Journal of Radiotherapy in Practice

cambridge.org/jrp

Efficacy and toxicity hypofractionated radiotherapy for centrally located non-small cell lung cancer

Tanzeel Janjua, Fei Sun, Katy Clarke, Pete Dickinson, Kevin Franks, Moses Arunsingh, Mark Teo and Pooja Jain

St James's University Hospital, Leeds, UK

Original Article

Cite this article: Janjua T, Sun F, Clarke K, Dickinson P, Franks K, Arunsingh M, Teo M, and Jain P. (2023) Efficacy and toxicity hypofractionated radiotherapy for centrally located non-small cell lung cancer. *Journal of Radiotherapy in Practice*. **22**(e5), 1–4.
doi: 10.1017/S1460396921000376

Received: 25 February 2021
Revised: 11 April 2021
Accepted: 12 April 2021

Key words:
central NSCLC; hypofractionated radiotherapy; radiotherapy toxicity

Author for correspondence:
Fei Sun, St James's University Hospital, Leeds, UK. E-mail: f.sun@nhs.net

Abstract

Aim: Centrally located early-stage non-small cell lung cancer in patients who are unfit for surgery are treated with fractionated radiotherapy. We present the outcomes of a moderately hypofractionated accelerated dose regimen of 50 Gy in 15 fractions from a single centre in the UK.
Materials and methods: Electronic case notes and radiotherapy records of lung cancer patients treated between January 2014 and December 2016 were retrospectively reviewed. Adult Comorbidity Evaluation-27 score was used to evaluate comorbidities. Mean lung doses and percentage of lung receiving more than 20 Gy were calculated for all patients. Survival outcomes were estimated using Kaplan–Meier curves.
Results: Fifty-three patients were included in the study; the median follow-up was 20.2 months. 87% of patients had stage I disease. There was no 30-day post-treatment mortality. Ninety-day mortality rate after radiotherapy was 3.8%. Grade 2 pneumonitis was seen in five patients while no grade 3 or 4 pneumonitis was observed. The median progression-free survival (PFS) and overall survival (OS) were 18.5 months and 28.2 months, respectively. The estimated 1 and 2 years PFS were 62.3% and 41.3%, respectively, and OS were 77.4% and 56.6%, respectively. Worsening performance status was associated with worse survival on cox regression analysis. Disease relapsed in 36% of patients. 7.5% of patients with relapsed disease had infield recurrence.
Findings: 50 Gy in 15 fractions radiotherapy for central early-stage lung cancer is a feasible choice that requires further randomised trials.

Introduction

Early-stage non-small cell lung cancer (NSCLC) refers to stage I and stage II disease.[1] In recent years, there have been increasing numbers of patients diagnosed with early lung cancer compared to advanced disease.[2,3] This is likely to be due to improved public awareness,[4] lung cancer screening[5] and the increase in incidentally found lung cancers due to increased utilisation of imaging in non-cancer specialities. Traditionally, surgery has been the standard treatment of early-stage NSCLC. A large percentage of lung cancer, however, is diagnosed in elderly patients with multiple comorbidities and poor lung function.[6]

Stereotactic ablative radiotherapy (SBRT) is associated with higher rates of tumour control and tolerability compared to conventionally fractionated radiotherapy and has become the standard of care for patients with inoperable early-stage peripheral lung cancer.[7,8] SBRT is not routinely used for more central lesions due to safety concerns from earlier studies.[9,10] A central lesion is defined as a lesion within 2 cm of the proximal bronchial tree.[11] Patients with inoperable, centrally located lesions receive a radical dose of radiation therapy in either conventional or moderate hypofractionation of 20–30 daily fractions.[12] 50 Gy in 15 daily fractions delivered over 3 weeks is a moderately hypofractionated radiotherapy regime that has been used in radiotherapy studies[13] for early-stage NSCLC and shown good safety and efficacy profile. This study investigates the local control, survival outcomes and safety profile of this radiotherapy regimen at a large cancer centre in the UK.

Methods

Patients were eligible for the study if they were diagnosed with centrally located, non-metastatic NSCLC and received 50 Gy in 15 daily fractions of radiotherapy between 01 January 2014 and 30 December 2017 at the Leeds Cancer Centre. Cancer diagnoses were made on either histological or radiological grounds. Radiological diagnoses were based on positron emission tomography (PET) scan findings, and all cases had multidisciplinary team consensus.

All radiotherapy treatments were planned using 4D simulation computerised tomography (CT) scans. Radiotherapy volume definition includes gross tumour volume (GTV), which encompassed only the visible tumour as seen on simulation CT scan. Clinical target volume (CTV) was GTV plus a 5–7 mm margin in all directions. Planning target volume was CTV plus a 5 mm margin in all directions. Organs at risk (OARS) include the oesophagus, pericardium, brachial plexus, spinal cord and percentage of lung receiving more than 20 Gy (V20) as well as the mean lung dose (MLD). OARs doses are kept to a minimum, with threshold established by Radiation Therapy Oncology Group (RTOG).[14] Treatment verification was performed with using cone beam CT scans daily in the first week, then on alternate days for the remainder of treatment.

Electronic case notes and radiotherapy records of lung cancer patients were reviewed. Information extracted included patient and tumour demographics and Adult Comorbidity Evaluation-27 (ACE-27) score, which was used to evaluate comorbidities.[15] Post treatment radiation pneumonitis was recorded; it was graded using Common Toxicity Criteria version 5.[16] 30- and 90-day post-treatment mortality was calculated. Overall survival (OS) was taken from date of diagnosis to date of death. Date of diagnosis is the date of histological confirmation for histologically diagnosed tumours or date of PET for radiologically diagnosed tumours. Progression-free survival (PFS) was taken from date of diagnosis to date of progression or death.

Statistics

Survival outcomes were estimated using Kaplan–Meier curves. Descriptive statistics was performed for categorical variables including sex, performance status, ACE-27 score, disease stage and histological subtype. Age is a continuous variable and is presented using median value and range. MLD is presented as a mean value with interquartile range. V20 is presented using a median value and interquartile range. Cox regression analysis was used to analyse factors which influenced survival outcomes. Statistical significance was set at $p < 0.05$. SPSS version 22 was used for statistical calculations.

Results

Fifty-three patients were identified and included in the study. Median follow-up was 20.2 months. Thirty-seven (70%) patients were female. The median age was 74.0 years, with a range of 69.5–79 years. 16 (30%), 33 (62%) and 4 (8%) patients had World Health Organisation performance status (WHO PS) of 1, 2 and 3, respectively. Thirty-seven (70%) patients had an ACE-27 score of 2 or above. Forty-six (87%) patients had stage I disease. Four (8%) of patients had stage II, lymph node negative disease. Thirty-seven (70%) patients had radiologically diagnosed disease. For patients with histologically confirmed disease, squamous cell carcinoma diagnosed in ten (19%) patients. A full summary of patient and tumour demographics is presented in Table 1.

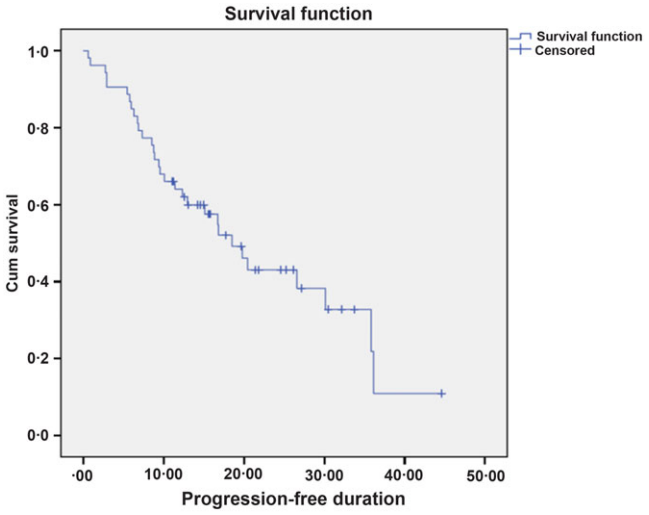
MLD was 7.3 Gy with an interquartile range of 5.8–8.8 Gy. Median V20 was 12.9% with an interquartile range of 9.5%–15%. Grade 2 pneumonitis was seen in five (9%) patients. No grade 3 or 4 pneumonitis was observed.

The median PFS and OS were 18.5 months (95% CI 12.2–24.8) and 28.2 months (95% CI 14.4–42.1), respectively, demonstrated in Graphs 1 and 2. The estimated 1- and 2-year PFS rates were 62.3% and 41.3%, respectively, and 1 and 2 years OS rates were 77·4% and 56·6%, respectively. There were no deaths within 30 days of treatment. Ninety-day mortality after treatment was 3.8% (two patients).

WHO PS had an impact on OS on cox regression analysis with poor performance status associated with worse survival (Table 2). Nineteen (36%) patients had relapsed disease. 4 (7.5%) had infield recurrence, 10 (19%) had out-of-field lung recurrence and the rest had distant metastases.

Table 1. Patient and tumour demographics.

Age	Median	74 years
	Range	69.5–79 years
Sex	Male	16 (30%)
	Female	37 (70%)
WHO PS	1	16 (30%)
	2	33 (62%)
	3	4 (8%)
ACE-27 comorbidity score	0	1 (2%)
	1	15 (28%)
	2	25 (47%)
	3	12 (23%)
Disease stage (TNM 7th edition)	I	46 (87%)
	II	4 (8%)
	III	3 (6%)
Histology	Radiological	37 (70%)
	Squamous cell	10 (19%)
	Adenocarcinoma	5 (9%)
	Neuroendocrine	1 (2%)

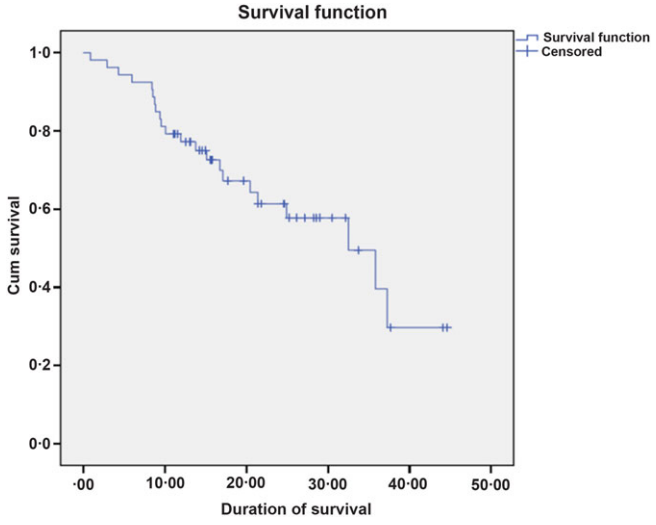


Graph 1. PFS (months).

https://doi.org/10.1017/S1460396921000376 Published online by Cambridge University Press

Table 2. Cox regression analysis of variables on OS in the cohort

Variable		Hazard ratio	Significance
Sex	Male	1.3	0.58
	Female	1	1
WHO PS	1	0.08	<0.01
	2	0.10	<0.01
	3	1	0.01
ACE-27 comorbidity score	0	0.43	0.12
	1	0.03	0.96
	2	0.01	0.01
	3	1	0.42
Disease stage	I	1	0.03
	II	0.28	0.13
	III	2.97	0.3
Histology	Radiological	1	0.28
	Squamous cell	0.15	0.12
	Adenocarcinoma	0.10	0.06
	Neuroendocrine	0.21	0.20



Graph 2. OS (months).

Discussion

The study population is typical of the patient group diagnosed with early-stage NSCLC in the UK, with respect to age, sex, comorbidities and performance status.[17] Majority of patients had radiologically diagnosed stage I disease. This reflects the difficulty of obtaining tissue biopsy in small central lung cancers[18] and the risk of complications[19] in an elderly population with prevalent cardiopulmonary conditions. V20 and MLD measurements were low in the cohort, reflecting the small radiotherapy treating volume for early lung cancer.

In the current cohort of patients, 50 Gy in 15 fractions was associated with good local control more than 90% at a median follow-up of 20.2 months. Regional and distant relapse occurred in less than 30% of patients. This is consistent with the published literature of SBRT to peripheral lesions,[20] conventionally fractionated radiotherapy to early lung cancer[12] and SBRT to central lesions in the recently published results from the RTOG 0813 study.[21] Survival times in the cohort appear in line with SBRT and appear superior to that reported in an interim analysis of a study of accelerated, hypofractionated radiotherapy for non-metastatic lung cancer.[22] WHO PS was strongly correlated with survival; this is unsurprising and confirms the importance of patient selection before treatment. There has been no large-scale, randomised studies comparing radiotherapy to surgery for early-stage NSCLC. Due to the difference in patient demographics and comorbidities, patients receiving radiotherapy are more likely to die from non-cancer causes.[23]

50 Gy in 15 fractions is associated with a good safety profile. There were no deaths within 30 days of treatment and two deaths within 90 days of treatment. No pneumonitis above grade 3 occurred. This is consistent with published toxicity profiles of SBRT.[24]

Patients with medically inoperable centrally located lung cancer have limited treatment options, as they are not routinely amenable to receive SBRT. 50 Gy in 15 fractions is associated with good tumour control with low rates of toxicity. In terms of biological effective dose (BED), using the time-adjusted BED formula outlined in the Machtay paper,[25] the time-adjusted BED for 55 Gy in 20 fractions is 68.16 Gy, and for 50 Gy in 15 fractions is 65.63 Gy, alpha/beta ratio was presumed to be 10. The regime spans 3 weeks and is 1 week shorter than the widely used 55 Gy in 20 fractions schedule. This is more convenient for patients, places less demand from radiotherapy services and decreases patients' contact with the hospital environment. Reducing exposure to clinical areas could reduce the risk of contracting the COVID virus, which in an elderly population with many comorbidities is associated with a high risk of death.[26,27]

This study has several limitations. It was carried out in a single cancer centre, and retrospective data were used for analysis. The cohort of patients is relatively small, and a large proportion of patients had radiological diagnosis of cancer. Not all radiotherapy parameters, including doses to other OARS, were analysed. The key strengths of this study are long follow-up duration, detailed documentation of patient demographics and pattern of disease relapse.

Conclusion

50 Gy in 15 fractions radiotherapy for central early-stage lung cancer is a feasible choice that requires further randomised trials.

Acknowledgements. None.

Financial support. No financial support was received for this project.

References

1. http://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/incidence#heading-One. Accessed on 16th March 2021.
2. http://wclc2017.iaslc.org/wp-content/uploads/2017/09/2017-WCLC-Fact-Sheet-Lung-Cancer-Final.pdf. Accessed on 16th March 2021.
3. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#ref-5. Accessed on 16th March 2021.

https://doi.org/10.1017/S1460396921000376 Published online by Cambridge University Press

4. Kennedy MPT, Cheyne L, Darby M et al. Lung cancer stage-shift following a symptom awareness campaign. Thorax 2018; 73 (12): 1128. doi: 10.1136/thoraxjnl-2018-211842.
5. Bansal S, Okoli S, Cole C, Jeannerat D. Beneficial lung cancer stage-shift: implementation of large scale lung cancer screening program in a community health care system. Chest 2019; 155 (4): 191A. doi: 10.1016/j.chest.2019.02.187.
6. Froesch P, Martucci F, Györik S, Dutly AE, Cafarotti S. Management of non-small cell lung cancer in the elderly. Eur J Intern Med 2014; 25 (10): 888–894. doi: 10.1016/j.ejim.2014.10.024. Epub 31 October 2014. Review.
7. https://www.nice.org.uk/guidance/cg121/chapter/1-guidance. Accessed on 16th March 2021.
8. Ball D, Mai GT, Vinod S et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol 2019; 20 (4): 494–503. doi: 10.1016/S1470-2045(18)30896-9.
9. Timmerman R, McGarry R, Yiannoutsos C et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006; 24: 4833–4839.
10. Fakiris AJ, McGarry RC, Yiannoutsos CT et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: Four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009; 75: 677–682.
11. Timmerman R, Mcgarry R, Yiannoutsos C et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy in medically inoperable early stage lung cancer. J Clin Oncol 2006; 24: 4833–4839.
12. Rowell N, Williams C. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). Cochrane Database Syst Rev 2001; (1). doi: 10.1002/14651858.CD002935.
13. Faria SL, Souhami L, Portelance L et al. Absence of toxicity with hypofractionated 3-dimensional radiation therapy for inoperable, early stage non-small cell lung cancer. Radiat Oncol 2006; 1: 42.
14. Kong FM, Ritter T, Quint DJ et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011; 81 (5): 1442–1457. doi: 10.1016/j.ijrobp.2010.07.1977.
15. Piccirillo JF, Creech CM, Zequeira R, Anderson S, Johnston AS. Inclusion of comorbidity into oncology data registries. J Reg Manag 1999; 26: 66–70.
16. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed on 16th March 2021.
17. https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018. Accessed on 16th March 2021.
18. Kothary N, Lock L, Sze DY, Hofmann LV. Computed tomography–guided percutaneous needle biopsy of pulmonary nodules: impact of nodule size on diagnostic accuracy. Clin Lung Cancer 2009; 10 (5): 360–363. doi: 10.3816/CLC.2009.n.049.
19. Heerink, W J, de Bock, G H, de Jonge, G J et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. Eur Radiol 2017; 27 (1): 138–148. doi: 10.1007/s00330-016-4357-8.
20. Prezzano KM, Ma SJ, Hermann GM, Rivers CI, Gomez-Suescun JA, Singh AK. Stereotactic body radiation therapy for non-small cell lung cancer: A review. World J Clin Oncol 2019; 10 (1): 14–27. doi: 10.5306/wjco.v10.i1.14.
21. Bezjak A, Paulus R, Gaspar LE et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non–small-cell lung cancer: NRG oncology/RTOG 0813 trial. JCO 2019; 37 (15): 1316–1325. doi: 10.1200/JCO.18.00622.
22. Iyengar P, Westover KD, Court LE et al. A phase III randomized study of image guided conventional (60 Gy/30 fx) versus accelerated, hypofractionated (60 Gy/15 fx) radiation for poor performance status stage II and III NSCLC patients—an interim analysis. Int J Radiat Oncol Biol Phy 2016; 96 (2): E451. doi: 10.1016/j.ijrobp.2016.06.1763.
23. Spencer KL, Kennedy MPT, Lummis KL et al. Surgery or radiotherapy for stage I lung cancer? An intention to treat analysis. Eur Respir J 2019: 1801568. doi: 10.1183/13993003.01568-2018.
24. Guckenberger M, Allgäuer M, Appold S et al. Safety and efficacy of stereotactic body radiotherapy for stage I non–small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. J Thorac Oncol 2013; 8 (8): 1050–1058. doi: 10.1097/JTO.0b013e318293dc45.
25. Machtay M, Bae K, Movsas B et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2012; 82 (1): 425–434. doi: 10.1016/j.ijrobp.2010.09.004.
26. Rakhsha A, Azghandi S, Taghizadeh-Hesary F. COVID-19 pandemic and patients with cancer: The protocol of a Clinical Oncology center in Tehran, Iran. Rep Pract Oncol Radiother 2020; 25 (5): 765–767, ISSN 1507-1367.
27. Faivre-Finn, C. et al. Reduced fractionation in lung cancer patients treated with curative-intent Radiotherapy during the COVID-19 Pandemic. Clin Oncol 2020; 32 (8): 481–489.

https://doi.org/10.1017/S1460396921000376 Published online by Cambridge University Press