International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Stereotactic Body Radiation Therapy for Oligometastases to the Lung: A Phase 2 Study

Joost J. Nuyttens, MD, PhD,* Noëlle C.M.G. van der Voort van Zyp, MD, PhD,* Cornelis Verhoef, MD, PhD,† A. Maat, MD,‡ Robertus J. van Klaveren, MD, PhD,§ Bronno van der Holt, PhD,‖ Joachim Aerts, MD, PhD,§ and Mischa Hoogeman, PhD*

*Departments of *Radiation Oncology, Surgical Oncology,† and §Pulmonology and ‖Clinical Trial Center, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; and ‡Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, The Netherlands*

Received Jun 28, 2014, and in revised form Sep 30, 2014. Accepted for publication Oct 10, 2014.

Summary

Patients with oligometastatic disease to the lung who refused chemotherapy were treated with stereotactic body radiation therapy. Depending on the tumor size and the location of the tumor, a different treatment schedule was given. These patients had a promising outcome: good local control, a 4-year overall survival of 38%, and tolerable toxicity.

Purpose: To assess, in a phase 2 study, the efficacy and toxicity of stereotactic body radiation therapy for oligometastases to the lung in inoperable patients.

Methods and Materials: Patients with lung metastases were included in this study if (*1*) the primary tumor was controlled; (*2*) patients were ineligible for or refused surgery and chemotherapy; and (*3*) patients had 5 or fewer metastatic lesions in no more than 2 organs. Large peripheral tumors were treated with a dose of 60 Gy (3 fractions), small peripheral tumors with 30 Gy (1 fraction), central tumors received 60 Gy (5 fractions), and mediastinal tumors or tumors close to the esophagus received 56 Gy (7 fractions).

Results: Thirty patients with 57 metastatic lung tumors from various primary cancers were analyzed. The median follow-up was 36 months (range, 4-60 months). At 2 years, local control for the 11 central tumors was 100%, for the 23 peripheral tumors treated to 60 Gy it was 91%, and for the 23 tumors treated in a single 30-Gy fraction it was 74% ($P = .13$). This resulted in an overall local control rate at 1 year of 79%, with a 2-sided 80% confidence interval of 67% to 87%. Because the hypothesized value of 70% lies within the confidence interval, we cannot reject the hypothesis that the true local control rate at 1 year is $\leq$70%, and therefore we did not achieve the goal of the study: an actuarial local control of the treated lung lesions at 1 year of 90%. The 4-year overall survival rate was 38%. Grade 3 acute toxicity occurred in 5 patients. Three patients complained of chronic grade 3 toxicity, including pain, fatigue, and pneumonitis, and 3 patients had rib fractures.

Conclusions: The local control was promising, and the 4-year overall survival rate was 38%. The treatment was well tolerated, even for central lesions.

Reprint requests to: Joost J. Nuyttens, MD, PhD, Department of Radiation Oncology, Erasmus MC Cancer Institute, Postbus 2040, 3000 CA Rotterdam, The Netherlands. Tel: (+31) 1-7041347; E-mail: j.nuyttens@erasmusmc.nl

Conflict of interest: Erasmus MC Cancer Institute has a research collaboration with Accuray Inc.

Int J Radiation Oncol Biol Phys, Vol. 91, No. 2, pp. 337–343, 2015
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.10.021

Introduction

Surgical series have reported good outcomes for early-stage non-small cell lung cancer. This is also true for stereotactic body radiation therapy (SBRT), a treatment modality that has been investigated mostly in patients unable to undergo surgery (1-4). Patients with metastatic disease to the lung, who are referred for radiation therapy, form a very different patient group for a number of reasons: they often have centrally located lesions, may have 1 or more lesions in each lung, have previously undergone a lobectomy or pneumonectomy, or are bad surgical candidates owing to their medical condition. Previous studies have shown potential for SBRT for the treatment of metastases to the lung (5-8). For centrally located lesions, we reported recently a 2-year local control (LC) rate of 64% and 2-year overall survival (OS) rate of 75% (9). The potential role of SBRT in the management of oligometastatic disease has been highlighted in recent reviews (10-13).

We thought it was important to further investigate the potential role of SBRT for oligometastases to the lung. To this end, we began a phase 2 study for the treatment of oligometastatic disease to the lung using SBRT with real-time tumor tracking. The primary objective of the study was to determine whether SBRT to a high biological dose delivered to a limited treatment volume could achieve a local control rate at 1 year (LCR_{1y}) of >70%. Additional objectives were to determine OS and disease-free survival (DFS) and to evaluate treatment-related toxicity.

Methods and Materials

Patient selection

Patients were considered eligible for SBRT if they had inoperable metastases to the lung, refused surgery or chemotherapy, were not eligible for chemotherapy, and if their age was >18 years. Patients were considered inoperable in the presence of severe comorbidity or when tumors were deemed unresectable. Comorbidity was registered using the Charlson comorbidity index and the cumulative illness ranking score. The patient was expected to have a minimum life expectancy of 6 months. The metastatic disease had to be limited to a maximum of 2 organs, and in total no more than 5 metastatic lesions in these 2 organs were allowed, but previous treated metastasis in other organs did not count. The primary tumor had to be controlled and had to be treated at least 4 months before the diagnosis of the metastasis. The diagnostic imaging included at least a positron emission tomography (PET) scan and CT scan of the thorax/abdomen, of which one was not older than 4 weeks at the time of referral for SBRT. Patients with synchronous metastases were not allowed to enter the study. The study was approved by the institutional review board of the Erasmus MC Cancer Institute, with approval number MEC-2008-292, and informed consent was obtained in all patients before registration. This trial was registered at www.trialregister.nl as NTR1788.

Treatment planning and delivery

All patients were treated with real-time tumor tracking to account for respiratory-induced tumor motion. During treatment delivery with the CyberKnife, tumor motion was detected by radiopaque markers that were implanted in or around the tumor (14). The gross tumor volume, defined as visible tumor, was contoured using lung window. We added a 5-mm margin to the gross tumor volume to account for microscopic tumor extension and residual inaccuracies of the real-time tumor tracking (15). The radiation schedule used depended on the size and location of the tumor. Large peripheral tumors (>3 cm) received 60 Gy in 3 fractions, and small peripheral tumors (≤3 cm) received 30 Gy in a single fraction. Central tumors (located within 2 cm of the trachea and main bronchus) received 60 Gy in 5 fractions unless the tumor was located close to the esophagus or in the mediastinum. In this case, the tumor was treated with 7 fractions of 8 Gy (56 Gy). The dose was prescribed to the 75% to 85% isodose line, covering at least 95% of the planning target volume. The maximum dose defined the 100% isodose line.

The treatment planning was carried out with a dedicated treatment planning system (Multiplan, version 3.5; Accuray, Sunnyvale, CA). The dose distribution was calculated using the equivalent path-length method to account for tissue heterogeneities. Table 1 lists the maximum dose limits to a point or volume within the relevant critical organs. A treatment plan that exceeded at least one of these limits was recorded as a major protocol violation.

Follow-up

The first clinical examination was performed 3 weeks after SBRT. Clinical visits and CT scans were performed 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after treatment. Follow-up PET scans were only obtained for evaluation of CT abnormalities. Toxicity was defined as acute if it occurred within 4 months and late if it occurred thereafter. All acute and late adverse events were reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events, version 3.0.

Definition of endpoints

Local control was calculated from the start of radiation therapy to the date of diagnosis of a local recurrence. Patients without a local recurrence were censored on the last day of contact. In the absence of biopsy confirming viable carcinoma, local recurrence was defined as a 20% increase in tumor size on the CT scan compared with the previous CT scan according to the Response Evaluation Criteria In Solid Tumors (version 1.0). In addition, a corresponding

Table 1 Dose constraints

Dose constraints for		Dose (Gy per fraction)			
Organ	Volume	1 × 30 Gy	3 × 20 Gy	5 × 12 Gy	7 × 8 Gy
Spinal cord	Any point	12.5	8	5.5	4.5
Esophagus	Any point	13	7	7	6
Heart	Any point	15	12	10	8
Trachea and main bronchus	Any point	16	10	10	8
Plexus brachialis	Any point	14	8	6	5
Liver	Any point	30	20	12	8
Lung	V_{20} (EQD2)	<31%	<31%	<31%	<31%

Abbreviation: V_{20} (EQD2): the volume (in %) receiving ≥20 Gy, expressed in equivalent dose of 2 Gy.
Values are dose (Gy per fraction) or percentage.

avid lesion on the PET scan was required, or the measurable tumor was biopsied confirming viable carcinoma. Disease-free survival was calculated from the start of radiation therapy to the date of a local recurrence, regional or distant metastasis, or death from any cause, whichever came first. Overall survival was measured from start radiation therapy until death from any cause. Patients still alive at the date of last contact were censored. A corrected DFS was calculated as follows: if a patient developed a new metastasis or a local recurrence and this event was treated with a local curative treatment such as SBRT or surgery, then this event was censored until the patient developed a new metastasis or a local recurrence that was not treated with a local therapy or until the patient died.

Statistical considerations

The aim of this trial was to assess the efficacy of SBRT as treatment for metastases to the lung. For the sample size calculation, the LCR_{1y} was considered as primary endpoint, whereby in patients with multiple metastases the time to first local recurrence was taken into account. For the design, a Simon 2-stage design was used (16). A true LCR_{1y} of 70% was considered insufficient, whereas a true LCR_{1y} of at least 90% would imply that the therapeutic activity is sufficiently high and therefore the proposed SBRT scheme should warrant further investigation in clinical trials. With $\alpha = 0.10$ and $\beta = 0.10$, the required number of eligible patients was 28. To account for dropout due to ineligibility, the target number of patients was 30. Local control, DFS, and OS at the patient level were estimated using the Kaplan-Meier method. A separate analysis (Kaplan-Meier method) was performed for LC per tumor.

Results

Thirty patients with 57 metastatic lung tumors were included in the trial and analyzed. Patient and tumor characteristics are shown in Table 2. Primary tumors included 19 colorectal tumors, 2 breast carcinoma, 2 lung carcinoma, 2 melanoma, 2 sarcoma, 1 bladder carcinoma, 1 cervix carcinoma, and 1 endometrium carcinoma. Five patients had a metastasis in the lung and in another organ at the time of referral for SBRT. Fifteen patients were previously treated for metastases elsewhere than in the lung (8 in the liver, 2 in the brain, and 1 each in the stomach, rib, kidney, skin, and ovary). Despite the positive PET scans of the lung nodules, the lung metastases of 7 patients were confirmed with a biopsy to ensure they were malign nodules. The total number of previous and current metastases was 1-3 in 19 patients and 4-10 in 11 patients. Only 1 patient was diagnosed with a solitary metastasis. Eleven tumors were centrally located; 4 of these were treated with 60 Gy in 5 fractions, and 7 were treated with 7 fractions of 8 Gy. Twenty-three peripheral tumors were treated to a total dose of 60 Gy in 3 fractions, and 23 were treated with a single fraction of 30 Gy. The median prescription isodose was 80% (range, 75%-93%). None of the patients received chemotherapy as primary treatment for the metastases.

Table 2 Patient, tumor, and treatment characteristics

Gender	
Male	16
Female	14
No. of lung metastasis treated with SBRT	
1	14
2	10
3	2
4	3
5	1
Time between primary tumor and metastases (mo)	34 (12-109)
Tumor size of the whole group (mm)	13 (6-67)
Tumor size central tumors (mm)	41 (10-67)
Tumor size treated with 1 fraction (mm)	10 (6-26)
Tumor size treated with 3 fractions (mm)	14 (8-33)
Age at time of irradiation (y)	66 (44-78)
Charlson comorbidity score	2 (0-11)
Cumulative illness score	4 (0-13)
Follow-up if still alive (m)	44 (21-60)

Values are number or median (range).

Marker placement

In total, 171 markers were placed for tumor tracking using 1 of 3 different methods: (*1*) the intravascular method was used to place 157 fiducials near 52 tumors (26 patients); (*2*) the percutaneous intrapulmonary method was used to place 7 fiducials in 3 tumors (2 patients); and (*3*) the endoscopic ultrasound was used to place 7 fiducials in 2 tumors (2 patients). A pneumothorax or other severe side effects from the fiducial placement did not occur.

Outcome

The primary endpoint was LC at the patient level. A total of 7 patients had local recurrence, among them 6 patients within 1 year. This resulted in an LCR_{1y} of 79%, with a 2-sided 80% confidence interval (CI) of 67% to 87%. Because the hypothesized value of 70% lies within the CI, we cannot reject the hypothesis that the true LCR_{1y} is $\leq$70%.

However, at 2 years, LC for central tumors was 100%, and LC for peripheral tumors treated with 3 fractions of 20 Gy was 90% (95% CI 67%-98%). A substantially lower LC at 2 years (74%, 95% CI 51%-87%) was found for peripheral tumors treated with a single fraction of 30 Gy (P = .13; Fig. 1). At the interim analysis, 3 local recurrences were diagnosed in the first 9 patients. These tumors were all treated with a single fraction of 30 Gy. As the protocol defined, an amendment was made to treat all small peripheral tumors with 60 Gy in 3 fractions. In total, 7 patients had 10 local recurrences: 7 tumors were treated with a single fraction of 30 Gy (5 patients), 2 with 3 fractions of 20 Gy (1 patient), and 1 patient with 7 fractions of 8 Gy. Three patients (5 tumors) were salvaged with surgery, and 1 patient with radiofrequency ablation (1 tumor). The other 3 patients (4 tumors) were inoperable. None of the patients were treated with adjuvant chemotherapy after the SBRT.

The 2-year and 4-year OS rates were 63% (95% CI 43%-78%) and 38% (95% CI 20%-56%), respectively (Fig. 2). Seventeen patients had died, all except 1 due to tumor progression. The median follow-up (time from start of radiation therapy until date last alive or date of death, whichever applicable) of all patients was 36 months (range, 4-60 months), and for the 13 patients who were still alive it was 44 months (range, 21-60 months). Patients with only peripheral tumors had a 3-year OS rate of 58% (95% CI 33%-76%), compared with an OS rate of 53% (95% CI 21%-77%) in patients with central tumors. Patients with a total of 4 or more metastases in their medical history had a 3-year OS rate of 64% (95% CI 30%-85%), compared with 53% (95% CI 29%-72%) in patients with a total of 1-3 metastases (P = .44). Twenty-six patients (87%) developed new metastases. Four metastases were treated with SBRT, 2 with radiofrequency ablation, 1 with a resection; 13 patients were treated with chemotherapy, and 6 patients were treated with best supportive care because they refused or were not eligible for chemotherapy. Disease-free survival at 2 years was 17% (95% CI 6%-32%), and the corrected DFS rate at 2 years was 33% (95% CI 18%-50%) (Fig. 2).

Toxicity

Three patients complained of an acute grade 3 fatigue; 2 of them had grade 2 and 1 had grade 3 fatigue before treatment. Two patients complained of an acute grade 3 chest pain; 1 of them had grade 2 chest pain before treatment.

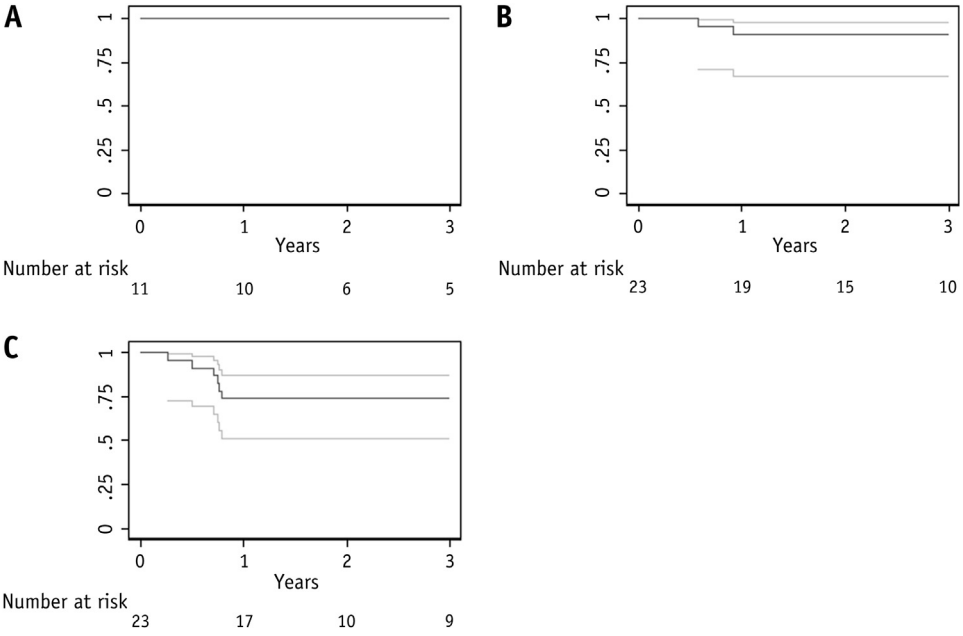

Fig. 1. Local tumor control for central tumors (A: 7 fractions of 8 Gy and 5 fractions of 12 Gy, n = 11) and for peripheral tumors (B: 3 fractions of 20 Gy, n = 23; and C: a single 30-Gy fraction, n = 23).

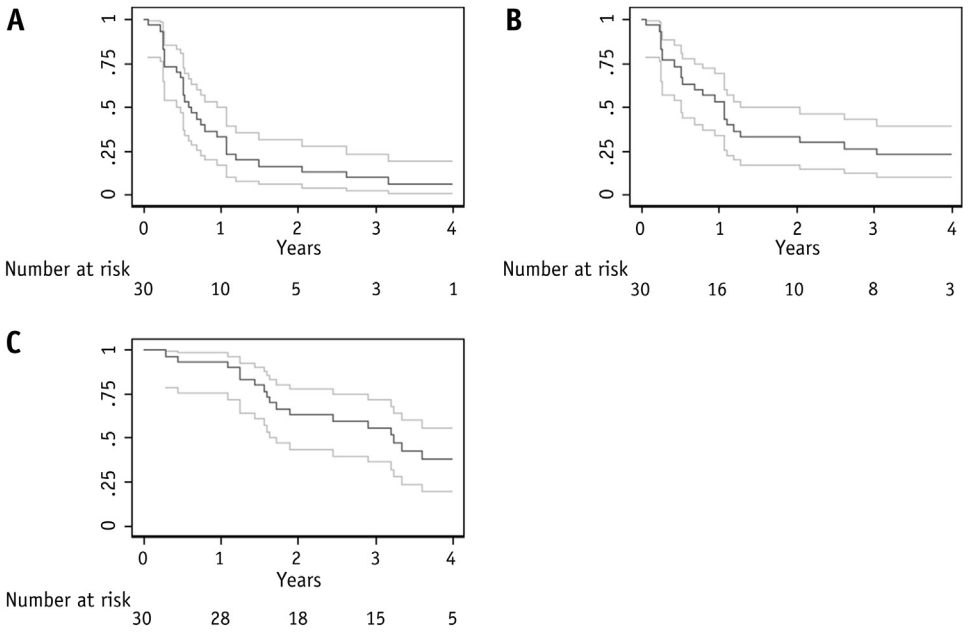

Fig. 2. Kaplan-Meier curves of (A) disease-free survival, (B) corrected disease-free survival, and (C) overall survival.

Four patients complained of an acute grade 3 dyspnea; 2 of them had grade 1 dyspnea and 1 grade 2 dyspnea before treatment. Table 3 shows the increase and decrease of acute complications relative to patient complaints before radiation therapy. Dyspnea worsened by 3 grades in 1 patient. Chest pain ameliorated in 3 patients but became worse in 5 patients.

Three patients complained of a chronic grade 3 toxicity: 1 patient had a chronic grade 3 pain, 2 patients had an episode of grade 3 fatigue (one had grade 2 fatigue before radiation therapy), and 1 patient had pneumonitis. Six patients complained of grade 2 fatigue, 4 of grade 2 cough, 1 of dyspnea grade 2, and 1 of a grade 2 chest pain. Three patients had a rib fracture. Table 4 shows the increase and decrease of late complications relative to patient complaints before radiation therapy.

Discussion

This study shows that excellent LC can be obtained for high-dose multiple-fraction treatments of peripheral and central lung metastases. Single-fraction (30 Gy) treatment was less efficacious, with an actuarial LCR_{1y} of 74%, and was abandoned during the trial. Other authors reported better outcomes with single-fraction treatments. Osti et al (17) treated 103 metastases in 66 patients with a single fraction of 23 and 30 Gy and reported an LCR_{1y} of 89%. Trakul et al (18) treated 62 tumors with a single fraction of 18-30 Gy (median 25 Gy) and reported an LCR_{1y} of 94%. A randomized, phase 2 study (Radiation Therapy Oncology Group protocol 0915) compared a single fraction of 34 Gy with 48 Gy in 4 fractions in 86 patients with early-stage lung cancer and found an actuarial LC rate of 97% in both treatment arms (19). Thus, there is no randomized evidence recommending any fractionation schedule over another in SBRT for pulmonary metastases. The low LC of the single fraction in our patient group can be caused by the treatment planning with equivalent path-length method. Previously we reported that recalculation with the Monte Carlo algorithm can result in a 33% dose reduction if the tumor is <3 cm (20). Because our median tumor size in this group was 10 mm, the real given dose could even have been much lower and could have resulted in a single dose of <20 Gy and therefore the cause of the local relapse. The overall survival at 2 years was very high (63%) for patients with oligometastatic disease, often in various locations. Although the patients were allowed to receive

Table 3 Change in symptoms in the acute phase after radiation therapy relative to pretreatment complaints

Toxicity	Increase of 3 grades	Increase of 2 grades	Increase of 1 grade	No change	Decrease of 1 grade	Decrease of 2 grades
Dyspnea	1	3	7	19	0	0
Fatigue	0	1	10	18	0	1
Chest pain	1	1	3	22	3	0
Cough	0	2	6	21	1	0
Dysphagia	0	0	6	24	0	0

Table 4 Change in symptoms in the late phase after radiation therapy relative to pretreatment complaints

Toxicity	Increase of 3 grades	Increase of 2 grades	Increase of 1 grade	No change	Decrease of 1 grade	Decrease of 2 grades
Dyspnea	1	0	5	15	0	1
Fatigue	1	0	8	6	6	1
Chest pain	1	1	0	17	2	1
Cough	0	4	5	12	1	0
Dysphagia	0	0	1	21	0	0

chemotherapy before the start of the SBRT, none of them did because they refused the chemotherapy or because they had too much comorbidity. They also did not receive chemotherapy shortly after the SBRT, as adjuvant treatment. We calculated a corrected DFS. This could also be called the chemo-free survival but is not because some patients had too much comorbidity and were therefore not eligible for chemotherapy. The corrected DFS at 2 years was 33%, meaning that we postponed theoretically the chemotherapy 2 years in one-third of the patients. Taking our findings of the corrected DFS together with the low toxicity, these outcomes suggest that local treatment of oligometastases with SBRT could prolong survival without seriously reducing a patient's quality of life. In a setting of oligometastatic disease SBRT has the potential to play a key role, but this should be further elucidated in randomized trials.

Stereotactic body radiation therapy for oligometastases has received increasing attention lately (10-12). The presumed state of oligometastasis, as described by Hellman and Weichselbaum (21), is one in which lesions are detected before the widespread distribution of malignant cells. In such a state an effective local therapy such as SBRT should, in theory, arrest the disease's progression and extend life. If a local therapy is associated with low toxicity, then life-extending treatment can be delivered without seriously impacting a patient's quality of life during or after treatment (12, 22). The use of modern imaging to detect smaller lesions and the combined use with surgical and chemotherapeutic approaches makes SBRT a powerful tool to control disease progression in the oligometastatic state. As in the present series, SBRT may also be applied in patients who cannot endure surgery or patients who have undergone repeated systemic treatments, thus extending the potential of a local treatment for patients who might have been treated palliatively.

Published reports of SBRT for lung oligometastases reveal a wide variety of dose and fractionation schemes, approaches to image guidance and motion management, and related margins to account for microscopic disease extension and radiation delivery errors. These reports typically show good long-term tumor control, but OS can be disappointing. For example, Milano et al (23) treated 121 patients with 5 or fewer metastases in 10 fractions of 5 Gy; 41% of patients had tumors in the lung. Overall survival was promising at the 2-year time point (50%), but at 6 years, although LC was maintained at relatively high levels, OS dropped to 20%. Similar outcomes have been reported frequently, with LC at 2-3 years ranging from 70% to 100% but overall survival generally being much lower, typically owing to progression outside the treated region (10). For example, in a phase 1/2 study in which 48-60 Gy was delivered in 3 fractions, Rusthoven et al (8) obtained a LC rate of 96% at 2 years, whereas median survival was only 19 months. In the present study 2-year and 4-year OS rates were not substantially different from those in prior studies. Two-year OS was 63%, although a majority of patients recurred distantly. Somewhat better OS may have been obtained despite recurrence, because several patients were eligible for additional curative treatment, either by SBRT or surgery. What we can conclude from this and other studies is that the selection of "oligometastatic" patients, who can benefit from long-term disease control, requires additional investigation.

Toxicity was generally low, including relatively few grade 2 or higher acute or chronic toxicities. In fact, several patients reported a lessening of complaints after SBRT. There were no grade 4 or 5 toxicities, and patients treated for central lesions endured SBRT well. Despite the risk to cause serious toxicity and death (24-26), the present study and others investigating SBRT for centrally located early-stage non-small cell lung cancer (9, 27-29) have shown that safe treatment in this region is possible if normal tissues are carefully protected. In the present study, in addition to tracking and correcting for respiratory motion in real time, the fractional dose was lowered when treating centrally, and a 7-fraction approach was selected for lesions near the esophagus. Especially given that many "oligometastatic" patients will eventually progress, it is critical that SBRT does not cause excessive toxicity or deterioration in quality of life.

Conclusion

Local control was excellent for peripheral and centrally located tumors treated with 3 or more fractions. The goal of the study was not reached owing to the low LC of the single fraction of 30 Gy, potentially because of limitations in the dose calculation to particularly small tumours included in this cohort. The 2- and 4-year OS rates were 63% and 38%, respectively. The overall local tumor control rate >90% at

1 year after 56-60 Gy, along with the low rate of toxicity, suggests that additional research is warranted to determine for which patients with oligometastases a survival benefit can be expected after treatment with SBRT.

References

1. Andratschke N, Zimmermann F, Boehm E, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: Patterns of failure. *Radiother Oncol* 2011;101:245-249.
2. Chi A, Liao Z, Nguyen NP, et al. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: Clinical implications. *Radiother Oncol* 2010;94:1-11.
3. 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.
4. Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. *Radiother Oncol* 2011;99:12-17.
5. Brown WT, Wu X, Fowler JF, et al. Lung metastases treated by CyberKnife image-guided robotic stereotactic radiosurgery at 41 months. *South Med J* 2008;101:376-382.
6. Okunieff P, Petersen AL, Philip A, et al. Stereotactic body radiation therapy (SBRT) for lung metastases. *Acta Oncol* 2006;45:808-817.
7. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for lung metastases. *Lung Cancer* 2012;75:77-81.
8. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009;27:1579-1584.
9. Nuyttens JJ, van der Voort van Zyp NC, Praag J, et al. Outcome of four-dimensional stereotactic radiotherapy for centrally located lung tumors. *Radiother Oncol* 2012;102:383-387.
10. Alongi F, Arcangeli S, Filippi AR, et al. Review and uses of stereotactic body radiation therapy for oligometastases. *Oncologist* 2012;17:1100-1107.
11. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: A systematic review. *J Thorac Oncol* 2010;5:1091-1099.
12. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013;14:e28-e37.
13. Lo SS, Teh BS, Mayr NA, et al. Stereotactic body radiation therapy for oligometastases. *Discov Med* 2010;10:247-254.
14. Nuyttens JJ, van de Pol M. The CyberKnife radiosurgery system for lung cancer. *Expert Rev Med Devices* 2012;9:465-475.
15. Hoogeman M, Prevost JB, Nuyttens J, et al. Clinical accuracy of the respiratory tumor tracking system of the cyberknife: Assessment by analysis of log files. *Int J Radiat Oncol Biol Phys* 2009;74:297-303.
16. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1-10.
17. Osti MF, Carnevale A, Valeriani M, et al. Clinical outcomes of single dose stereotactic radiotherapy for lung metastases. *Clin Lung Cancer* 2013;14:699-703.
18. Trakul N, Chang CN, Harris J, et al. Tumor volume-adapted dosing in stereotactic ablative radiotherapy of lung tumors. *Int J Radiat Oncol Biol Phys* 2012;84:231-237.
19. Videtic GM, Hu C, Singh A, et al. Radiation Therapy Oncology Group (RTOG) protocol 0915: A randomized phase 2 study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;87(Suppl.):S3.
20. van der Voort van Zyp NC, Hoogeman MS, van de Water S, et al. Clinical introduction of Monte Carlo treatment planning: A different prescription dose for non-small cell lung cancer according to tumor location and size. *Radiother Oncol* 2010;96:55-60.
21. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8-10.
22. van der Voort van Zyp NC, Prevost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010;77:31-37.
23. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: Long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012;83:878-886.
24. Le QT, Loo BW, Ho A, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol* 2006;1:802-809.
25. Milano MT, Chen Y, Katz AW, et al. Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy. *Radiother Oncol* 2009;91:301-306.
26. 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.
27. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685-692.
28. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol* 2009;4:838-844.
29. van der Voort van Zyp NC, van der Holt B, van Klaveren RJ, et al. Stereotactic body radiotherapy using real-time tumor tracking in octogenarians with non-small cell lung cancer. *Lung Cancer* 2010;69:296-301.