Received:
5 October 2015

Revised:
7 March 2016

Accepted:
15 March 2016

<http://dx.doi.org/10.1259/bjr.20150824>

Cite this article as:

Mollà M, Saez J, Ramos M, Giraldo A, Seoane A, Andreu J, et al. Hypofractionated 3D radiotherapy for inoperable T1-3 NO-1 non-small-cell lung cancer. *Br J Radiol* 2016; **89**: 20150824.

FULL PAPER

Hypofractionated 3D radiotherapy for inoperable T1-3 NO-1 non-small-cell lung cancer

¹MERITXELL MOLLÀ, MD, PhD, ²JORDI SAEZ, PhD, ¹MONICA RAMOS, MD, ¹ALEXANDRA GIRALDO, MD, ²ALEJANDRO SEOANE, MSc, ³JORDI ANDREU, MD, PhD, ⁴MARC SIMÓ, MD and ¹JORDI GIRALT, MD, PhD

¹Department of Radiation Oncology, Hospital de la Vall d'Hebron, Barcelona, Spain

²Department of Medical Physics, Hospital de la Vall d'Hebron, Barcelona, Spain

³Department of Radiology, Hospital de la Vall d'Hebron, Barcelona, Spain

⁴Department of Nuclear Medicine, Hospital de la Vall d'Hebron, Barcelona, Spain

Address correspondence to: Dr Meritxell Mollà

E-mail: molla@clinic.cat

Objective: This study assessed the toxicity and clinical outcomes of three-dimensional (3D) hypofractionated radiotherapy (HFRT) for medically inoperable T1-3 NO-1 non-small-cell lung cancer (NSCLC).

Methods: 34 patients with inoperable early-stage NSCLC were treated from August 2008 to April 2013. Prior to enrolment, patients were required to be evaluated by an experienced thoracic surgeon to determine the "operability". All received 57 Gy in 19 fractions followed by escalated doses of 3-Gy fractions, up to a total dose of 66 Gy using a 3D conformal technique. Toxicities were measured using the Common Terminology Criteria for Adverse Effects v. 4.0.

Results: The median follow-up was 33 months (7–74 months). Toxicity grades ≥ 3 were not observed. Local control (LC) was 80.4% at 2 years, whereas regional control (RC) was

78%. The overall survival (OS), time to progression (TTP) and time to distant metastasis (TTM) at 2 years were 60%, 59% and 80%, respectively. For patients with T1-2 NO and a tumour size <45 mm ($n = 19$), rates of OS, TTP and TTM at 2 years were 71%, 75% and 94%, respectively. LC and RC at 2 years were 85% and 94%, respectively.

Conclusion: HFRT using 3.0-Gy fractions amounting to a total dose of 66 Gy is the recommended dose. A Phase 2 trial is warranted in order to assess the safety and efficacy of this fractionation scheme.

Advances in knowledge: HFRT results in a favourable outcome in early-stage lung cancer without the usual restrictions in tumour size and/or location associated with previous treatment methods. No special equipment is required, therefore permitting its application in any centre.

INTRODUCTION

To date, anatomical resection has been the standard treatment for early-stage lung cancer. Some patients cannot tolerate surgery owing to their comorbidity condition. These patients who are medically inoperable are therefore generally treated with conventional radiotherapy (RT) dose-fractionation schedules of 1.8–2.0 Gy day⁻¹ to a total dose of 50–70 Gy, resulting in suboptimal, *i.e.* unsatisfactory, control of the primary tumour^{1,2} and 2-year overall survival (OS) rates of $<40\%$.^{3,4}

Stereotactic body radiation therapy (SBRT) is a non-invasive cancer treatment where numerous small, highly focused and accurate radiation beams are used to deliver a high dose fraction in one to up to eight RT sessions to tumour targets in extracranial sites. Several single-institution studies have shown that this treatment is effective and well tolerated for early-stage non-small-cell lung cancer (NSCLC) in patients who are medically inoperable.^{5,6} The Radiation Therapy Oncology Group trial 0236 has reported a survival rate of

55.8% at 3 years, with high rates of local tumour control (90.6%) and moderate treatment-related morbidity.⁷

Although no Phase III trials have been published comparing surgery with SBRT, the introduction of SBRT has improved the survival of patients with medically inoperable Stage I NSCLC in a population-based analysis in the Netherlands⁸ and could be an option in patients who are operable, according to the results of a pooled analysis of two randomized trials [stereotactic ablative radiotherapy in stage 1 non-small-cell lung cancer patients who can undergo lobectomy (STARS) and radiosurgery or surgery for operable early stage non-small-cell lung cancer (ROSEL)].⁹ However, studies of current patterns of practice for NSCLC on 424 American Society for Radiation Oncology (ASTRO)-affiliated radiation oncologists in the USA found that only a minority of physicians have employed SBRT to treat patients with Stage I NSCLC. The reasons were that either SBRT was not available at their centre or they would rather adhere to a more conventional radiation therapy regime.¹⁰

Hypofractionated RT (HFRT) using three-dimensional (3D) RT can be considered in centres without SBRT capability or in patients not eligible for SBRT, those with a large tumour size, nodal involvement or those who have been treated with lung surgery previously. Some studies of HFRT using various radiation-dose schedules resulted in improved outcomes beyond those achieved with conventionally fractionated RT.^{11–13}

The purpose of this study was to assess the toxicity and clinical outcome of dose-escalation HFRT with 3D RT for medically inoperable early-stage NSCLC.

METHODS AND MATERIALS

Patient selection

In this registry study, the eligibility criteria included patients with early-stage NSCLC who were medically inoperable. This included American Joint Committee on Cancer Stages T1-3 (chest wall tumours only) N0 and N1, if N1 tumours were next to the primary tumour. In addition, new primary tumours in patients who were previously operable could be included. If chemotherapy treatment was indicated, the patients were not eligible for the study. All patients were required to give written informed consent before enrolment in this study.

Furthermore, to determine “operability”, patients were evaluated prior to enrolment by an experienced thoracic surgeon. Standard indications defining a patient to be “medically inoperable” included baseline forced expiratory volume in 1 s <40% predicted; post-operative forced expiratory volume in 1 s <30% predicted; carbon monoxide-diffusing capacity <40% predicted; baseline hypoxaemia or hypercapnia; severe pulmonary hypertension; diabetes mellitus with end-organ damage; severe cerebral, cardiovascular or peripheral vascular disease; or severe chronic heart disease.

Initial staging consisted of chest and brain imaging using CT, and positron emission tomography (PET) was required before being admitted to the study.

The age-adjusted Charlson score (CS) was scored for each patient.¹⁴ The primary lung tumour was not scored as comorbidity.

The maximum standardized uptake value (SUVmax) of the primary tumour was determined to study the prognostic significance of the pre-radiation SUVmax in early lung cancer treated with a hypofractionated RT regime. This was performed by outlining the area of interest, using the attenuation-corrected fluorine-18 fludeoxyglucose PET reconstruction images around it, and then calculating its volume automatically by the use of the formula $SUV(t) = C(t)/(\text{injected activity/body weight})$, where $C(t)$ is the tissue radioactivity concentration (MBq kg^{-1}) at time t .

Radiotherapy technique

Patients were immobilized with a conventional wing board. Slow CT scans and fast CT scans were obtained for all patients, with a CT slice thickness of 2.5 mm. The gross tumour volume was defined in both CT scans, and the internal target volume was

defined as the fusion of the gross tumour volume from the slow and fast CT scans.^{15–17}

The planning target volume was obtained by a 1-cm uniform expansion from the internal target volume. Patients were treated with four to six coplanar beams. The beam energy used for all patients was 6 MV, and the dose was prescribed for the mean planning target volume with heterogeneity correction.

All patients received HFRT to 57 Gy in 19 fractions followed by escalated doses, in 3-Gy fractions, up to a total dose of 66 Gy in 22 fractions. Dose escalation criteria required at least three patients per dose level and an absence of grade 3 or larger toxicity for more than 3 months. Dose escalation continued until either dose-limiting toxicities were reached or 66 Gy. If a dose-limiting toxicity was reached in a dose level, we considered the previous dose level the maximum tolerated dose. Thus, the radiation doses were 57, 60, 63 and 66 Gy in 11.8%, 20.6%, 44.0% and 23.6% of patients, respectively. The total dose of 66 Gy in 22 fractions was the maximum recommended dose for this study based on hypofractionated and SBRT studies,^{12,18} which had less restrictive criteria in terms of tumour size and late toxicity and proposed biological equivalent doses in the range of 83.2–146 Gy.

The dose–volume constraints were as follows: the maximum dose to the spinal cord ($\alpha/\beta = 2$) was not to exceed 40 Gy; the mean dose to the oesophagus and heart ($\alpha/\beta = 3$) was 20 Gy; and the volume of lungs receiving 20 Gy or more was to be kept <20%.

For treatment verification, standard portal images were taken of the orthogonal fields once per week and compared with the digitally reconstructed radiographs obtained from the planning CT.

Response and toxicity evaluation

Patients underwent a chest CT within 8 weeks of treatment completion. CT scans were repeated at 4 months and every 6 months thereafter. At each follow-up visit, patients were screened for acute and late toxicities and graded according to the Common Terminology Criteria for Adverse Effects v. 4.0.

Local failure was defined as progressive disease per CT. Tumour viability could be affirmed either through biopsy-confirmed carcinoma or by PET imaging, with uptake intensities similar to those in the pre-treatment staging.

Tumour size was assessed using the response evaluation criteria in solid tumours, where complete response is total disappearance and partial response is a decrease in the longest tumour diameter of 30% or more.¹⁹

Outcomes and statistical analysis

The study outcomes were defined as follows: OS was defined as from the time of diagnosis to last follow-up or time of death. The time to progression (TTP) was defined as the time of diagnosis to development of the first evidence of clinical or radiological disease, either local or regional or metastatic

disease (patients dying without development of evidence of disease were censored at the time of death). Local control (LC) was defined as from the time of diagnosis to development of local recurrence. Similarly, regional control (RC) and time to distant metastasis (TTM) were defined as from the time of diagnosis to development of regional and metastatic recurrence, respectively.

Kaplan–Meier estimates were obtained for OS, LC, RC, locoregional control (LRC), TTP and TTM. Tumour size (<45 vs ≥ 45 mm), CS (≤ 5 vs >5), T-stage (T1–2 vs others), SUVmax (<7 vs ≥ 7) and age (<75 vs ≥ 75 years) were evaluated as predictors of outcome. The log-rank test was used to compare the survival distributions, and a *p*-value was considered statistically significant if <0.05 . All analyses were performed using R software v. 3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From August 2008 to April 2013, 34 patients with inoperable early-stage NSCLC (28 patients with primary tumour and 6 patients with isolated relapse) were treated with HFRT. The median follow-up time was 33 months (range 7–74 months).

Patient and tumour characteristics are summarized in Table 1. The patient median age was 75 years (range 37–90 years) and the median CS was 5 (range 2–8). The mean tumour size was 32.3 mm (range 12–60 mm), and 20.6% were clinical Stage T1. All RT treatment-planning constraints for the organs at risk were met, and all patients completed the treatment as planned with no unscheduled interruptions. Treatment was well tolerated without any grade 3 or higher acute/late treatment-related toxicity. Five patients experienced grade 2 acute toxicity, occurring within 8 weeks of treatment (dyspnoea $n = 5$ and cough $n = 1$). Grade 2 late side effects, occurring more than 8 weeks after treatment, were seen in five patients (dyspnoea $n = 4$ and cough $n = 1$).

As many as 33 of the 34 patients with follow-up CT scan were available for tumour response assessment. One patient could not be evaluated because of a bilateral lung infection process during the follow-up that finally caused a non-cancer-related death. Of the 33 patients who could be evaluated, we observed complete response in 8 (24%) patients; a partial response in 13 (39%) patients; a demonstrated stable disease in 7 (21%) patients; and lastly, 5 (15%) patients with local progression.

LC was 80.4% at 2 years [95% confidence interval (CI) = 66.1–97.9%], and RC was 78% (95% CI = 63.7–95.5%). LRC was 67.2% (95% CI = 51.4–87.7%) (Figure 1). The OS and TTP at 2 years were: 60.2% (95% CI = 45.4–79.8%) and 59.2% (95% CI = 43.6–80.3%), respectively. The median OS was 33 months. TTM was 80% (95% CI = 66.8–95.8%).

Collectively, 12 patients had recurrence of cancer. Their patterns of failure are graphically depicted in Figure 2 and included five patients with primary local tumours: one patient with a single primary local tumour and the other four patients with combining local and regional recurrence (one patient); local and

metastatic disease (two patients); or local, regional and metastatic disease (one patient). Metastatic or regional recurrence alone was reported in three patients and one patient, respectively.

Table 1. Patient and tumour characteristics

Characteristic	Value
Age (years)	
Median	75
Range	37–90
Gender, number (%)	
Male	32 (94)
Female	2 (6)
FEV1 (% predicted)	
Mean	1.4 (55)
Range	0.88–2.49 (29–91)
FVC, value (%)	
Mean	2.36 (60.3)
Range	0.85–3 (18–85)
DLCO (%)	
Mean	28
Range	15–86
CS value	
Mean	4
Range	2–8
Tumour volume (mm)	
Mean	32.3
Range	12–60
Pathology, number (%)	
Adenocarcinoma	12 (35.3)
Squamous-cell carcinoma	16 (48)
Others	3 (8.8)
Not verified	3 (8.8)
TMN category, number (%)	
T1 N0	7 (20.6)
T2 N0	14 (41.2)
T3 N0	4 (11.8)
N1	3 (8.8)
Isolated relapse	6 (17.6)
Tumour location, number (%)	
Central	4 (13.3)
Peripheral	30 (86.7)

CS, Charlson score; DLCO, diffusion capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

Figure 1. Kaplan-Meier estimates of overall survival (a), local control (b), regional control (c) and time to distant metastasis (d).

4 of the 16 patients who died during the period of observation after treatment did so because of lung cancer (12% of the entire population). 12 (88%) patients died of other causes related to comorbidities.

For T1-2 N0 and tumour size <45 mm in diameter ($n = 19$), the OS and TTP at 2 years were 71.3% (95% CI = 52.6–96.4%) and 75.1% (95% CI = 56.6–99.7%), respectively (Figure 3). In addition, LC and

Figure 2. Patterns of failure. Venn diagram showing the number of patients with local, regional, metastases or combined failure.

RC at 2 years were 85.1% (95% CI = 68–100%) and 93.8% (95% CI = 82.6–100%), respectively.

Univariate analysis

Table 2 presents the variables and results of the univariate analysis. T-stage and tumour size were statistically significant in OS, TTP, RC and TTM. The analysis included the variables, T-stage, tumour size, CS, age and total dose.

All the patient characteristics and pre-treatment SUVmax values were analyzed in the univariate analysis. T1-2 N0 stage and tumour volume <45 mm were a significant prognostic factor that correlated with OS (71% vs 47%, $p = 0.009$), LRC (94% vs 54%, $p = 0.014$) and TTP (75% vs 37%, $p = 0.008$).

No significant correlation was found related to CS ≥ 3 , 4 or 5 with OS, TTP, LC, LRC or TTM.

DISCUSSION

The purpose of this study was to evaluate the clinical outcome of HFRT for patients with early-stage NSCLC who were medically inoperable. This included local recurrence or new primary tumours in patients who were previously operable, and N1 if these were proximal to the primary tumour. All patients were discussed in a multidisciplinary tumour board and received exclusive RT. A 2-year OS of 60% and primary control rate of 80% suggest that HFRT is safe and has better results than those obtained with more conventional schedules, as reported in the past.²⁰

The results of this study were achieved with rather simple RT technical requirements, *i.e.* fast and slow CTs, 3D dose planning and portal vision imaging for treatment verification. These favourable results could therefore be effectively applied in centres lacking SBRT technology or in patients ineligible for SBRT. Moreover, this hypofractionated schedule could also be an option to explore for Stages II–III lung cancer.

Our results are similar to those reported in previous HFRT studies. The National Cancer Institute of Canada (NCIC) Clinical Trials Group BR 35 study¹³ revealed a 2-year tumour control rate of 87.4% and a 2-year OS of 68.7% after delivering 60 Gy in 15 fractions using 3D for peripherally located tumours <5 cm and with Stages T1-3 N0 M0 NSCLC. Furthermore, the Cancer and Leukemia Group B (CALGB)

39904 trial¹¹ in a Phase I study comprised 39 patients with NSCLC T1-2 N0 M0 <4 cm, who were treated with increasing hypofractionated RT to a total dose of 70 Gy and with reduced number of fractions. They reported a tumour LC of 77% at 2 years and an actuarial median OS of 38.5 months. However, our study is not biased in patient selection, as there was no restriction in tumour size. Our study had a higher proportion of large tumours (T1 67% in CALGB 39904 trial and 63.8% in NCIC BR 25 trials vs 20.6% in our trial). Furthermore, our study was not limited to peripheral lesions, and the ratio of female patients was in proportion to epidemiological data in early medically inoperable NSCLC. We report a 60% OS and 80% LC at 2 years. When patients with favourable outcomes were separately analyzed (T1-2 N0 with tumour size <45 mm), an OS value of 71% and an LC of 85% were observed, similar to previously reported trials.

The incidence of regional failure (RF) is higher in our study (22% at 2 years) than in the CALGB 39904 trial, 2.7% at 2 years, and 8.8% at 2 years in the NCIC BR 25 trial. This could be related to a less favourable TNM selection (N1, second primary tumours and large tumour size) in spite of the mandatory PET/CT screening. If only the more favourable group of patients is analyzed (T1-2 N0 with tumour size <45 mm), the RF would be significantly reduced to 6% at 2 years. These results suggest that despite achieving acceptable results with this scheme of RT, patients who are unfavourably staged could benefit from some sort of systemic treatment.

In our study, the comorbidity was severe, since 22 (61%) patients had CS ≥ 5 . This score has been shown to correlate with an increased risk of mortality.¹⁴ Kopek et al²¹ in 88 patients with consecutive medically inoperable early-lung cancer treated with SBRT identified that CS ≥ 5 was a significant predictor of OS, whereas Mokhes et al²² in 425 consecutive patients (216 surgery, 209 SBRT) showed that CS was associated with long-term mortality in the surgical group of older age (CS = 4) and in the SBRT group (CS ≥ 5). We expected that this parameter could minimize the subjective factors involved in the clinical assessments when indicating a radical HFRT. Nevertheless, we did not find any correlation with OS, probably because of the limitation in the number of patients included in our study. However, despite the high CS in our study, the OS remained at 60% at 2 years, which does not differ from other SBRT studies.²³

A dose response was not observed, although the small number of patients in each cohort limits this analysis.

There are conflicting results in examining the effect of tumour size on LC. Most of the publications refer to tumours <4–5 cm, not only for LRC and distant failure but also for toxicity owing to larger irradiated volumes. Even though our study allowed for larger tumour sizes, *i.e.* >45 mm, there were no statistically significant relationships between the large tumour size vs increased toxicity (any patient who developed G3 toxicity or needs to stop the treatment) or between tumour size vs decreased LC. However, our data confirmed that the dominant pattern of relapse in these large

Figure 3. Kaplan-Meier estimates and log-rank test comparison of the group having T1-2 N0 and tumour size <45 mm vs others for overall survival (a), local control (b), regional control (c) and time to distant metastasis (d).

tumours is not connected with local failure, as was similarly reported by other authors in both SBRT²⁴ and hypofractionated studies.¹³ However, large tumours were associated with poorer rates of OS, TTP, RF and TTM. Thus, these findings suggest that systemic therapy could be an option for large tumours with concurrent hypofractionated RT.

We can conclude that the recommended dose is 66 Gy in 22 fractions. However, in order to evaluate the safety and efficacy of this dose fractionation schedule, a Phase 2 trial is warranted. HFRT remains a good option for patients who are considered inappropriate for SBRT or in centres that lack SBRT capability.

Table 2. The variables and results of univariate analysis on overall survival, local control, locoregional control, relapse-free survival and distant progression-free survival

Characteristic	Overall survival (%)	Local control (%)	Locoregional control (%)	Time to progression (%)	Time to distant metastasis (%)
Age (years) (number at risk)	$p = 0.6$	$p = 0.37$	$p = 0.84$	$p = 0.929$	$p = 0.95$
≤75 (15)	66 (45.7–95.4)	74 (13.2–52.2)	65.8 (43.30–100)	59.2 (37.1–94.5)	83.9 (65.7–100)
>75 (19)	54.4 (35.1–84.4)	84.4 (10.4–66.2)	67.5 (47.2–96.6)	58.4 (38.6–88.3)	76.8 (59.2–99.8)
T stage	$p = 0.02$	$p = 0.7$	$p = 0.13$	$p = 0.03$	$p = 0.11$
T1-2 N0	67.4 (48.9–93)	80.6 (62.9–100)	75.6 (57.2–100)	71.2 (52.6–96.3)	89.2 (76–100)
Other	50 (29.6–84.4)	81.5 (61.1–100)	54.4 (31.2–94.9)	39.9 (19.3–82.6)	64.5 (41.3–100)
Tumour size	$p = 0.02$	$p = 0.33$	$p = 0.06$	$p = 0.008$	$p = 0.014$
<45 mm (30)	64.9 (49.4–85.3)	82.11 (67.4–100)	70.3 (53.9–91.8)	63.8 (47.3–86.1)	84.68 (71.9–99.7)
≥45 mm (4)	25 (4.6–100)	75 (42.6–100)	50 (18.8–100)	25 (4.6–100)	50 (18.8–100)
SUVmax	$p = 0.166$	$p = 0.583$	$p = 0.726$	$p = 0.51$	$p = 0.265$
<7 (17)	81.5 (64.5–100)	85.2 (68–100)	65.8 (43.3–100)	61.4 (41.3–91.3)	87.5 (72.7–100)
≥7 (15)	35.6 (17–74.4)	68.4 (43.4–100)	64.2 (42.8–96.1)	52.1 (29.9–90.8)	68.5 (46.7–100)
Charlson score	$p = 0.513$	$p = 0.891$	$p = 0.355$	$p = 0.965$	$p = 0.642$
<5 (12)	73.3 (51.5–100)	81.5 (61.1–100)	58.3 (36.2–94.1)	58.3 (36.2–94.1)	82.5 (63.1–100)
≥5 (22)	52.9 (35.1–79.6)	80.7 (62.9–100)	75 (54.7–100)	59.9 (40.4–88.7)	78.5 (61.8–99.8)

SUVmax, maximum standardized uptake value.

REFERENCES

- Kaskowitz L, Graham MV, Emami B, Halverson KJ, Rush C. Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1993; **27**: 517–23. doi: [http://dx.doi.org/10.1016/0360-3016\(93\)90374-5](http://dx.doi.org/10.1016/0360-3016(93)90374-5)
- Dosoretz DE, Katin MJ, Blitzer PH, Rubenstein JH, Galmarini DH, Garton GR, et al. Medically inoperable lung carcinoma: the role of radiation therapy. *Semin Radiat Oncol* 1996; **6**: 98–104. doi: [http://dx.doi.org/10.1016/S1053-4296\(96\)80006-3](http://dx.doi.org/10.1016/S1053-4296(96)80006-3)
- McGarry RC, Song G, des Rosiers P, Timmerman R. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. *Chest* 2002; **121**: 1155–8.
- Raz DJ, Zell JA, Ou SH, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest* 2007; **132**: 193–9. doi: <http://dx.doi.org/10.1378/chest.06-3096>
- Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1427–31. doi: <http://dx.doi.org/10.1016/j.ijrobp.2005.05.034>
- Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 685–92. doi: <http://dx.doi.org/10.1016/j.ijrobp.2007.10.053>
- Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303**: 1070–6. doi: <http://dx.doi.org/10.1001/jama.2010.261>
- Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010; **28**: 5153–9. doi: <http://dx.doi.org/10.1200/JCO.2010.30.0731>
- Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16**: 630–7. doi: [http://dx.doi.org/10.1016/S1470-2045\(15\)70168-3](http://dx.doi.org/10.1016/S1470-2045(15)70168-3)
- Kong FM, Cuneo KC, Wang L, Bonner JA, Gaspar LE, Komaki R, et al. Patterns of practice in radiation therapy for non-small cell lung cancer among members of the American Society for Radiation Oncology. *Pract Radiat Oncol* 2014; **4**: e133–41. doi: <http://dx.doi.org/10.1016/j.prro.2013.05.002>
- Bogart JA, Hodgson L, Seagren SL, Blackstock AW, Wang X, Lenox R, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. *J Clin Oncol* 2010; **28**: 202–6. doi: <http://dx.doi.org/10.1200/JCO.2009.25.0753>
- Lee JH, Wu HG, Kim HJ, Park CI, Lee SH, Kim DW, et al. Hypofractionated three-dimensional conformal radiotherapy for medically inoperable early stage non-small-cell lung cancer. *Radiat Oncol J* 2013; **31**:

- 18–24. doi: <http://dx.doi.org/10.3857/roj.2013.31.1.18>
13. Cheung P, Faria S, Ahmed S, Chabot P, Greenland J, Kurien E, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. *J Natl Cancer Inst* 2014; **106**(8). doi: <http://dx.doi.org/10.1093/jnci/dju164>.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83. doi: [http://dx.doi.org/10.1016/0021-9681\(87\)90171-8](http://dx.doi.org/10.1016/0021-9681(87)90171-8)
15. Lagerwaard FJ, Van Sornsens de Koste JR, Nijssen-Visser MR, Schuchhard-Schipper RH, Oei SS, Munne A, et al. Multiple “slow” CT scans for incorporating lung tumor mobility in radiotherapy planning. *Int J Radiat Oncol Biol Phys* 2001; **51**: 932–7. doi: [http://dx.doi.org/10.1016/S0360-3016\(01\)01716-3](http://dx.doi.org/10.1016/S0360-3016(01)01716-3)
16. Jaramillo OC, Armada MM, Seoane A, León LA, Delgado C, Campos A, et al. Slow CT scan for incorporating lung tumor mobility in radiotherapy planning. *Rep Pract Oncol Radiother* 2013; **18**(Suppl. 1):S259. doi: <http://dx.doi.org/10.1016/j.rpor.2013.03.297>
17. Wurstbauer K, Deutschmann H, Kopp P, Sedlmayer F. Radiotherapy planning for lung cancer: slow CTs allow the drawing of tighter margins. *Radiother Oncol* 2005; **75**: 165–70. doi: <http://dx.doi.org/10.1016/j.radonc.2005.02.003>
18. Zhang J, Yang F, Li B, Li H, Liu J, Huang W, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; **81**: e305–16. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.04.034>
19. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16. doi: <http://dx.doi.org/10.1093/jnci/92.3.205>
20. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. *Thorax* 2001; **56**: 628–38. doi: <http://dx.doi.org/10.1136/thorax.56.8.628>
21. Kopeck N, Paludan M, Petersen J, Hansen AT, Grau C, Hoyer M. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. *Radiother Oncol* 2009; **93**: 402–7. doi: <http://dx.doi.org/10.1016/j.radonc.2009.06.002>
22. Mokhles S, Nuytens JJ, Maat AP, Birim Ö, Aerts JG, Bogers AJ, et al. Survival and treatment of non-small cell lung cancer stage I-II treated surgically or with stereotactic body radiotherapy: patient and tumor-specific factors affect the prognosis. *Ann Surg Oncol* 2015; **22**: 316–23. doi: <http://dx.doi.org/10.1245/s10434-014-3860-x>
23. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman B, Senan S. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiother Oncol* 2011; **101**: 240–4. doi: <http://dx.doi.org/10.1016/j.radonc.2011.06.029>
24. Allibhai Z, Taremi M, Bezjak A, Brade A, Hope AJ, Sun A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013; **87**: 1064–70. doi: <http://dx.doi.org/10.1016/j.ijrobp.2013.08.020>