ORIGINAL ARTICLE

Improving Outcomes in NSCLC: Optimum Dose Fractionation in Radical Radiotherapy Matters

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ABSTRACT

Introduction: We analyzed a comprehensive national radiotherapy data set to compare outcomes of the most frequently used moderate hypofractionation regimen (55 Gy in 20 fractions) and conventional fractionation regimen (60–66 Gy in 30–33 fractions).

Methods: A total of 169,863 cases of NSCLC registered in England from January 2012 to December 2016 obtained from the Public Health England were divided into cohort 1 (training set) diagnosed in 2012 to 2013 and cohort 2 (validation set) diagnosed in 2014 to 2016. Radiotherapy data were obtained from the National Radiotherapy Dataset and linked by National Health Service number to survival data from the Office of National Statistics and Hospital Episode Statistics, from which surgical data and Charlson comorbidity index were obtained. Of 73,186 patients with stages I to III NSCLC, 12,898 received radical fractionated radiotherapy (cohort 1—4894; cohort 2—8004). The proportional hazards model was used to investigate overall survival from time of diagnosis. Survival was adjusted for the prognostic factors of age, sex, stage of disease, comorbidity, other radical treatments, and adjuvant chemotherapy, and the difference between the treatment schedules was summarized by hazard ratio (HR) and 95% confidence interval. The significance of any difference was evaluated by the log likelihood test.

Results: Of patients with stages I to III NSCLC, 17% to 18% received radical fractionated radiotherapy. After adjustment for independent prognostic factors of age, stage, comorbidity, and other radical and adjuvant treatments, patients in cohort 1 treated with the 2.75 Gy per fraction regimen had a median survival of 25 months compared with 29 months for patients treated with the 2 Gy per fraction regimen (HR = 1.16, $p = 0.001$). Similarly, in cohort 2, the respective median survival values were 25 and 28 months (HR = 1.10, $p = 0.02$).

Conclusions: Big data analysis of a comprehensive national cohort of patients with NSCLC treated in England suggests that compared with a 4-week regimen of 55 Gy in 20 fractions, a 6-week regimen of conventional daily fractionation to a dose of 60 to 66 Gy at 2 Gy per fraction is associated with a survival benefit. Within the limitations of the retrospective big data analysis with potential selection bias and in the absence of randomized trials, the results suggest that conventional fractionation regimens should remain the standard of care.

Keywords: Localized and locally advanced non–small cell lung cancer; Radical radiotherapy fractionation; Prognosis by dose fractionation; Hypofractionated radiotherapy

Introduction

Radical radiotherapy remains the principal treatment of inoperable locally advanced NSCLC and operable

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tumor not medically suitable for surgery. The addition of sequential or concurrent chemotherapy[1–3] and more recently adjuvant immunotherapy[4,5] is associated with improved survival outcome. The last three decades have seen considerable improvements in radiotherapy technologies which allow for improved sparing of critical normal tissues and enable dose escalation.[6–9] Nevertheless, survival benefit for the use of innovative technologies alone and for dose escalation remains unproven.[10]

Altered fractionation provides an alternative strategy for improving radiotherapy outcomes. Extremely hypofractionated treatments delivered using high-precision techniques (stereotactic ablative or body radiotherapy [SABR, SBRT]) have become accepted practice for small localized NSCLC and seem superior to conventionally fractionated standard dose radical radiotherapy.[11]

More moderately hypofractionated treatments (using doses-per-fraction of 2.5–2.75 Gy) have also entered clinical practice for radiotherapy of locally advanced NSCLC. Compared with conventionally fractionated radiotherapy (at 2 Gy per fraction), moderate hypofractionation permits shorter and more convenient treatments, which modeling studies suggest should provide equivalent or potentially superior efficacy, although this has not been subject to randomized studies. In the United Kingdom, the prevalent dose fractionation in patients with inoperable localized and locally advanced NSCLC not suitable for surgery or SABR is moderate hypofractionation, usually 55 Gy in 20 fractions in 4 weeks (2.75 Gy per fraction).

In the absence of randomized studies, the belief in efficacy of moderately hypofractionated regimens is based on outcomes reported in noncomparative retrospective studies.[12,13] Owing to its popularity and convenience, the 55-Gy 20-fraction regimen has gained the status of "standard" radiotherapy in a randomized phase 2 study of concomitant versus sequential chemoradiotherapy (SOCCAR)[14] and has since been considered a standard arm in new randomized studies (AdScan).[15] To reduce attendance in the hospital during the coronavirus disease 2019 (COVID-19) pandemic, the regimen has become widely adopted as an alternative to a more prolonged 6-week treatment.

The availability of a comprehensive national radiotherapy data set in England enables big data analysis of different radiotherapy regimens. Population analysis of a comprehensive national data set has already been found to be valuable, revealing a relationship between radiotherapy use and NSCLC population survival.[16] The earlier analysis also provided indirect evidence of a survival benefit for radical radiotherapy,[16] a finding not so far subject to a randomized trial.

In this study, we analyzed a comprehensive national data set to evaluate the comparative efficacy of radical radiotherapy fractionation regimens in localized and locally advanced NSCLC, with a particular focus on the efficacy of the most frequently used hypofractionation regimen of 55 Gy in 20 fractions compared with conventional fractionation at 2 Gy per fraction, which is considered the international standard.

Materials and Methods

Cohort Studied

A list of all NSCLCs registered in England from 2012 to 2016 was obtained from the Public Health England. Data were initially available for NSCLC diagnosed in 2012 to 2013 (cohort 1) and have been reported previously in relation to radiotherapy use.[16] In this analysis, it has been used as a training data set, with NSCLC diagnosed from 2014 to 2016 inclusive (cohort 2) forming a validation data set. In total, 169,863 cases of NSCLC were identified.

Data items obtained from the registry database included the National Health Service (NHS) number, date of birth, sex, diagnosis codes, stage of disease (seventh edition of TNM staging), and postcode of residence, which was used to compute geographic area of residence (lower layer super output area codes) and deprivation index (www.gov.uk/government/statistics/english-indices-of -deprivation-2015).

Cancer records were linked with survival data from the Office of National Statistics by patients' NHS numbers. In the absence of a death record, patients were assumed to be alive on December 31, 2017. There were six cases excluded because of an inconsistent date of death.

Charlson comorbidity index scores were calculated from diagnosis codes recorded in the Hospital Episode Statistics database[17–19] to identify the relevant diagnoses associated with admitted patient care episodes in the period from 30 to 3 months before diagnosis.

Patients technically eligible for radical radiotherapy (stages 0–III) were suitable for analysis. Disease stage was not recorded in 18,655 cases (14% of cohort 1 and 9% of cohort 2). These patients had a very poor prognosis with a median survival of just 1 month (worse than patients with stage IV disease), with 85% (n = 15,947) receiving no anticancer treatment. With a few exceptions, it is likely that these patients represent a group presenting acutely with advanced disease or unfit to be considered for the full diagnostic process and treatment, and consequently they have been excluded from further analysis. Of the remaining 151,202 cases, 78,016 patients had stage IV disease, also not eligible for radiotherapy, and 73,186 (48%) had stage 0 to III diseases,

potentially suitable for radical radiotherapy (Fig. 1). For the purpose of analysis, one stage 0 case (carcinoma in situ) was included in the stage I disease category.

Treatment

Details of all radiotherapy treatments were obtained from the National Radiotherapy Dataset. All records where the radiotherapy diagnosis was anything other than "neoplasms of respiratory and intrathoracic organs" were subsequently excluded. In addition, any treatment that commenced more than 1 week before the diagnosis of NSCLC was assumed to be for a different diagnosis and was excluded. Radiotherapy was classified as palliative, radical, or "extremely hypofractionated" (coded as SABR) according to the criteria in Table 1. There were 88 cases that could not be classified. The radical radiotherapy group (excluding SABR) forms the analysis data set (Fig. 1). Radical radiotherapy was further classified by dose per fraction into conventionally fractionated, hyperfractionated (continuous hyperfractionated accelerated radiotherapy [CHART][20]), and hypofractionated treatments (Table 2). Although a range of dose fractionations were given, most of the hypofractionated patients were treated using 2.75 Gy per fraction and received full or part of 55 Gy in 20 fractions (Fig. 2*A*), and most conventional fractionation patients were treated using 2 Gy per fraction and received full or part of 60 to 66 Gy in 30 to 33 fractions (Fig. 2*B*). Patients not completing the full course as planned were included, which is equivalent to analysis by treatment intent rather than treatment delivered.

The NHS number was used for linkage with the Hospital Episode Statistics database. Any lung excision procedures (lobectomy or pneumonectomy) that occurred within a time window from 6 months before to 18 months after diagnosis were recorded and classified as "surgery."

Chemotherapy data were obtained from the NHS England and were classified as adjuvant if given from 150 days before the start and not more than 60 days after the completion of radical radiotherapy.

Statistical Analysis

The NSCLC cases were split into two cohorts on the basis of date of diagnosis: cohort 1 diagnosed in 2012 to 2013 (2 y) and cohort 2 diagnosed in 2014 to 2016 (3 y). The cohorts were compared to determine potential systematic differences in demographics or disease characteristics, assessing significance using the chi-square test or the *t* test.

The multivariate proportional hazards model was used to investigate overall survival from time of diagnosis. Separate analyses were performed for the two cohorts. Survival was adjusted for the prognostic factors of age, sex, stage of disease, comorbidity and other radical treatment (SABR and surgery) and adjuvant chemotherapy, and the difference between the treatment schedules was summarized by the hazard ratio

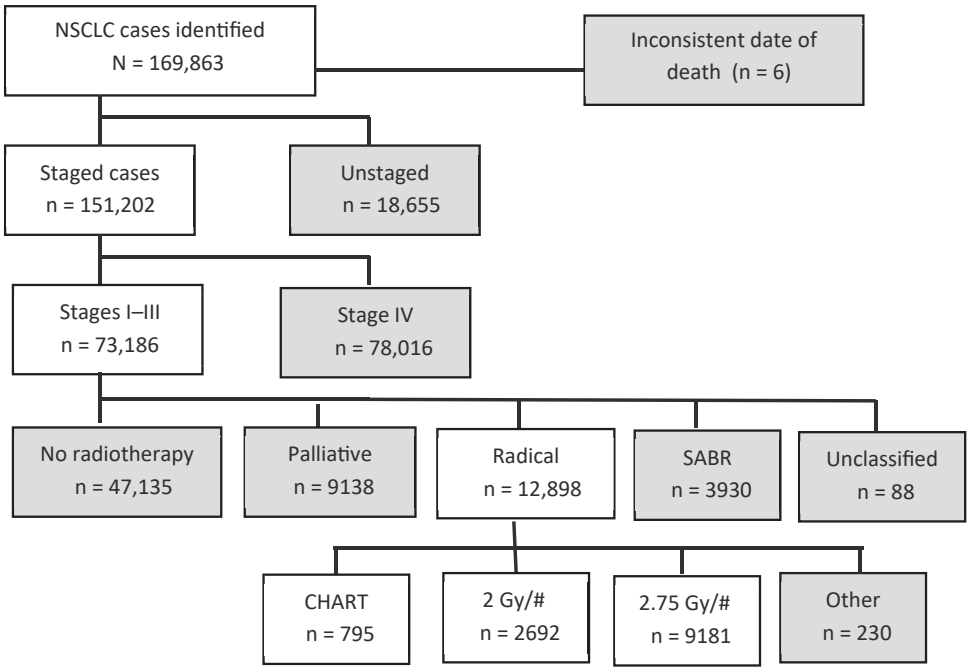

Figure 1. Consort diagram of the analysis data set. #, fraction of radiotherapy. CHART, continuous hyperfractionated accelerated radiotherapy; SABR, stereotactic ablative body radiotherapy.

Table 1. Classification of Radiotherapy

Dose Fractionation	Category
Total dose >100 Gy	Unknown
<1.5 Gy/#	Unknown
≥3 Gy/# and dose <40 Gy	Palliative
Dose omitted and 1#, 10#, 12#, 13#	Palliative
Dose omitted and 5# and stage ≠ 1	Palliative
>3 Gy/# and dose ≥40 Gy and >10#	Radical
1.5-3 Gy/#	Radical
Dose omitted and ≥20#	Radical
≥3 Gy/# and dose ≥40 Gy and ≤10#	SABR
Dose omitted and 5# and stage = 1	SABR
Remainder	Unknown

#, fraction of radiotherapy; radical, fractionated radical radiotherapy; SABR, stereotactic ablative body radiotherapy; dose omitted, total dose not available in the records.

(HR) and 95% confidence interval. The significance of any difference was assessed by the log likelihood test.

Results

Of 66,914 patients with NSCLC diagnosed in England in 2012 to 2013, 27,068 had stage I to III diseases, and of these, 4894 received fractionated radiotherapy with radical intent (cohort 1). Of 102,943 patients diagnosed in 2014 to 2016, 46,118 had stage I to III diseases, and of these, 8004 received radical radiotherapy (cohort 2).

The two cohorts were similar in terms of demographics (Supplementary Appendix A). Comorbidity scores were higher in cohort 2 (mean ± SD = 0.58 ± 1.13 in cohort 1, 0.69 ± 1.26 in cohort 2, $p < 0.0005$), which may reflect improved data recording rather than increased comorbidity. There were fewer cases with unrecorded stage in cohort 2 (9% versus 14%), and among staged cases, more cohort 2 patients were of a lower stage.

Of the stage I to III NSCLC cases, the proportion receiving radical radiotherapy stayed largely constant at 17% to 18% between 2012 and 2016, while the number treated by SABR increased steadily from 3% to 8%, and there was a fall in numbers receiving palliative radiotherapy (Fig. 3*A*).

Use of each of the three radical fractionated treatment schedules (CHART, conventional fractionation, hypofractionation) has remained almost constant over the 5 years (Fig. 3*B*). The breakdown of the three treatment schedules and of SABR by stage of disease is found in Table 3. SABR was used mainly for stage I disease while fractionated treatment was used largely for stage III.

Survival After Radical Radiotherapy

Age at diagnosis, sex, stage, comorbidity, and surgery were independent prognostic factors for survival of stages I to III NSCLC in both cohorts 1 and 2, whereas use of adjuvant chemotherapy was prognostic only in cohort 2. The deprivation index was not an independent predictor of survival (Tables 4 and 5).

Survival after adjusting for the independent prognostic factors is shown for patients diagnosed from 2012 to 2013 (cohort 1) in Table 4 and Figure 4*A*. Patients treated with the hypofractionated regimen had poorer survival than patients treated with conventional fraction (median 25 mo versus 29 mo, HR = 1.16, $p = 0.001$).

A similar pattern was seen in patients diagnosed from 2014 to 2016 (cohort 2). Median survival was 25 months for those treated with hypofractionation compared with 28 months for those treated with conventional fractionation (HR = 1.10, $p = 0.02$) (Table 5 and Fig. 4*B*).

In cohort 1, the survival of patients with NSCLC treated by CHART was equivalent to that of patients treated with the hypofractionated regimen (median = 25 mo) (Fig. 5*A*). In cohort 2, patients treated with CHART had similar survival (median = 29 mo) to those receiving the conventional fraction regimen (Fig. 5*B*). Although CHART was used throughout the period of analysis, the number of cases was relatively low and the observed difference in survival between the two cohorts was not statistically significant ($p = 0.1$). For comparison, the median survival of patients treated by SABR was 39 months in both cohorts.

Discussion

Fractionated radiotherapy continues to be the mainstay of treatment for localized and locally advanced NSCLC not amenable to surgery. Although the international standard dose fractionation regimen is 60 to 66 Gy in 2 Gy daily fractions, the protracted 6-week daily treatment is onerous and shorter

Table 2. Classification of Radical Radiotherapy to Treatment Schedules

Treatment Group	Fractionation	Dose Per Fraction
CHART	Hyperfractionation	1.5 Gy/# (54 Gy in 36#)
2 Gy per fraction	Conventional	1.7 → 2.3 Gy/#
2.75 Gy per fraction	Hypofractionation	2.4 → 3.1 Gy/#

#, fraction of radiotherapy
CHART, continuous hyperfractionated accelerated radiotherapy.

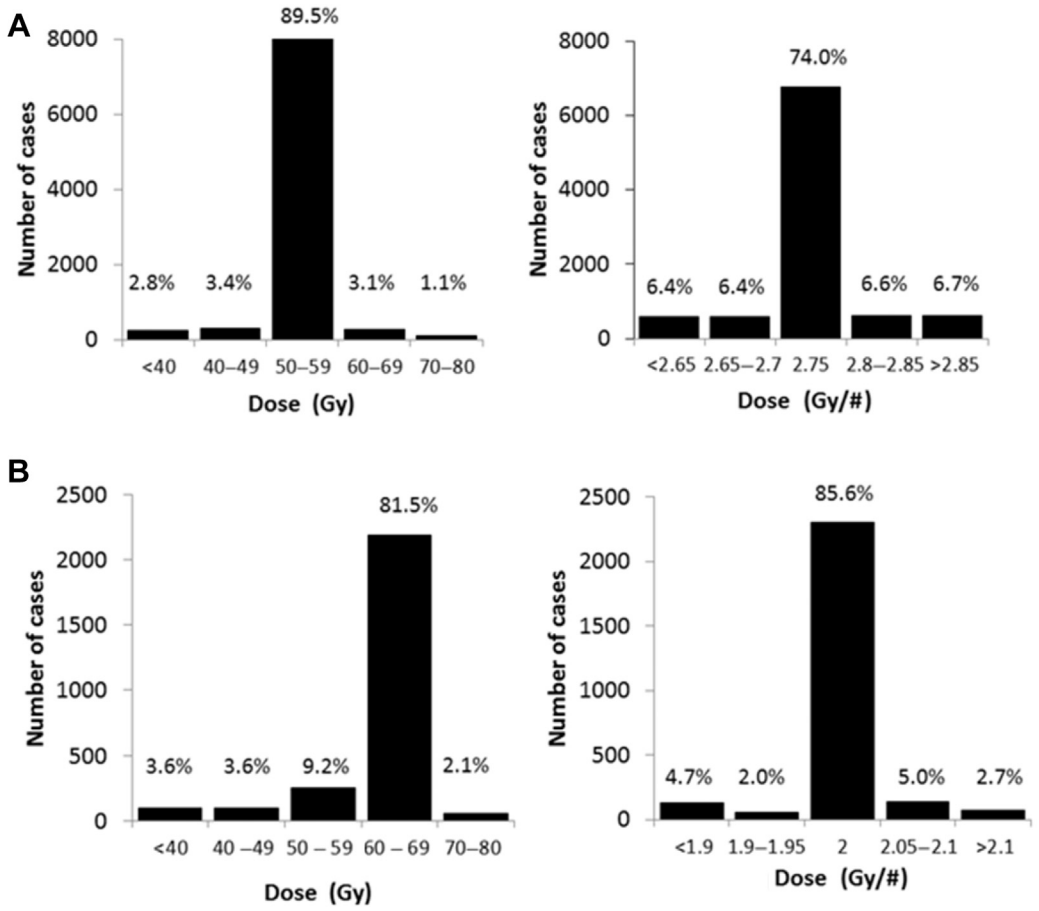

Figure 2. Total treatment dose and dose per fraction received by patients using (*A*) 2.75 Gy per fraction and (*B*) 2 Gy per fraction. #, fraction of radiotherapy.

moderately hypofractionated regimens have found favor on the basis of apparent radiobiological equivalence or even potential benefit, albeit without high-level clinical evidence of equivalent efficacy and toxicity. Interest in moderately hypofractionated schedules has been further fueled by their successful adoption in radiotherapy of prostate cancer[21] and breast cancer.[22,23] During the COVID-19 pandemic, the shorter regimen has also been favored to reduce the risk of viral exposure through protracted hospital attendance. Although this is a reasonable pragmatic step, patients should be offered the best available dose fractionation after the recovery of radiotherapy services to normal standards.

This study has found worse survival outcome for patients treated with a moderately hypofractionated regimen in an unselected comprehensive national cohort of patients with NSCLC corrected for all available prognostic factors. To ensure the reliability of the initial finding in an earlier cohort, the results have been validated in an independent and similarly comprehensive cohort treated in subsequent years.

A retrospective study of this type cannot evaluate the relative side effect profile of the two fractionation schemes although the prevailing view is that conventional fractionation carries lesser risk of normal tissue toxicity.[24,25]

Although corrected for the most important prognostic factors of age, stage, comorbidity, and use of surgery, the absence of randomization cannot exclude some selection bias. For example, the apparent superiority of conventional fractionation could be due to patient selection, with less well patients being offered shorter treatment regimens. Although this cannot be excluded with certainty, the survival results were corrected for age and comorbidity and the distribution of dose fractionation is region specific (Fig. 6). The predominance of conventional fractionation is only found in southern counties. In addition, the percentage of patients with stage III disease was higher in the conventional fractionation regimen cohort.

National recording of chemotherapy was not mandated before 2017, and therefore, chemotherapy

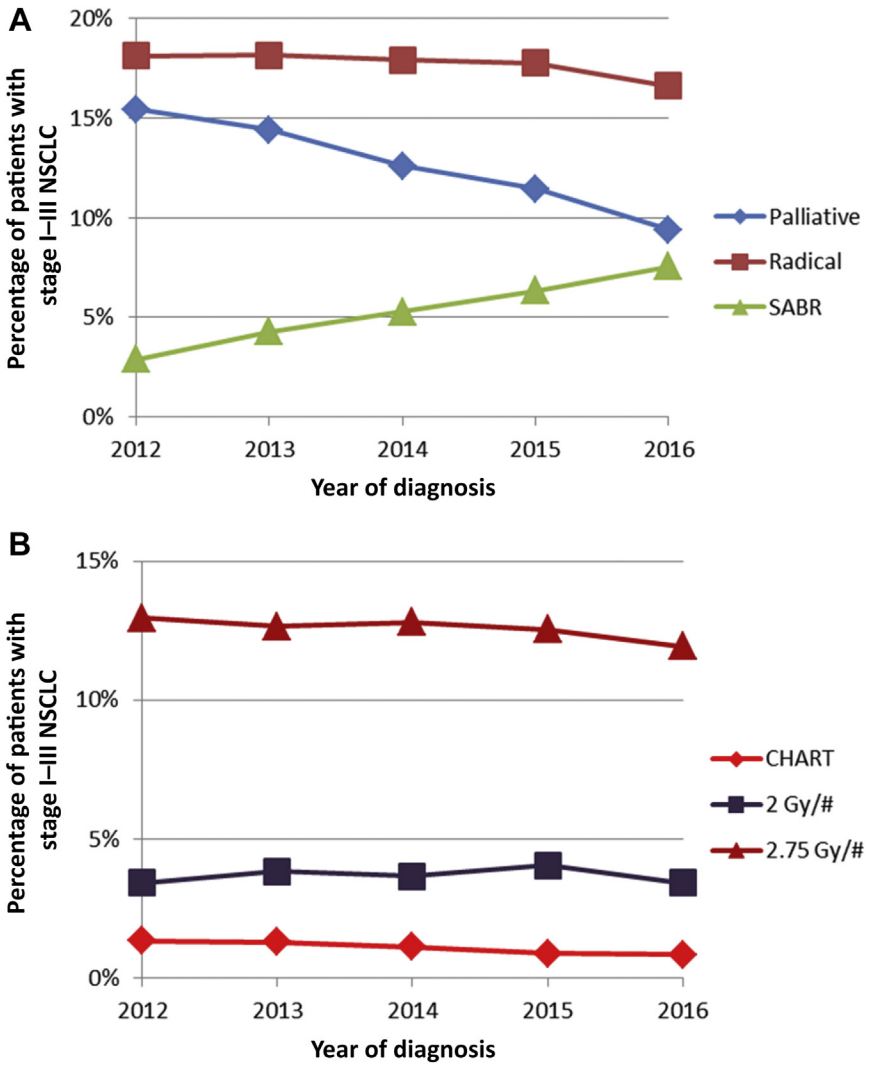

Figure 3. Radiotherapy treatment for stages I to III NSCLC and year of diagnosis (*A*) by intent and (*B*) by radical treatment schedule. #, fraction of radiotherapy; CHART, continuous hyperfractionated accelerated radiotherapy; SABR, stereotactic ablative body radiotherapy.

data are likely to be incomplete. Adjuvant (sequential and concurrent) chemotherapy information as recorded revealed more frequent use in patients treated with conventional (61% of patients) compared with hypofractionated regimens (32% of patients) (Fig. 7). The use of chemotherapy was an independent predictor of outcome only in cohort 2, and the outcome data were corrected for it.

Although the difference in outcome may reflect patient selection with more favorable prognosis in patients receiving a more protracted regimen, this was corrected for in terms of age and Charlson comorbidity index. In addition, the 4% to 5% survival difference at 2 years found with adjuvant chemotherapy in randomized studies[1,3] does not explain the survival difference found here.

It was not possible to distinguish between sequential and concurrent chemotherapies. On the basis of the recognized survival benefit of concurrent chemotherapy, which is a 1-month survival benefit at the median time point (5% at 2 y),[2] even if all patients in the conventional fractionation cohort had received concurrent

Table 3. Breakdown of Treatment Schedules by Stage of Disease (Combined Cohorts)

Radiotherapy Schedule	I	II	III
CHART	240 (30.2)	168 (21.1)	387 (48.7)
2 Gy per fraction	269 (10)	447 (16.6)	1976 (73.4)
2.75 Gy per fraction	2320 (25.3)	2008 (21.9)	4853 (52.9)
SABR	3434 (87.4)	303 (7.7)	193 (4.9)

Note: Values presented in the table represent n (%).
CHART, continuous hyperfractionated accelerated radiotherapy; SABR, stereotactic ablative body radiotherapy.

Table 4. Independent Prognostic Factors for Survival, and Survival Adjusted for Prognostic Factors of Patients Treated Using 2 Gy Per Fraction Versus 2.75 Gy Per Fraction in Cohort 1

Prognostic Factor	HR	95% CI	Significance
Age at diagnosis	1.14[a]	1.10-1.18	<0.0005
Sex			
Male	1.19	1.12-1.28	
Female	1.0		<0.0005
Stage of disease			
I	1.0		
II	1.24	1.18-1.29	<0.0005
III	1.53	1.40-1.67	
Comorbidity score			
0	1.0		
1	1.06	1.03-1.10	<0.0005
2	1.13	1.06-1.20	
Surgery			
None	1.0		<0.0005
Surgery	0.48	0.44-0.53	
Adjuvant chemotherapy			N.S.

Adjusted survival				Median surv. (mo)
Regimen				
2 Gy/#	1.0			29
2.75 Gy/#	1.16	1.07-1.27	0.001	25

Note: Significance evaluated by the log likelihood test. N.S. indicates $p > 0.05$.
[a]HR for each 10-year increase in age.
#, fraction of radiotherapy; CI, confidence interval; HR, hazard ratio; N.S., not significant; surv., survival.

Table 5. Independent Prognostic Factors for Survival, and Survival Adjusted for Prognostic Factors of Patients Treated Using 2 Gy Per Fraction Versus 2.75 Gy Per Fraction in Cohort 2

Prognostic Factor	HR	95% CI	Significance
Age at diagnosis	1.10[a]	1.06-1.14	<0.0005
Sex			
Male	1.21	1.14-1.29	
Female	1.0		<0.0005
Stage of disease			
I	1.0		
II	1.31	1.26-1.37	<0.0005
III	1.72	1.58-1.88	
Comorbidity score			
0	1.0		
1	1.06	1.04-1.09	<0.0005
2	1.13	1.07-1.19	
Surgery			
None	1.0		<0.0005
Surgery	0.45	0.40-0.50	
Adj chemo			
None	1.0		
Adj chemo	0.90	0.84-0.97	0.004

Adjusted survival				Median surv. (mo)
Regimen				
2 Gy/#	1.0			28
2.75 Gy/#	1.10	1.02-1.19	0.02	25

Note: Significance evaluated by the log likelihood test.
[a]HR for each 10-year increase in age.
#, fraction of radiotherapy; Adj chemo, adjuvant chemotherapy; CI, confidence interval; HR, hazard ratio; surv., survival.

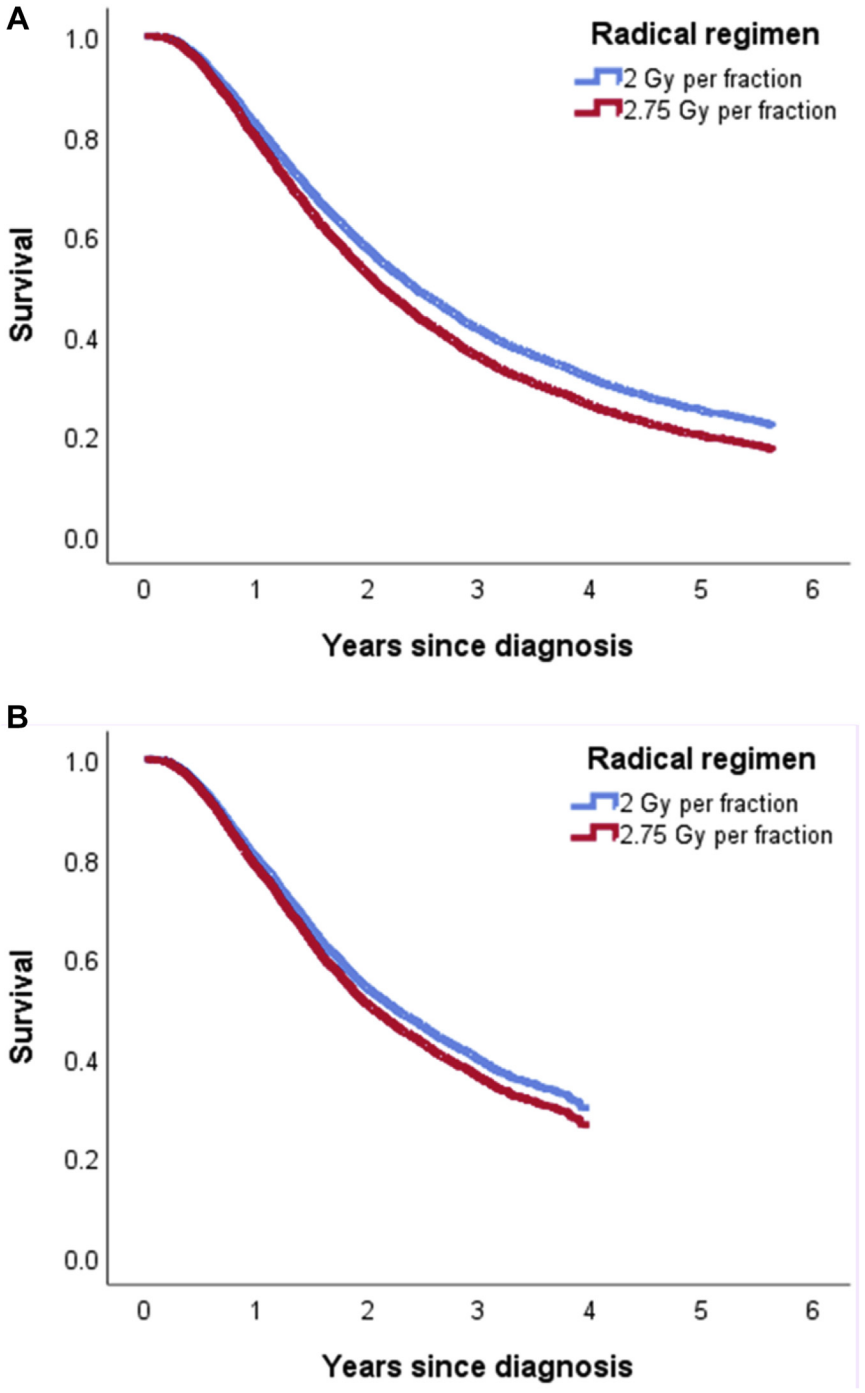

Figure 4. Survival in patients with stages I to III NSCLC treated with radical radiotherapy adjusted for prognostic factors, plotted for patients receiving conventional fractionation versus hypofractionated treatment in (*A*) cohort 1, diagnosed in 2012 to 2013, and (*B*) cohort 2, diagnosed in 2014 to 2016.

chemotherapy and all patients in the hypofractionated cohort sequential chemotherapy, which is clearly not the case, the actual survival difference of 3 to 4 months is well beyond the benefit of the concurrent treatment (at the median time point). The timing of chemotherapy in relation to radiotherapy therefore does not explain the difference between the fractionation groups.

The apparent inferiority of a moderately hypofractionated treatment of NSCLC is not easily explicable with conventional modeling using orthodox radiobiological parameter values.[26,27] Nevertheless, it concurs with other reports of moderately shortened, 5-week, schedules faring less well than expected.[28,29] Similarly, although dose escalation has been predicted to result in

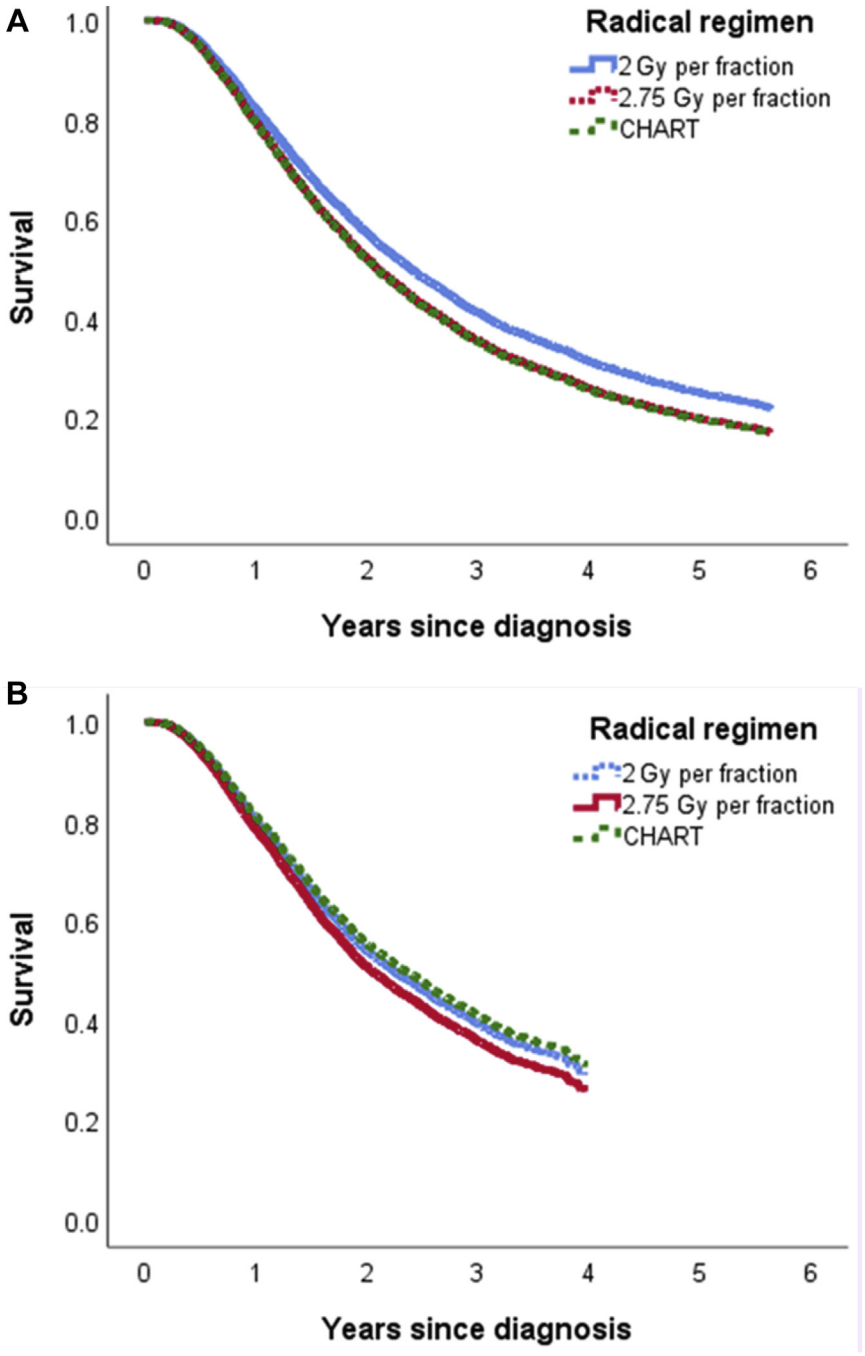

Figure 5. Survival in patients with stages I to III NSCLC treated with radical radiotherapy adjusted for prognostic factors, plotted for patients treated using conventional fractionation versus hypofractionation versus CHART in (*A*) cohort 1, diagnosed in 2012 to 2013, and (*B*) cohort 2, diagnosed in 2014 to 2016. CHART, continuous hyperfractionated accelerated radiotherapy.

improved outcome, the poorer results obtained in a randomized study[10] were also contrary to the prevalent radiobiological thinking.

It is concluded that in the absence of randomized trials comparing moderately hypofractionated radiotherapy with conventional fractionation in the treatment of localized and locally advanced NSCLC, big data analysis of a comprehensive national cohort of patients with NSCLC treated in England suggests that conventional fractionation is associated with superior overall survival compared with a 4-week regimen of 55 Gy in 20 fractions at the cost of longer treatment episode. The magnitude of survival difference is larger than the survival gain obtained with adjuvant chemotherapy.

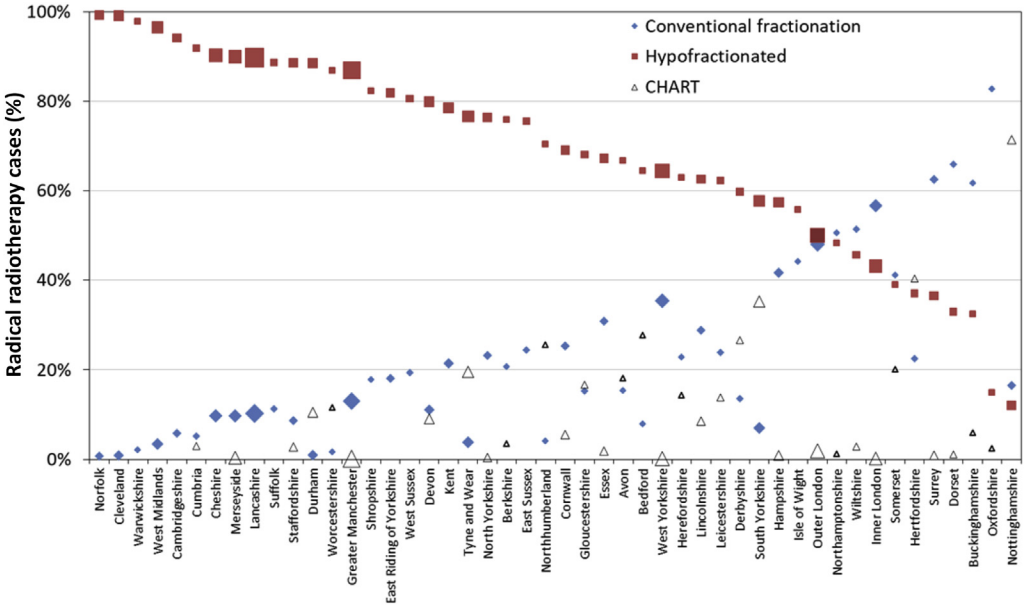

Figure 6. Relative distribution of radical radiotherapy regimens for 48 ceremonial counties of England. Marker size is proportional to the total number of radically treated cases in the county. CHART, continuous hyperfractionated accelerated radiotherapy.

Nevertheless, some degree of selection bias affecting the magnitude of the difference cannot be excluded. Thus, on the basis of nonrandomized population big data with its uncertainties, a 6+ week regimen of daily fractionation to a dose of 60 to 66 Gy at 2 Gy per fraction should remain a standard arm in comparative trials. The results would also argue that at the time of recovery of cancer services from the conditions of the COVID-19 pandemic, conventional fractionation should remain the standard treatment. Whether the current results suggesting inferiority of a shorter regimen should be subject to a randomized trial comparing moderate hypofractionation with conventional fractionation poses an ethical dilemma, which requires a discussion involving both professionals and the public. A full trial with appropriate stopping power would also provide more comprehensive information of quality of life and other patient-reported outcomes to give a more balanced view of the pros and cons of the two widely used fractionation regimens.

CRediT Authorship Contribution Statement

Michael Brada: Concept, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Helen Forbes: Resources, Data curation, Investigation, Methodology, Software, Writing - review & editing.

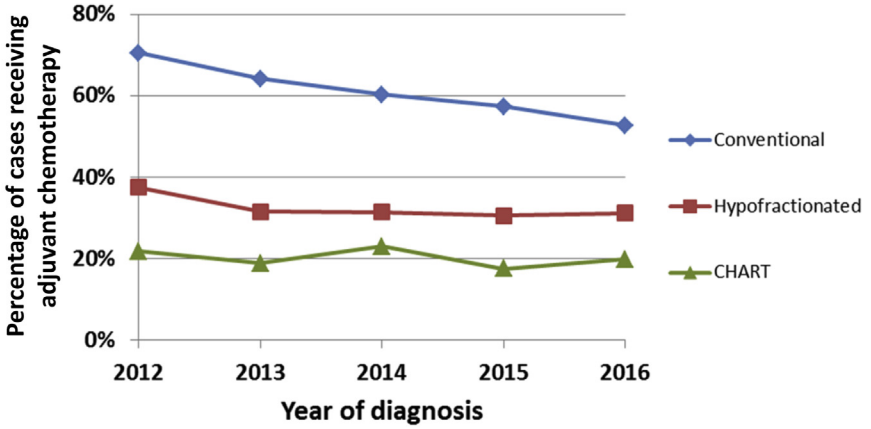

Figure 7. Proportion of patients receiving concurrent and sequential (adjuvant) chemotherapy for each fractionation regimen by year of diagnosis. CHART, continuous hyperfractionated accelerated radiotherapy.

Susan Ashley: Data curation, Statistical analysis, Writing - original draft, Writing - review & editing.

John Fenwick: Methodology, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.01.006.

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