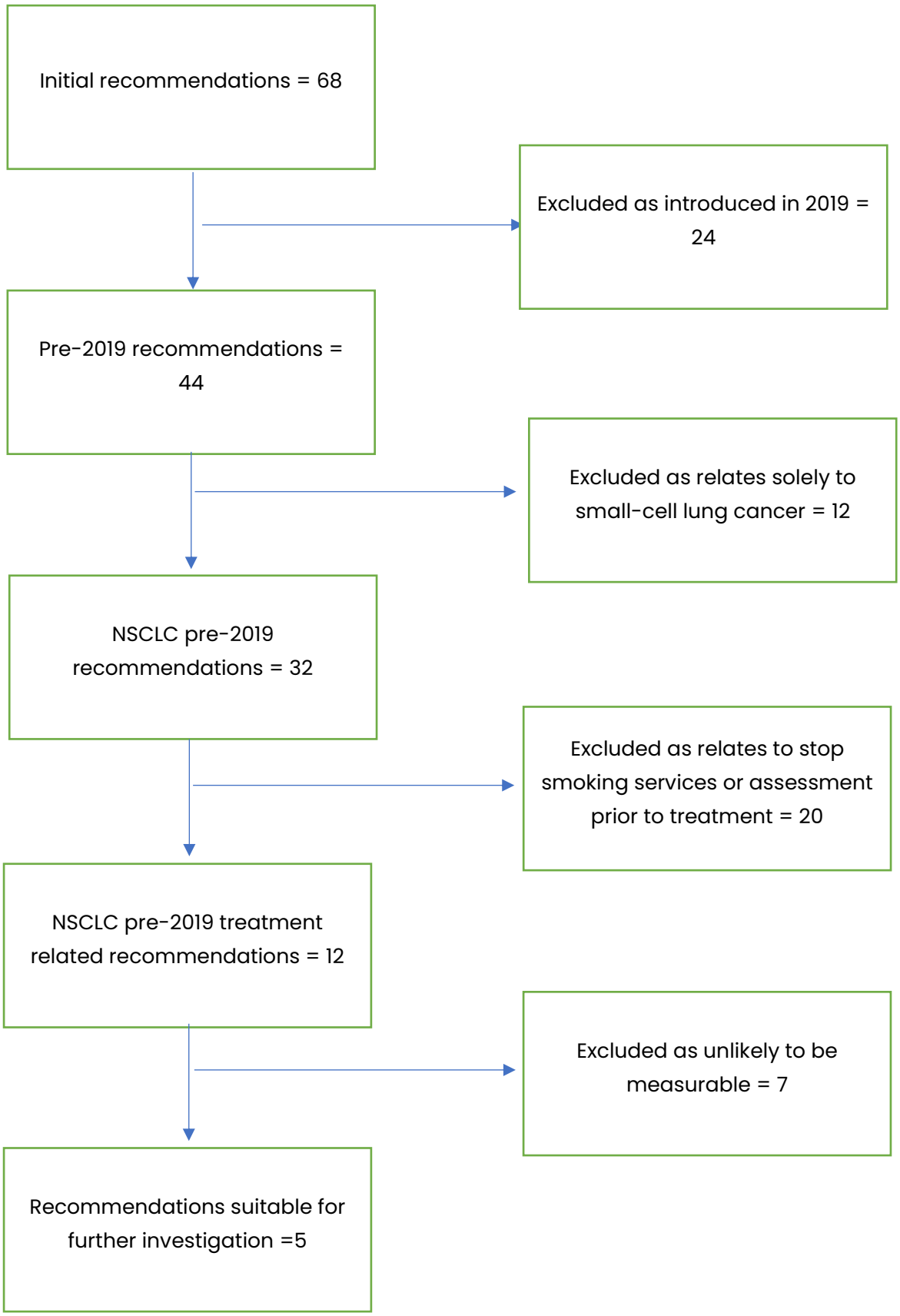
The first NICE clinical guideline for lung cancer diagnosis and management was published in 2011 (CG121), updated in 2019 (NG122). For this project we focused on only recommendations included in the 2011 guideline document as the cohort were diagnosed in 2015-2018.

The guideline gives several recommendations divided into six main themes:

1. Access to services and referral
2. Communication
3. Diagnosis and staging
4. Treatment
5. Palliative interventions and support
6. Follow-up and patient perspective

As this project was focussed on and used treatment datasets, only recommendations from the treatment section ('4') were considered.

Figure 1: Flow diagram demonstrating how many recommendations were investigated and exclusion reasons



The five recommendations suitable for assessment with the available data were as follows:

- 1.4.32 - Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery. Balance potential benefit in survival with the risk of additional toxicities. [2011]
- 1.4.34 - Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. [2011]
- 1.4.35 - Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter. [2011]
- 1.4.36 - Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [2011]
- 1.4.37 - For people with stage I–II NSCLC that are suitable for surgery, do not offer neoadjuvant treatment outside a clinical trial. [2011, amended 2019]

Each of these recommendations are to 'consider' or 'offer' treatment. However, data is only available on the treatment delivered to a patient and so the nuance of whether a treatment was 'considered' or 'offered' to a patient, but declined, or clinical factors meant the recommended treatment was not appropriate for a patient was not able to be investigated in this analysis.

Defining the cohorts and concordance

Overall cohort

This was defined as patients who had a record of a C33-C34 International Classification of Diseases (10th edition) (ICD10) code tumour (with morphology not including 8041, 8042, 8043, 8044, 8045 to exclude small cell lung cancer) diagnosed between 2015 and 2018 within the National Cancer Registration Dataset (NCRD) (25). Further inclusion criteria for patients were applied as standard (26) with only patients resident in England, finalised, non-duplicated cases with a sensible age (between 0 and 200 years old) and known gender included. Patients recorded as death certificate only or with multiple malignant tumours (excluding C44) at any point were excluded due to the likely impact that this would have on their treatment history. Patients were also excluded where the TNM stage at diagnosis (1-4) was unknown. This overall cohort was subsequently used for sub-cohort definitions (see below).

Defining receipt of treatment

Surgery was defined as a patient having a record of major lung cancer site-specific surgery (an attempt to surgically remove the whole of the primary tumour defined using lung cancer specific Operating Procedure Codes Supplement (OPCS) codes for resection of primary tumour taken from previous work (27)) within one month pre-diagnosis to six months post-diagnosis in the Hospital Episode Statistics Admitted Patient Care (HES APC) or NCRD treatment dataset.

Chemotherapy was defined as a patient having a record of chemotherapy recorded in the systemic anti-cancer therapy (SACT) or NCRD treatment dataset within one month pre-diagnosis and six months post-diagnosis. Adjuvant/postoperative chemotherapy was further defined as chemotherapy within 84 days inclusive of a patient's first surgery date, with this definition based on clinician guidance, with the overall chemotherapy inclusion time frame extended to allow for adjuvant chemotherapy delivered after surgery which took place towards the end of the six-month time frame for surgery.

Radiotherapy was defined as a patient having a record of radiotherapy recorded in the Radiotherapy Data Set (RTDS) or NCRD treatment dataset within one month pre-diagnosis and six months post-diagnosis. Radical radiotherapy was defined as a patient having a record of radiotherapy in the RTDS with a prescribed dose greater than 50 Gray and more than 20 fractions, within six months of diagnosis, with this definition based on clinician guidance.

Treatment given as part of a clinical trial was defined as a patient having a record of being treated in a clinical trial in either the SACT or NCRD treatment dataset.

Specific sub-cohorts

Cohort for recommendation 1.4.32 - Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery. Balance potential benefit in survival with the risk of additional toxicities.

This sub-cohort was restricted to patients with stages 2-3a and good performance status (0-1), with this definition based on clinician guidance.

Hence, the cohort for recommendation 1.4.32 was defined as patients from the overall NSCLC cohort diagnosed at stage 2 -3a (including those with stage recorded as 3 with no substage recorded) who had no record of surgery and a performance status of 0 or 1 recorded from the National Lung Cancer Audit.

Concordance with recommendation 1.4.32 was defined as patients who had chemotherapy and radical radiotherapy recorded, with chemotherapy occurring before radiotherapy but within 90 days of each other and both within one month pre-diagnosis and six months post-diagnosis.

Cohort for recommendation 1.4.34 - Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC.

The cohort for 1.4.34 was defined as patients from the overall NSCLC cohort diagnosed at TNM stage T1a-4, N1-2, M0 with performance status of 0 or 1 recorded from the National Lung Cancer Audit, who had surgery.

Concordance to recommendation 1.4.34 was defined as patients who had postoperative chemotherapy recorded. A sensitivity analysis was also included where the time frame of postoperative chemotherapy occurring within 84 days of surgery was based on the latest date of relevant surgery for a patient, rather than the first relevant surgery.

Cohort for recommendation 1.4.35 - Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter.

Tumour size is not recorded in routine datasets, so it is not possible to restrict cohort appropriately here, although T2b-T4 provides a rough proxy for the tumour size.

The cohort for 1.4.35 was defined as patients from the overall NSCLC cohort diagnosed at TNM stage T2b–4, N0, M0 NSCLC who had surgery and performance status of 0 or 1 recorded from the National Lung Cancer Audit.

Concordance to recommendation 1.4.35 was defined as patients who had postoperative chemotherapy recorded. A sensitivity analysis was also included where the time frame of postoperative chemotherapy occurring within 84 days of surgery was based on the latest date of relevant surgery for a patient, rather than the first relevant surgery.

Cohort for recommendation 1.4.36 - Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy.

Adjuvant chemotherapy was defined as within 84 days of surgery but only the first chemotherapy treatment post-surgery was chosen so that only first line treatment was used.

The cohort for 1.4.36 was defined as patients from the overall NSCLC cohort who had surgery and adjuvant chemotherapy. A sensitivity analysis was also included where the time frame of adjuvant chemotherapy occurring within 84 days of surgery was based on the latest date of relevant surgery for a patient, rather than the first relevant surgery.

Concordance to recommendation 1.4.36 was defined as patients where the first adjuvant chemotherapy treatment was cisplatin in combination with at least one other drug.

Cohort for recommendation 1.4.37 - For people with stage I–II NSCLC that are suitable for surgery, do not offer neoadjuvant treatment outside a clinical trial.

The cohort for 1.4.37 was defined as patients from the overall NSCLC cohort diagnosed at stage 1-2 who had surgery and who had no record of being treated in a clinical trial prior to surgery.

Concordance to recommendation 1.4.37 was defined as patients who had neither chemotherapy nor radiotherapy recorded prior to the date of surgery.

Statistical analysis

All statistical analysis was conducted using R version 4.4.0 with regression analyses carried out using the lme4 package. A p value of <0.05 was taken as significant. Details of patient demographics and tumour characteristics including stage, gender, age, ethnicity, deprivation, and comorbidity score were extracted from routinely collected datasets held

by the NDRS. Performance status was extracted from the National Lung Cancer Audit datasets for the appropriate years.

Age at treatment start date was grouped into five broad categories (<45, 45-54, 55-64, 65-74 and 75+ years), deprivation quintile was based on the full 2019 Index of Multiple Deprivation for patient area of residence. The relatively small numbers within the cohorts for each recommendation meant it was not feasible to use granular ethnic categories and so ethnicity was grouped into White and Minority ethnic groups categories, with the latter defined as Asian, Black, Mixed or Other ethnicity based on the Census groupings (28). Comorbidity score was defined based on the Charlson comorbidity index looking at the period from 27 months to 3 months prior to the cancer diagnosis and grouped to a score of 0, 1, 2 or 3+. For non-ordered categorical variables, the most common category was used as the reference category. This meant that male gender, 65-74 age group, White ethnicity, the least deprived quintile, 0 comorbidity score and diagnosed in 2015 were the reference groups. The earliest stage included in each sub-cohort was used as the reference and West Midlands was used as the reference Cancer Alliance.

Concordance was defined as a binary yes or no variable and percentages concordant within each category of the explanatory variables were calculated. Unadjusted logistic regression was then carried out for gender, age, ethnicity, deprivation, comorbidity score, stage and diagnosis year to calculate an unadjusted odds ratio for concordance to the recommendation. A mixed effects model was then produced using Cancer Alliance as the random effect to generate adjusted odds ratios for each potential explanatory variable, accounting for potential clustering of observations within Cancer Alliances. An additional mixed effects model with an interaction term between age and comorbidity score was also produced.

The relationship between Cancer Alliance and concordance to each recommendation was assessed by using an ANOVA test to compare the full mixed effects model to a model including all the predictor variables but no Cancer Alliance random effect.

Results

Recommendation 1.4.32 - Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery. Balance potential benefit in survival with the risk of additional toxicities

There were 5,517 patients in the sub-cohort for recommendation 1.4.32, of whom 1,001 received treatment concordant to this recommendation (18.1%). The highest percentage receiving chemoradiotherapy was for those aged 45-54 (34.2%) and the lowest percentage for those with 3+ comorbidity score (6.7%). In the adjusted model, age group was significantly associated with receiving chemoradiotherapy, with those in the 45-54 and 55-64 age groups being significantly more likely than those in the 65–74 age group to receive chemoradiotherapy (adjusted odds ratio (AOR) of 1.85 and 1.55 respectively) and those in the 75+ age group less likely (AOR of 0.33). Those with a comorbidity score of 2 or 3+ were significantly less likely to receive chemoradiotherapy compared to those with comorbidity score of 0 (AOR of 0.63 and 0.36 respectively). Those in the most and third most deprived quintile were significantly less likely to receive chemoradiotherapy compared to the least deprived quintile (AOR of 0.68 and 0.73 respectively). There was no evidence for an association between gender and receipt of chemoradiotherapy. Broad ethnic category was significantly associated with receipt of chemoradiotherapy, chiefly relating to patients whose ethnicity was not stated/known, who were less likely to receive concordant treatment (AOR of 0.55). Stage had a statistically significant relationship with receipt of chemoradiotherapy with individuals diagnosed at stage 3 significantly more likely than those diagnosed at stage 2 to receive concordant treatment (AOR of 2.00). More recent diagnosis year was also associated with receipt of chemoradiotherapy with those diagnosed in 2018 more likely to receive concordant treatment than those diagnosed in 2015 (AOR of 1.48) (Table 1). There was considerable variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted analyses (Figure 2), and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.535 and the coefficient ranged from -0.911 to 0.812.

There was no statistically significant interaction between age and comorbidity score in the likelihood of a patient receiving chemoradiotherapy.

Table 1: Demographic breakdown of the cohort for recommendation 1.4.32, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[1]	Adjusted odds ratio (95% CI)	Adjusted overall p value[2]
Total	Total	5,517	100.0	1,001	18.1				
Gender	Female	2,337	42.4	412	17.6	0.94 (0.82-1.08)	0.395	0.92 (0.80-1.07)	0.296
	Male (ref)	3,180	57.6	589	18.5	1 (ref)		1 (ref)	
Age group	0-45	39	0.7	9	23.1	1.13 (0.53-2.40)	<0.001	1.02 (0.47-2.22)	<0.001
	45-54	298	5.4	102	34.2	1.97 (1.51-2.55)*		1.85 (1.41-2.44)*	
	55-64	1,027	18.6	300	29.2	1.56 (1.31-1.85)*		1.55 (1.29-1.85)*	
	65-74 (ref)	2,011	36.5	421	20.9	1 (ref)		1 (ref)	
	75+	2,142	38.8	169	7.9	0.32 (0.27-0.39)*		0.33 (0.27-0.40)*	
Ethnicity	Minority ethnic groups	171	3.1	31	18.1	0.99 (0.67-1.47)	0.171	0.72 (0.47-1.12)	0.026
	Not stated or known	151	2.7	19	12.6	0.64 (0.40-1.04)		0.55 (0.33-0.91)*	
	White (ref)	5,195	94.2	951	18.3	1 (ref)		1 (ref)	

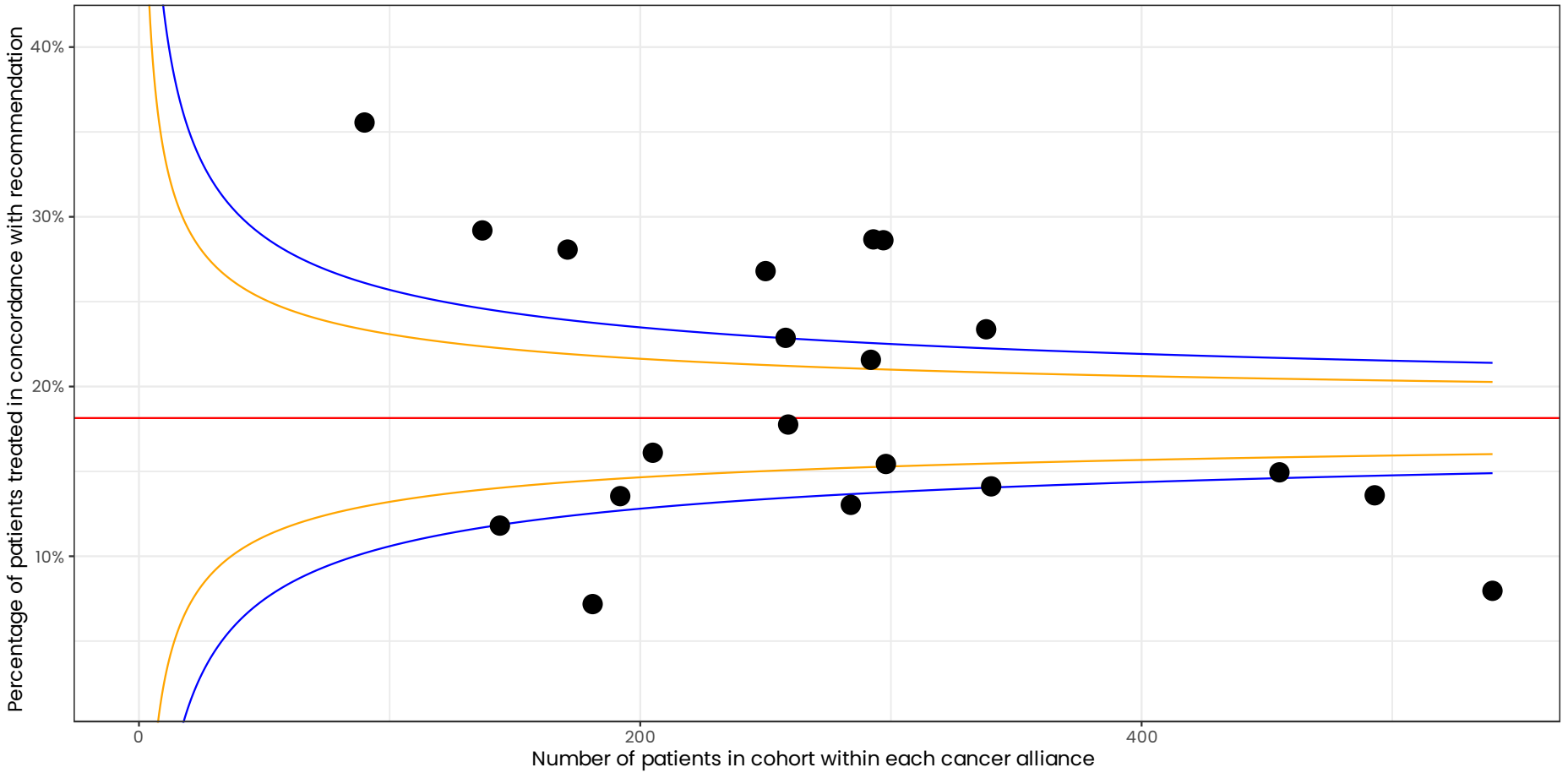
[1] Overall p value calculated using the likelihood ratio test

[2] Overall p value calculated using the chi-squared test

*denotes statistical significance at the p<0.05 confidence interval

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[1]	Adjusted odds ratio (95% CI)	Adjusted overall p value[2]
Deprivation quintile	1 - most deprived	1,472	26.7	255	17.3	0.86 (0.69-1.07)	0.421	0.68 (0.53-0.87)*	0.024
	2	1,151	20.9	221	19.2	0.97 (0.77-1.22)		0.83 (0.65-1.06)	
	3	1,105	20.0	187	16.9	0.83 (0.66-1.05)		0.73 (0.57-0.94)*	
	4	975	17.7	178	18.3	0.91 (0.72-1.16)		0.84 (0.65-1.09)	
	5 - least deprived (ref)	814	14.8	160	19.7	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	4,153	75.3	832	20.0	1 (ref)	<0.001	1 (ref)	<0.001
	1	754	13.7	115	15.3	0.72 (0.58-0.89)*		0.83 (0.66-1.04)	
	2	356	6.5	37	10.4	0.46 (0.33-0.66)*		0.63 (0.44-0.91)*	
	3+	254	4.6	17	6.7	0.29 (0.17-0.47)*		0.36 (0.22-0.61)*	
Stage group	2 (ref)	1,387	25.1	139	10.0	1 (ref)	<0.001	1 (ref)	<0.001
	3	4,130	74.9	862	20.9	2.37 (1.96-2.87)*		2.00 (1.64-2.45)*	
Diagnosis year	2015 (ref)	1,416	25.7	245	17.3	1 (ref)	<0.001	1 (ref)	<0.001
	2016	1,473	26.7	221	15.0	0.84 (0.69-1.03)		0.87 (0.71-1.08)	
	2017	1,441	26.1	278	19.3	1.14 (0.94-1.38)		1.19 (0.97-1.45)	
	2018	1,187	21.5	257	21.7	1.32 (1.09-1.61)*		1.48 (1.20-1.82)*	

Figure 2: Funnel plot for percentage of patients treated in concordance with recommendation 1.4.32 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean percentage for the whole cohort, blue lines indicate 95% confidence intervals around overall mean and yellow lines 80% confidence intervals.



Recommendation 1.4.34 - Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC

There were 3,280 patients in the sub-cohort for recommendation 1.4.34, of whom 1,689 received treatment concordant to this recommendation (51.5%). The highest percentage receiving postoperative chemotherapy was for those aged 45-54 (64.9%) and the lowest for those aged 75+ (27.2%). In the adjusted model, age group was significantly associated with receiving postoperative chemotherapy, with those in the 45-54 and 55-64 age groups significantly more likely than those in the 65–74 age group to receive this (AOR of 1.43 and 1.36 respectively) and those in the 75+ age group less likely (AOR of 0.29). Those with a comorbidity score of 2 or 3+ were significantly less likely to receive postoperative chemotherapy compared to those with comorbidity score of 0 (AOR of 0.59 and 0.53 respectively). There was no evidence for an association between gender, ethnicity, deprivation or diagnosis year and receiving treatment concordant to this recommendation. Stage had a statistically significant relationship with receiving postoperative chemotherapy with individuals diagnosed at stages 3&4 significantly more likely than those diagnosed at stages 1&2 to receive this (AOR of 1.27) (Table 2). There was variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted analyses (Figure 3), and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.311 and the coefficient ranged from -0.391 to 0.570.

There was no statistically significant interaction between age and comorbidity score in the likelihood of a patient receiving postoperative chemotherapy.

Table 2: Demographic breakdown of the cohort for recommendation 1.4.34, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[3]	Adjusted odds ratio (95% CI)	Adjusted overall p value[4]
Total	Total	3,280	100.0	1,689	51.5				
Gender	Female	1,538	46.9	822	53.4	1.16 (1.01-1.33)*	0.036	1.12 (0.97-1.29)	0.138
	Male (ref)	1,742	53.1	867	49.8	1 (ref)		1 (ref)	
Age group	0-45	71	2.2	35	49.3	0.80 (0.50-1.29)	<0.001	0.74 (0.45-1.20)	<0.001
	45-54	248	7.6	161	64.9	1.53 (1.15-2.02)*		1.43 (1.07-1.91)*	
	55-64	857	26.1	538	62.8	1.39 (1.17-1.66)*		1.36 (1.14-1.63)*	
	65-74 (ref)	1,387	42.3	760	54.8	1 (ref)		1 (ref)	
	75+	717	21.9	195	27.2	0.31 (0.25-0.37)*		0.29 (0.24-0.36)*	
Ethnicity	Minority ethnic groups	144	4.4	74	51.4	0.99 (0.71-1.39)	0.798	0.89 (0.62-1.28)	0.364
	Not stated or known	39	1.2	18	46.2	0.81 (0.43-1.52)		0.64 (0.33-1.26)	
	White (ref)	3,097	94.4	1,597	51.6	1 (ref)		1 (ref)	

[3] Overall p value calculated using the likelihood ratio test

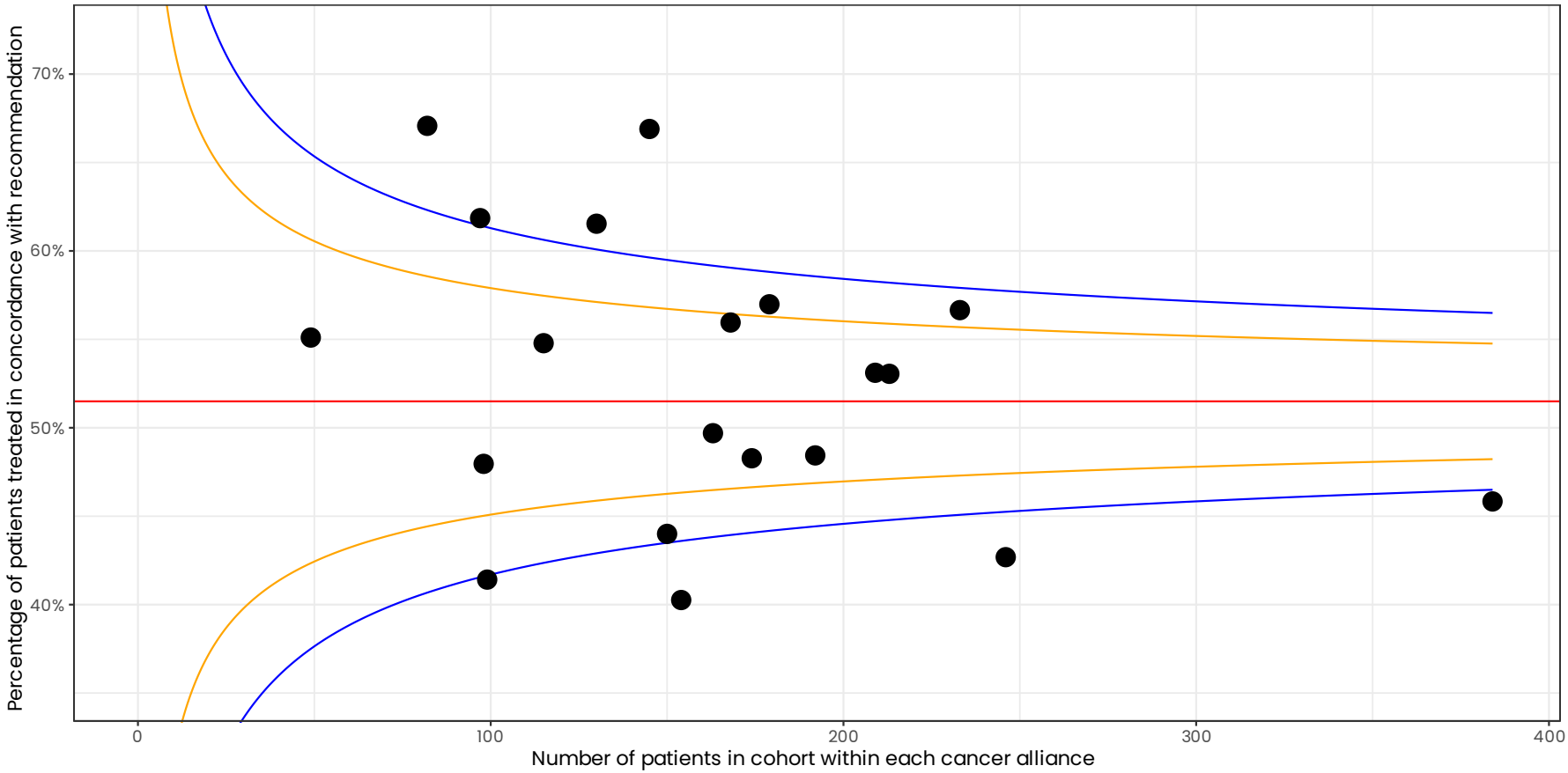
[4] Overall p value calculated using the chi-squared test

*denotes statistical significance at the p<0.05 confidence interval

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[3]	Adjusted odds ratio (95% CI)	Adjusted overall p value[4]
Deprivation quintile	1 - most deprived	852	26.0	440	51.6	1.03 (0.82-1.29)	0.895	0.92 (0.72-1.18)	0.636
	2	690	21.0	350	50.7	0.99 (0.79-1.25)		0.94 (0.73-1.21)	
	3	616	18.8	328	53.2	1.10 (0.87-1.39)		1.09 (0.85-1.41)	
	4	635	19.4	323	50.9	1.00 (0.79-1.26)		0.99 (0.77-1.28)	
	5 - least deprived (ref)	487	14.8	248	50.9	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	2,489	75.9	1,346	54.1	1 (ref)	<0.001	1 (ref)	<0.001
	1	482	14.7	226	46.9	0.75 (0.62-0.91)*		0.82 (0.67-1.01)	
	2	205	6.2	82	40.0	0.57 (0.42-0.76)*		0.59 (0.43-0.80)*	
	3+	104	3.2	35	33.7	0.43 (0.28-0.65)*		0.53 (0.34-0.82)*	
Stage group	1 & 2 (ref)	1,340	40.9	639	47.7	1 (ref)	<0.001	1 (ref)	0.001
	3 & 4	1,940	59.1	1,050	54.1	1.29 (1.13-1.49)*		1.27 (1.10-1.48)*	
Diagnosis year	2015 (ref)	728	22.2	385	52.9	1 (ref)	0.055	1 (ref)	0.062
	2016	832	25.4	398	47.8	0.82 (0.67-1.00)*		0.81 (0.66-1.01)	
	2017	887	27.0	454	51.2	0.93 (0.77-1.14)		0.91 (0.74-1.12)	
	2018	833	25.4	452	54.3	1.06 (0.87-1.29)		1.06 (0.86-1.31)	

In sensitivity analyses where the latest surgery date was used for the adjuvant chemotherapy inclusion timeframe rather than the first surgery date, there were some minor changes to odds ratios and p-values, but the statistically significant associations remained the same and the standard deviation for the random effect of Cancer Alliance remained similar.

Figure 3: Funnel plot for percentage of patients treated in concordance with recommendation 1.4.34 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean percentage for the whole cohort, blue lines indicate 95% confidence intervals around overall mean and yellow lines 80% confidence intervals.



Recommendation 1.4.35 - Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter

There were 2,067 patients in the sub-cohort for recommendation 1.4.35, of whom 736 received treatment concordant to this recommendation (35.6%). The highest percentage receiving postoperative chemotherapy was for those aged 45-54 (53.8%) and the lowest for those aged 75+ (14.4%). In the adjusted model age group was significantly associated with receiving postoperative chemotherapy, with those in the 45-54 and 55-64 age groups being significantly more likely than those in the 65–74 age group to receive this (AOR of 1.79 and 1.75 respectively) and those in the 75+ age group less likely (AOR of 0.28). Those with a comorbidity score of 2 or 3+ were significantly less likely to receive postoperative chemotherapy compared to those with comorbidity score of 0 (AOR of 0.5 and 0.42 respectively). There was no evidence for an association between gender, ethnicity, deprivation, or diagnosis year with receiving postoperative chemotherapy. Stage had a significant relationship with receiving postoperative chemotherapy with individuals diagnosed at stage 3 significantly more likely than those diagnosed at stages 1&2 to receive this (AOR of 1.63) (Table 3). There was some variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted alliances (Figure 4), and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.307 and the coefficient ranged from -0.540 to 0.456.

There was no statistically significant interaction between age and comorbidity score in the likelihood of a patient receiving postoperative chemotherapy.

Table 3: Demographic breakdown of the cohort for recommendation 1.4.35, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[5]	Adjusted odds ratio (95% CI)	Adjusted overall p value[6]
Total	Total	2,067	100.0	736	35.6				
Gender	Female	904	43.7	328	36.3	1.05 (0.88-1.26)	0.572	1.01 (0.83-1.22)	0.954
	Male (ref)	1,163	56.3	408	35.1	1 (ref)		1 (ref)	
Age group	0-45	31	1.5	7	22.6	0.47 (0.20-1.11)	<0.001	0.46 (0.19-1.11)	<0.001
	45-54	130	6.3	70	53.8	1.89 (1.30-2.73)*		1.79 (1.22-2.64)*	
	55-64	464	22.4	242	52.2	1.76 (1.40-2.21)*		1.75 (1.39-2.22)*	
	65-74 (ref)	879	42.5	336	38.2	1 (ref)		1 (ref)	
	75+	563	27.2	81	14.4	0.27 (0.21-0.36)*		0.28 (0.21-0.37)*	
Ethnicity	Minority ethnic groups	93	4.5	28	30.1	0.77 (0.49-1.21)	0.411	0.65 (0.40-1.08)	0.121
	Not stated or known	33	1.6	10	30.3	0.77 (0.37-1.64)		0.60 (0.27-1.33)	
	White (ref)	1,941	93.9	698	36.0	1 (ref)		1 (ref)	

[5] Overall p value calculated using the likelihood ratio test

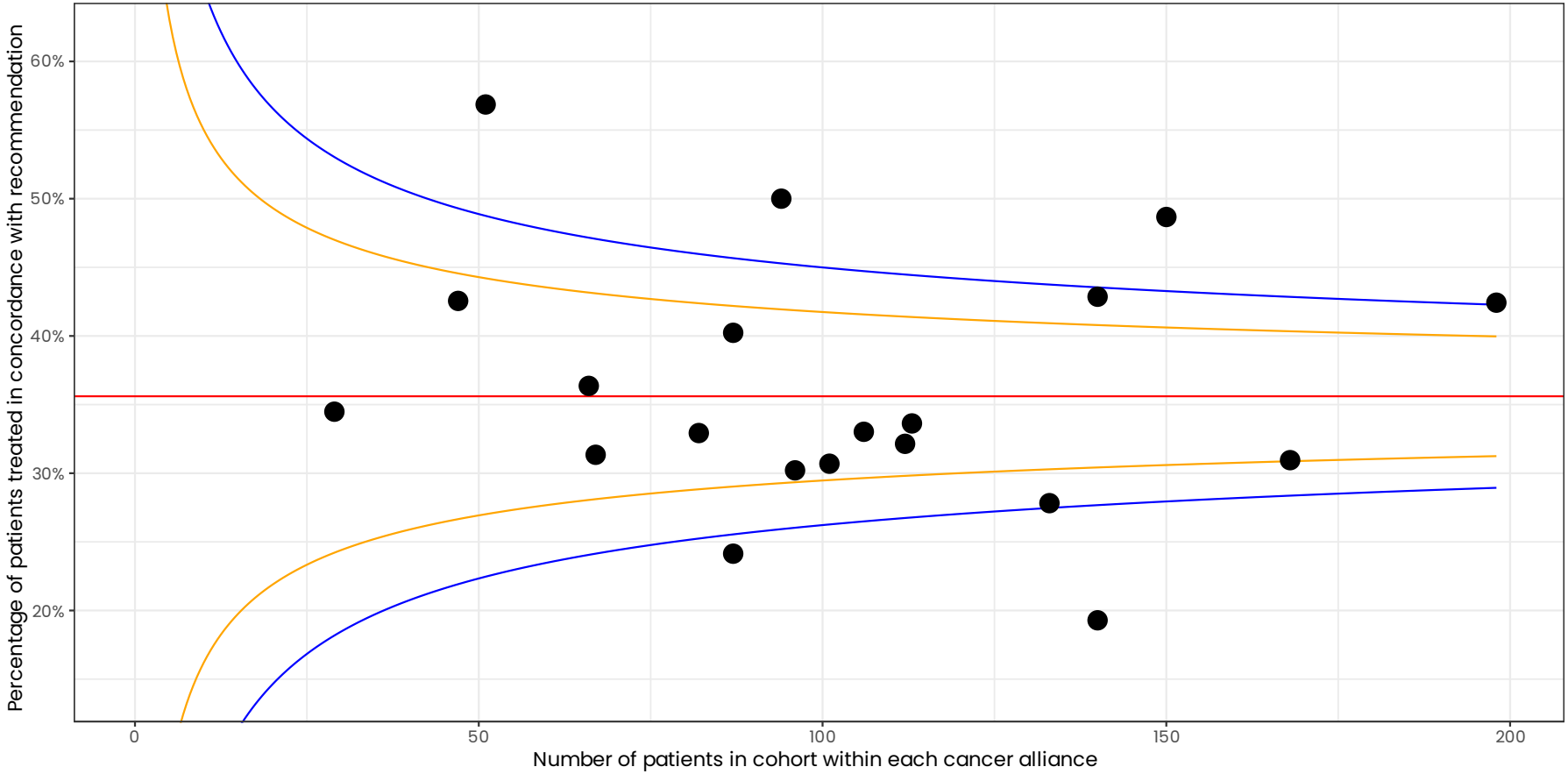
[6] Overall p value calculated using the chi-squared test

*denotes statistical significance at the p<0.05 confidence interval

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[5]	Adjusted odds ratio (95% CI)	Adjusted overall p value[6]
Deprivation quintile	1 - most deprived	481	23.3	204	42.4	1.52 (1.14-2.01)*	0.005	1.19 (0.87-1.64)	0.182
	2	415	20.1	152	36.6	1.19 (0.89-1.60)		1.05 (0.76-1.45)	
	3	425	20.6	138	32.5	0.99 (0.73-1.33)		0.87 (0.63-1.20)	
	4	376	18.2	121	32.2	0.98 (0.72-1.33)		0.85 (0.61-1.19)	
	5 - least deprived (ref)	370	17.9	121	32.7	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	1,590	76.9	612	38.5	1 (ref)	<0.001	1 (ref)	<0.001
	1	277	13.4	83	30.0	0.68 (0.52-0.90)*		0.75 (0.56-1.00)	
	2	121	5.9	26	21.5	0.44 (0.28-0.68)*		0.50 (0.31-0.80)*	
	3+	79	3.8	15	19.0	0.37 (0.21-0.66)*		0.42 (0.23-0.76)*	
Stage group	1 & 2 (ref)	1,809	87.5	618	34.2	1 (ref)	<0.001	1 (ref)	<0.001
	3	258	12.5	118	45.7	1.62 (1.25-2.11)*		1.63 (1.22-2.19)*	
Diagnosis year	2015 (ref)	387	18.7	148	38.2	1 (ref)	0.511	1 (ref)	0.715
	2016	516	25.0	175	33.9	0.83 (0.63-1.09)		0.91 (0.68-1.22)	
	2017	483	23.4	177	36.6	0.93 (0.71-1.23)		0.97 (0.72-1.30)	
	2018	681	32.9	236	34.7	0.86 (0.66-1.11)		0.86 (0.65-1.14)	

In sensitivity analyses where the latest surgery date was used for the adjuvant chemotherapy inclusion timeframe rather than the first surgery date, there were some minor changes to odds ratios and p-values, but the statistically significant associations remained the same and the standard deviation for the random effect of Cancer Alliance remained very similar.

Figure 4: Funnel plot for percentage of patients treated in concordance with recommendation 1.4.35 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean percentage for the whole cohort, blue lines indicate 95% confidence intervals around overall mean and yellow lines 80% confidence intervals.



Recommendation 1.4.36 - Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy

There were 3,506 patients in the sub-cohort for recommendation 1.4.36, of whom 2,228 received treatment concordant to this guideline (63.5%). The highest percentage receiving cisplatin-based combination adjuvant chemotherapy was for those aged <45 (76.7%) and the lowest for those with a comorbidity score of 3+ (29.9%) In the adjusted model age group was significantly associated with receiving recommended treatment, with those in the <45, 45-54 and 55-64 age groups being significantly more likely than those in the 65–74 age group to receive this (AOR of 2.57, 2.17 and 1.6 respectively) and those in the 75+ age group less likely (AOR of 0.40). Those with a comorbidity score of 2 or 3+ were significantly less likely to receive cisplatin-based combination adjuvant chemotherapy compared to those with comorbidity score of 0 (AOR of 0.63 and 0.22 respectively). There was no evidence for an association between gender, ethnicity, or deprivation and receiving recommended treatment. Stage had a significant relationship with receiving cisplatin-based combination adjuvant chemotherapy with individuals diagnosed at stage 4 significantly less likely than those diagnosed at stage 1 to receive this (AOR of 0.27). More recent diagnosis year was also associated with receiving recommended treatment with those diagnosed in 2017 and 2018 more likely to receive this than those diagnosed in 2015 (AOR of 1.37 and 1.39 respectively) (Table 4). There was considerable variation in the levels of concordance to this recommendation by Cancer Alliance, both in unadjusted analyses (Figure 5), and the adjusted regression analyses with an overall p value of <0.001 for the inclusion of Cancer Alliance as a random effect in the model. The standard deviation for the Cancer Alliance random effect was 0.598 and the coefficient ranged from -1.15 to 1.16.

There was no statistically significant interaction between age and comorbidity score in the likelihood of a patient receiving cisplatin-based combination adjuvant chemotherapy.

Table 4: Demographic breakdown of the cohort for recommendation 1.4.36, number and percentage of the cohort treated in concordance with the recommendation and odds ratios for recommendation-concordance from unadjusted analyses and adjusted for all the other variables

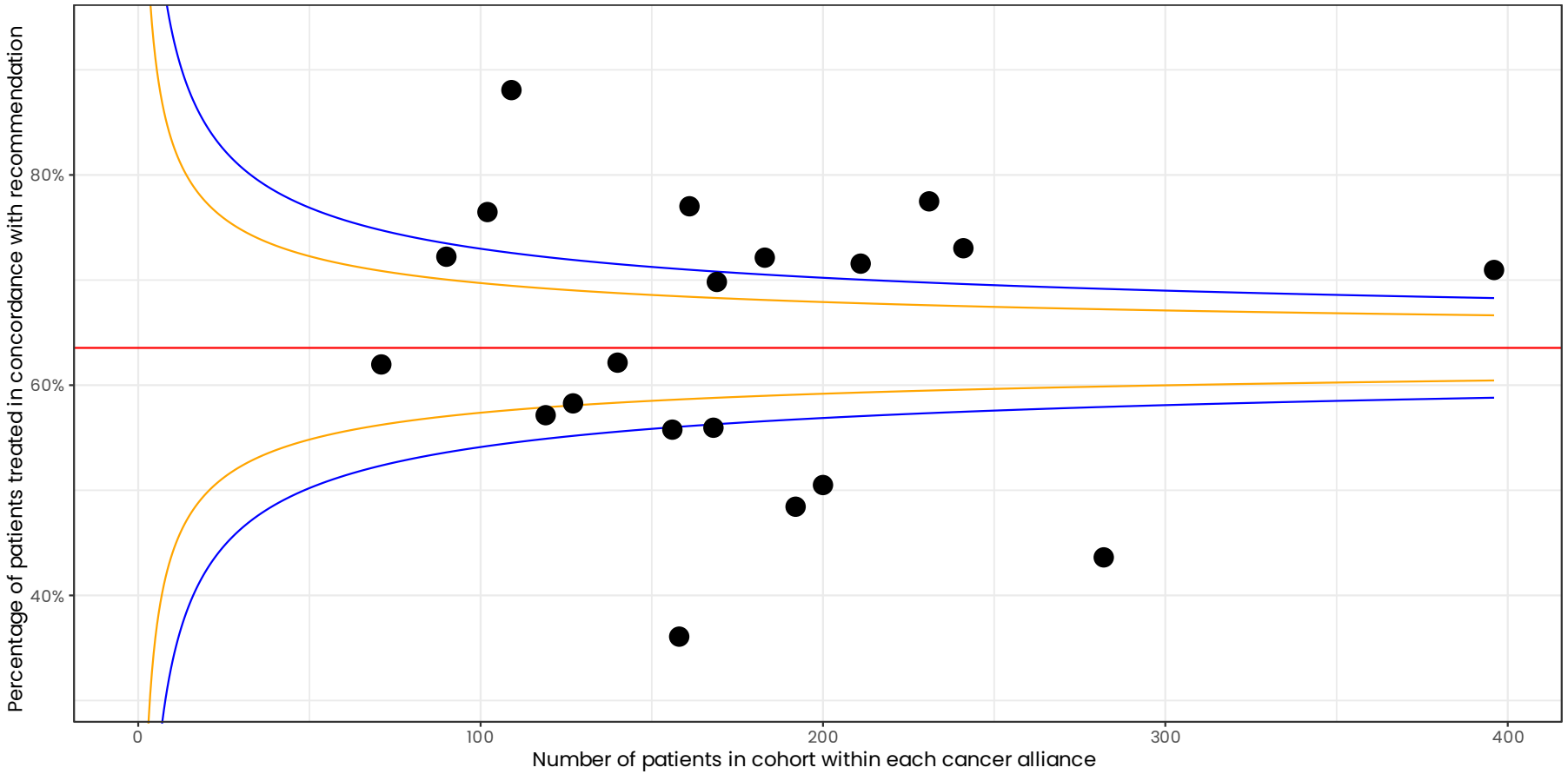
Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[7]	Adjusted odds ratio (95% CI)	Adjusted overall p value[8]
Total	Total	3,506	100.0	2,228	63.5				
Gender	Female	1,676	47.8	1,082	64.6	1.09 (0.95-1.25)	0.234	1.08 (0.93-1.25)	0.324
	Male (ref)	1,830	52.2	1,146	62.6	1 (ref)		1 (ref)	
Age group	0-45	73	2.1	56	76.7	2.08 (1.2-3.61)*	<0.001	2.57 (1.43-4.63)*	<0.001
	45-54	335	9.6	252	75.2	1.91 (1.46-2.50)*		2.17 (1.62-2.90)*	
	55-64	1,108	31.6	793	71.6	1.59 (1.35-1.87)*		1.6 (1.34-1.91)*	
	65-74 (ref)	1,562	44.6	958	61.3	1 (ref)		1 (ref)	
	75+	428	12.2	169	39.5	0.41 (0.33-0.51)*		0.40 (0.31-0.5)*	
Ethnicity	Minority ethnic groups	181	5.2	117	64.6	1.05 (0.77-1.44)	0.804	0.99 (0.69-1.43)	0.999
	Not stated or known	52	1.5	35	67.3	1.19 (0.66-2.13)		1.01 (0.54-1.89)	
	White (ref)	3,273	93.4	2,076	63.4	1 (ref)		1 (ref)	
	1 - most deprived	921	26.3	608	66.0	1.21 (0.97-1.51)	0.213	1.01 (0.78-1.30)	0.523

[7] Overall p value calculated using the likelihood ratio test
[8] Overall p value calculated using the chi-squared test
*denotes statistical significance at the p<0.05 confidence level

Characteristic	Category	Number in cohort	Percentage of cohort (%)	Number concordant	Percentage concordant (%)	Unadjusted odds ratio (95% CI)	Unadjusted overall p value[7]	Adjusted odds ratio (95% CI)	Adjusted overall p value[8]
Deprivation quintile	2	741	21.1	470	63.4	1.08 (0.86-1.36)		1.01 (0.79-1.31)	
	3	658	18.8	400	60.8	0.97 (0.77-1.22)		0.93 (0.72-1.20)	
	4	642	18.3	415	64.6	1.14 (0.90-1.45)		1.16 (0.90-1.50)	
	5 - least deprived (ref)	544	15.5	335	61.6	1 (ref)		1 (ref)	
Comorbidity score	0 (ref)	2,799	79.8	1,828	65.3	1 (ref)	<0.001	1 (ref)	<0.001
	1	462	13.2	285	61.7	0.86 (0.70-1.05)		0.89 (0.71-1.11)	
	2	168	4.8	92	54.8	0.64 (0.47-0.88)*		0.63 (0.45-0.89)*	
	3+	77	2.2	23	29.9	0.23 (0.14-0.37)*		0.22 (0.13-0.38)*	
Stage group	1 (ref)	363	10.4	230	63.4	1 (ref)	<0.001	1 (ref)	<0.001
	2	1,507	43.0	992	65.8	1.11 (0.88-1.41)		1.19 (0.92-1.53)	
	3	1,373	39.2	913	66.5	1.15 (0.90-1.46)		1.18 (0.91-1.53)	
	4	263	7.5	93	35.4	0.32 (0.23-0.44)*		0.27 (0.19-0.39)*	
Diagnosis year	2015 (ref)	854	24.4	506	59.3	1 (ref)	0.012	1 (ref)	0.008
	2016	847	24.2	534	63.0	1.17 (0.97-1.43)		1.22 (0.99-1.51)	
	2017	903	25.8	592	65.6	1.31 (1.08-1.59)*		1.37 (1.11-1.69)*	
	2018	902	25.7	596	66.1	1.34 (1.10-1.63)*		1.39 (1.12-1.72)*	

In sensitivity analyses where latest surgery date was used for the inclusion timeframe for adjuvant chemotherapy rather than the first surgery date, there were some minor changes to odds ratios and p-values, but the statistically significant associations remained the same and the standard deviation for the random effect of Cancer Alliance remained very similar.

Figure 5: Funnel plot for percentage of patients treated in concordance with recommendation 1.4.36 by Cancer Alliance. Black dots represent Cancer Alliances, red line indicates overall mean percentage for the whole cohort, blue lines indicate 95% confidence intervals around overall mean and yellow lines 80% confidence intervals.



Recommendation 1.4.37 - For people with stage I–II NSCLC that are suitable for surgery, do not offer neoadjuvant treatment outside a clinical trial

There were 13,705 patients in the sub-cohort for recommendation 1.4.37, of whom 13,633 received treatment concordant to this recommendation (99.5%). This extremely high concordance meant it was not feasible or meaningful to provide demographic breakdowns or regression analyses for this recommendation.

Discussion

Findings from analysis

The highest concordance was seen for recommendation 1.4.37 (do not offer neoadjuvant treatment outside a clinical trial for stage I-II NSCLC suitable for surgery) at 99.5%, followed by 1.4.36 (offer cisplatin based combination chemotherapy regimen for adjuvant chemotherapy) at 63.5%, then 1.4.34 (offer postoperative chemotherapy for those with good performance status and T1a-4, N1-2, M0) at 51.5%, while the similar recommendation 1.4.35 only had 35.6% concordance indicating that postoperative chemotherapy is less likely to be used for those with T2b-4, N0, M0 disease compared to those with nodal involvement. The lowest concordance was seen for 1.4.32 (consider chemoradiotherapy for stage II or III patients not suitable for surgery), perhaps reflecting the strength of this recommendation to 'consider' rather than 'offer' this treatment and in agreement with the NLCA (4) and previous studies that have shown low usage of chemoradiotherapy (16).

For each recommendation where adjusted analyses were possible, the likelihood of concordance decreased with increasing age group and comorbidity score, as seen for previous studies from other countries (7; 8; 11; 12; 18; 19; 20; 21; 22). Age group was the variable with the largest AOR range, with comorbidity score and stage also tending to have large AOR ranges. Only recommendation 1.4.32 (use of chemoradiotherapy) showed a statistically significant relationship between deprivation quintile and concordance where the most deprived and middle quintiles were less likely to be concordant compared to the least deprived quintile. Our data offers no clear explanation for this, but a range of hypotheses are plausible, including high frequency of healthcare facility attendances required for chemoradiotherapy (so travel cost and time required may be having a greater impact for those most deprived), residual confounding by morbidity or performance status not accounted for in the measured variables, or differential assessment of the benefits and risks by clinicians and/or patients. There was no statistically significant variation by ethnicity, except for recommendation 1.4.32 and in this case this is likely to be driven by those with unknown or unreported ethnicity being less likely to be guideline concordant.

For recommendations 1.4.34 and 1.4.35 concordance was more likely at later compared to earlier stages, which may be due to assessment that later stage patients having surgery have a higher risk of recurrence justifying more frequent use of adjuvant treatment. However, for patients who had both surgery and adjuvant chemotherapy and so were included in the cohort eligible for recommendation 1.4.36, concordance was least likely at stage 4, perhaps due to these patients being more likely to have carboplatin-based chemotherapy than cisplatin. The relationship between concordance and diagnosis year was varied, with concordance to 1.4.32 and 1.4.36 more likely with increasing diagnosis year, but no significant relationship for 1.4.34 or 1.4.35, perhaps indicating that the latter

two recommendations were already well established while the others have taken more time to be implemented fully.

There was significant variation in the levels of concordance to each treatment recommendation by Cancer Alliance. The Cancer Alliance random effect was statistically significant, and the alliances had a range of coefficients. This suggests that there may be geographical variation in the use of guideline recommended treatments and could potentially highlight areas for improvement. Recommendation 1.4.36 had the largest standard deviation and coefficient range by Cancer Alliance and recommendations 1.4.34 and 1.4.35 had the smallest.

Limitations

This project has several limitations. It was only possible to assess concordance to a small proportion of the treatment related NSCLC treatment guideline recommendations using currently available data, which meant that concordance was determined on a recommendation-by-recommendation basis, and it was not possible to assess whether the full spectrum of treatment that a patient received was as recommended by the guideline. Our analyses of the recommendations are based on cohorts of patients who either did or did not have major resective surgery, and so may incorrectly characterise some patients who receive more minor surgery. Additionally, the percentage of patients receiving surgery varies by demographics and geography (29) so the percentage of patients receiving both appropriate surgery and recommendation concordant adjuvant treatment is likely to be lower. The role of surgery would be useful to investigate to provide a fuller picture of whether overall treatment for a patient was as recommended.

Additionally, this study used data on patients diagnosed from 2015-2018 and looked at recommendations included in the 2011 NICE guideline, which was superseded by a more recent guideline in 2019. The analysis reports on practice prior to the COVID-19 pandemic, which is known to have had an impact on cancer treatment practice (30) and so perhaps limits the findings that could be taken from this study to inform current practice, and the trends seen here, particularly around increasing concordance by diagnosis year for recommendations 1.4.32 and 1.4.36, may have been interrupted by COVID. However, as the first study looking at concordance to lung cancer treatment guideline recommendations in England the findings provide a valuable baseline for adherence and possible areas for investigation around inequalities in concordance.

The comprehensiveness of this analysis relies on availability and completeness of treatment data, with missing data potentially leading to incorrect concordance status for an individual. Additionally, the analytical approach taken here places population wide restrictions on treatment such as timings between treatment events whereas real-world treatment decisions might have more flexibility i.e., longer time to starting adjuvant treatment if longer needed for surgical recovery or multiple surgeries potentially meaning chemotherapy began later. Some of these issues were investigated in sensitivity analyses

however, with latest surgery date used instead of earliest for inclusion of adjuvant chemotherapy and this did not alter which variables had a statistically significant relationship with concordance. Furthermore, a substantial limitation of the analysis is that the recommendations are to 'consider' or 'offer' treatment to patients, but it is not possible from currently available data to determine whether a particular treatment was 'considered' or 'offered' to a patient, but only whether a patient received a particular treatment. This may mean that the recommendation was actually met for a higher percentage of patients than identified here.

An additional potential limitation is around the stage variable. This variable is derived using all the appropriate registry data available within a 4-month period from the date of diagnosis or until the date of the first post-treatment MDT (whichever is shorter). However, this may also include staging from pathology reports and so may not accurately reflect the staging information that the clinicians had when deciding on treatment options for the patient.

While these analyses included multiple years to include relatively large numbers of patients, the cohorts for each individual recommendation were relatively small in most cases and so the analyses may have limited power to detect differences in concordance. This was especially the case for recommendation 1.4.37 which had an extremely low percentage of patients non-concordant which meant further breakdowns were not feasible, but also limited the granularity of data that could be presented for concordance by ethnic category. A further potential impact of small numbers was the finding of no statistically significant interaction between age and comorbidity score. The relatively small numbers available for these analyses mean that analyses splitting by multiple variables may be underpowered and comorbidity score has limitations as a proxy for how well someone is likely to tolerate treatment. However, the finding here of an independent contribution of age could illustrate that there are genuine inequalities in treatment by age that could be improved.

There are also several wider questions that were not within the scope of this project, but which are important for understanding the wider context of guideline concordance, such as the association between NICE guideline concordance and survival or quality of life. It would also be useful to investigate the reasons for non-concordance with guideline recommended treatment including the role that patient choice may play in this. Reasons for non-concordance and patient choice could be explored through qualitative analysis or clinical audits of a portion of patients who received non-concordant treatment. We excluded patients with multiple tumours from the cohort for this study, but further research could potentially analyse whether patients with multiple tumours are more or less likely to be treated in concordance with recommendations compared to patients with a single tumour. It would also be useful to investigate what treatment, if any, patients are having if they are identified as not having recommendation concordant treatment.

What would be needed for a more comprehensive analysis

The high proportion of recommendations that were identified here as unsuitable currently for their concordance to be assessed suggests that there is the potential for improving the quality and scope of data collection or the potential for NICE guidelines of the future to have more of an explicit focus on how progress and concordance to the recommendations of these guidelines could be measured. It would be particularly useful to have a more comprehensive understanding of a patient's condition than comorbidity score (such as frailty etc.) to further investigate the interaction between age and patient fitness, and hence whether the differences in concordance seen by age reflects decisions based on a patient's fitness for treatment or treatment inequalities. It would also be useful to have data on reasons for a patient not having treatment, including whether patient choice played a part in non-concordant treatment and the potential contribution of barriers patients face to taking up an offer of treatment.

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