Radical Treatment of Non-Small-Cell Lung Cancer Patients with Synchronous Oligometastases Long-Term Results of a Prospective Phase II Trial (Nct01282450)

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Long-Term Results of a Prospective Phase II Trial (Nct01282450)

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Background: Stage IV non–small-cell lung cancer (NSCLC) patients with oligometastases (< 5 metastatic lesions) may experience long-term survival when all macroscopic tumor sites are treated radically, but no prospective data on NSCLCs with synchronous oligometastases are available.

Methods: A prospective single-arm phase II trial was conducted. The main inclusion criteria were pathologically proven NSCLC stage IV with less than five metastases at primary diagnosis, amendable for radical local treatment (surgery or radiotherapy). The study is listed in clinicaltrials.gov, number NCT01282450.

Results: Forty patients were enrolled, 39 of whom were evaluable (18 men, 21 women); mean age was 62.1 ± 9.2 years (range, 44–81). Twenty-nine (74%) had *local* stage III; 17 (44%) brain, seven (18%) bone, and four (10%) adrenal gland metastases. Thirty-five (87%) had a single metastatic lesion. Thirty-seven (95%) of the patients received chemotherapy as part of their primary treatment. Median overall survival (OS) was 13.5 months (95% confidence interval 7.6–19.4); 1-, 2-, and 3-year OS was 56.4%, 23.3%, and 17.5%, respectively. Median progression-free survival (PFS) was 12.1 months (95% confidence interval 9.6–14.3); 1-year PFS was 51.3%, and both 2- and 3-year PFS was 13.6%. Only two patients (5%) had a local recurrence. No patient or tumor parameter, including volume and ^{18}F-deoxyglucose uptake was significantly correlated with OS or PFS. The treatment was well tolerated.

Conclusion: In this phase II study, long-term PFS was found in a subgroup of NSCLC patients with synchronous oligometastases when treated radically. Identification of this favorable subgroup before therapy is needed.

Key Words: Non–small-cell lung cancer, Oligometastases, Radiotherapy, Chemotherapy, stage IV, Combined modality treatment, Individualized.

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Non–small-cell lung cancer (NSCLC) continues to be the leading cause of cancer deaths.[1] At diagnosis, approximately 50% of the patients have already overt disseminated cancer. These stage IV patients are generally considered to be incurable and are mostly treated palliatively. However, a transition between macroscopic local disease and multiple metastases (*polymetastases*) has been proposed and is referred to as *oligometastases*, being a limited number of metastases (usually <5), which also should be amenable for radical local therapy.[2–5] The hypothesis is that patients with less than five distant metastases may be curable when all detectable disease can be treated radically with a local modality, that is, surgery or radiotherapy.

The widespread introduction of stereotactic radiotherapy (stereotactic body radiotherapy [SBRT] or stereotactic ablative radiotherapy [SABR]) and of minimally invasive surgery has fuelled research in treating patients with oligometastases.[6–23] Indeed, local control of metastases can be obtained in virtually all parts of the body with a low proportion of patients experiencing severe side effects. However, only a few prospective studies have been published.[9–11,13,15] In these series, patients with several cancer sites have been included and both synchronous and metachronous metastases were studied. It is therefore not possible to separate the outcome of NSCLC from that of other tumors and to exclude the selection bias of the time distant metastases occur, although in retrospective series, subgroups of stage IV NSCLC patients may fare better than some stage III patients.[16] In the absence of prospective data in NSCLC with synchronous oligometastases, we launched a single-arm prospective phase II trial to investigate whether it would be possible to obtain a significant 2- and 3-year survival in these patients when treated radically.

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PATIENTS AND METHODS

Eligibility Criteria

Inclusion criteria were: histologically or cytologically proven NSCLC, Union International Centre le Cancer (UICC) stage IV (6th edition)[24] with less than five metastases at the time of diagnosis. All tumor sites (local, regional, and distant) had to be amenable for radical treatment (surgery or radiotherapy to a biological dose[25] of at least 60 Gy in 30 daily fractions of 2 Gy, except for brain metastases in which lower radiation doses were allowed) according to the multidisciplinary team. Both surgery and radiotherapy were allowed in the same patient (e.g., radiotherapy as local treatment for the *local* N3-IIIB disease and surgery for a solitary adrenal metastasis). Systemic treatment was not mandatory. There were no size limitations to the primary tumor or its metastases. Intracranial metastases alone were allowed. Patients had to have a World Health Organization (WHO) performance status 0 to 2 and any other malignancy should be controlled, that is, in clinical complete remission, at the time of diagnosis. The exclusion criteria were: not NSCLC or mixed NSCLC and other histologies (e.g., small-cell carcinoma), and a T4 tumor because of a malignant pleural or pericardial effusion.

Endpoints

The primary endpoint was overall survival (OS) at 2 and 3 years. The secondary endpoints were, progression-free survival (PFS), dyspnea, dysphagia, and patterns of recurrence.

Staging

Patients were staged with a calibrated[26] whole-body ^{18}F-deoxyglucose positron emission tomography computed tomography (CT) scan and a CT with intravenous contrast or a contrast-enhanced magnetic resonance imaging of the brain. Pathological confirmation of at least one distant metastasis was mandatory; for brain metastases, this was done only when the multidisciplinary team considered this diagnosis as *most likely.*

Comorbidity

Comorbidity at the time of diagnosis was scored using the Charlson comorbidity index.[27]

Treatment

Treatment of the primary tumor and the hilar and mediastinal lymph nodes. Loco-regional treatment was previously described and included image and dose-quality control.[28,29] Patients with *local stage* T1-3 N0-1 disease were offered a lobectomy and a lobe-specific nodal dissection, stereotactic body radiation therapy (SBRT) or more fractionated radiotherapy for central lesions. Patients with local stage III (T4 and/or N2-3) NSCLC received either sequential of concurrent individualized iso-toxic chemoradiotherapy.[28,29]

Radiotherapy dose was specified according to International Commission on Radiation Units and Measurements (ICRU) 50 guidelines[30] and European Organization for Research and Treatment of Cancer recommendations were used.[31]

Treatment of distant metastases. Patients with brain metastases were either treated with resection followed by whole-brain radiotherapy to a dose of 30 Gy in 10 daily fractions of 3 Gy, or with stereotactic radiosurgery (SRS) to a dose of 18 to 20 Gy per one fraction or 24 Gy per three fractions, depending on the volume and the location of the brain metastase(s).32 No prophylactic whole-brain irradiation was given after SRS.

When surgery was considered in case of extracranial metastases, a radical resection was envisaged. In case of a microscopic incomplete resection, postoperative radiotherapy was given to a dose of 60 Gy in 30 fractions in 6 weeks to the areas at risk.

The timing and sequencing treatment (e.g., first radiotherapy, then surgery…) was not specified in the protocol and left to the discretion of the multidisciplinary group. Systemic treatment was not mandatory, but was considered to be the standard in stage IV patients. When a recurrence developed, the treatment was left at the discretion of the physician.

Post-treatment follow-up. The follow-up after all therapy consisted of a visit after 3 weeks and thereafter every 3 months, comprising history taking and physical examination; these were performed by the pulmonologist and radiation oncologist for the first 2 years. After this period, visits were performed every 6 months until 5 years post-treatment. A CT scan of the thorax and the upper abdomen and of the treated metastatic site was performed 3 and 6 months after completion of treatment and every 6 months thereafter. In case of brain metastases, a contrast-enhanced magnetic resonance imaging scan of the brain was done every 3 months. At the time of first recurrence, additional diagnostic imaging procedures was left at the decision of the physician, as indicated by the presence of symptoms. A pathological confirmation of recurrence was not required.

Local tumor control of all radical treated locations (both the primary tumor and the metastases) was evaluated according to the criteria of Green[33] after radiotherapy and according to Response Evaluation Criteria In Solid Tumors for nonirradiated sites.[34] Tumor progression was scored when one or both occurred.

Toxicity was scored according to the Common Toxicity Criteria for Adverse Events (CTCAE) 3.0 criteria (http://ctep.cancer.gov) before the start of therapy, at the weekly visits during treatment, and at the follow-up visits mentioned above by the physician and by the patient, the latter from 2009 onward.

Statistics. We hypothesized that the 2-year survival with this radical therapy should be at least 20% with a one-sided 95% confidence interval (CI) not including 10% being the benchmark of 2-year survival with chemotherapy only.[35] A sample size of 40 patients would be sufficient for this purpose.

Results are either expressed as mean ± SD with the range within parentheses or as a proportion with 95% CI. OS and PFS rates were calculated with the Kaplan–Meier method, on an intention-to-treat basis, starting from the date of diagnosis. OS and PFS comparisons were done using a log-rank test, and for multiple variables a Cox regression analysis was performed using SPSS 17.0.

Ethics. The trial was approved by the required authorities and all patients gave informed consent. The study is listed in clinicaltrials.gov, number NCT01282450.

RESULTS

Patients

Forty patients were included from July 27, 2006 until July 23, 2010, with one patient being ineligible. Analysis was performed on December 5, 2011. One patient was excluded from the analysis because of a protocol violation (61-year-old man with a small-cell lung cancer stage T1N3M1, with a solitary symptomatic brain metastasis, treated with resection, followed by whole-brain irradiation therapy (WBRT) and concurrent cisplatin-etoposide and chest radiotherapy to a dose of 70 Gy. He is free of disease progression at 2 years). Patient and tumor characteristics are depicted in Table 1.

A biopsy of the primary tumor was available in 18 of 39 patients (46%); in the remaining patients, only cytological material was obtained. As determination of the epidermal growth factor receptor (EGFR) mutation status was not required and was not standard of care when the study began; this was only obtained in patients in patients with recurrent adenocarcinoma and only at the time when erlotinib became available. The EGFR mutation status was determined in three of 39 patients. In one of these, an exon 21 mutation was found and the patient was treated with erlotinib at relapse. Local stage (thus ignoring the M1 status) was I or II in 10 of 39 patients, stage IIIA in nine (23.1%), and IIIB in 20 (51.3%).

The brain was the most frequent location of metastases (17 of 39 patients or 43.9%), followed by the bone (7 of 39, 17.9%), and adrenal gland (4 of 39, 10.3%). The overwhelming majority of patients were diagnosed with a single distant metastasis (34 of 39, 87.2%).

For the whole patient group, the mean volumes were: primary tumor: $92.3 \pm 122.7\,cm^3$ (0–583.5) (median $51.9\,cm^3$), lymph nodes: $44.2 \pm 57.9\,cm^3$ (0–238.8) (median $23.5\,cm^3$), distant metastasis: $20.2 \pm 27.4\,cm^3$ (0.3–113.1) (median $9.9\,cm^3$), total tumor volume $144.3 \pm 138.9\,cm^3$ (9.5–696.5) (median $117.9\,cm^3$).

The mean maximal standardized uptake value (SUVmax) of the primary tumor was 11.9 ± 5.7 (2.1–27) (median 10.2). Excluding brain metastases because of high physiological cerebral ^{18}F-deoxyglucose uptake, the mean SUVmax of metastases was 6.7 ± 3.3 (2.3–14.4) (median 5.8).

Treatment

The primary tumor and its regional lymph nodes were treated with radiotherapy or chemoradiation, none with surgery (Table 2). One primary tumor was treated with SBRT to a dose of 54 Gy in three fractions. Only two patients did not receive chemotherapy, one with stage T3N0 with one rib metastasis and one 82-old-man with a T2N2 tumor with a metastasis in the left major teres muscle. These two patients had a distant recurrence.

Three of the four patients with adrenal metastases were treated with surgery, and one was treated with radiotherapy

TABLE 1. Patient and Tumor Characteristics ($n = 39$)

Age (yrs) (mean ± SD) (range)	62.1 ± 9.2 (44–81)
Sex	
Male	18 (46.2%)
Female	21 (53.8%)
Comorbidity (modified Charlson)	
None	18 (46.2%)
1	20 (51.3%)
2	1 (2.6%)
WHO performance status	
0	12 (30.8%)
1	26 (66.7%)
2	1 (2.6%)
Pathology	
Adenocarcinoma	13 (33.3%)
Large cell carcinoma	7 (17.9%)
Large cell neuro-endocrine carcinoma	1 (2.6%)
Non–small-cell lung cancer (NOS)	8 (20.5%)
Undifferentiated carcinoma	2 (5.2%)
Squamous cell carcinoma	8 (20.5%)
T-stage	
T0	2 (5.1%)
T1	5 (12.8%)
T2	14 (35.9%)
T3	8 (20.5%)
T4	10 (25.6%)
N-stage	
N0	12 (30.8%)
N1	4 (10.3%)
N2	12 (30.8%)
N3	11 (28.2%)
Local stage (ignoring M1 status)	
I	4 (10.3%)
II	6 (15.4%)
IIIA	9 (23.1%)
IIIB	20 (51.3%)
Localization metastasis	
Adrenal gland	4 (10.3%)
Bone	7 (17.9%)
Brain	17 (43.9%)
Gastro-hepatic ligament	1 (2.6%)
Liver	1 (2.6%)
Lung	1 (2.6%)
Lymph node	2 (5.1%)
Muscle	2 (5.1%)
Ovary	1 (2.6%)
Pleura	3 (7.7%)
Number metastases	
1	34 (87.2%)
2	4 (10.3%)
3	1 (2.6%)

WHO, World Health Organization; NOS, Not otherwise specified.

TABLE 2. Treatment for Primary Tumor and Lymph Nodes (n = 39)

Surgery	0
Radiotherapy alone	2 (5.1%)
Sequential chemoradiotherapy	15 (38.5%)
Cisplatin-gemcitabine	11
Carboplatin-gemcitabine	1
Cisplatin-pemetrexed	3
Concurrent chemoradiotherapy	21 (53.8%)
Cisplatin-etoposide	7
Cisplatin-vinorelbine	14
Adjuvant after radiotherapy	1 (2.6%)
Cisplatin-gemcitabine	—
Radiotherapy dose	62.3 ± 10.1 Gy (18–79.2)
Number of fractions	35.9 ± 8.4 [3–44]
Overall treatment time of radiotherapy	30.56 ± 10.3 days [3–44]

because of irresectability (Table 3). All patients with bone metastases were treated with radiotherapy (54 Gy in 30 twice-daily fractions of 1.8 Gy). Four of 17 patients with brain metastases were surgically treated, and the rest were treated with SRS. Resection was performed in the patients with a solitary liver, a contralateral lung, and an ovarian metastasis.

Survival

With a median follow-up of 27.7 ± 10.5 months (mean 28.3 months; minimum 16.7 months, maximum 46.1 months), the median OS was 13.5 months (95% CI 7.6–19.4) (Fig. 1). The 1-year OS was 56.4%, the 2-year 23.3%, and the 3-year 17.5%.

The median PFS was 12.1 months (95% CI 9.6–14.3) (Fig. 2). The 1-year PFS was 51.3%, both the 2- and 3-year PFS 13.6%. When split-up according to the location of the metastases, the median survival for adrenal locations was 10.2 months, for bone 13.5 months, for brain 13.6 months, and for muscle 5.5 months ($p = 0.52$).

Patterns of Recurrence

At the time of analysis, 6 patients (15.4%) of patients did not show a recurrence (Table 4). Of the 33 patients with a recurrence, 31 (79.5%) had the recurrence outside the radiotherapy field (= planning target volume) or the surgical bed and two (5.1%) in-field (primary lung tumor in a T3N3M1 NSCLC and mediastinal lymph nodes (T2N3M1).

TABLE 3. Radical Treatment of Metastases

Metastasis Location at Diagnosis	Radical Local Therapy of Metastases
Single metastasis	
Solitary adrenal	Resection
Solitary adrenal	Resection
Solitary adrenal	Resection
Solitary adrenal	Radiotherapy
Solitary bone	Radiotherapy
Solitary bone	Radiotherapy
Solitary bone	Radiotherapy
Solitary bone	Radiotherapy
Solitary bone	Radiotherapy
Solitary bone	Radiotherapy
Solitary brain	Resection
Solitary brain	SRS
Solitary brain	SRS
Solitary brain	SRS
Solitary brain	Resection
Solitary brain	SRS
Solitary brain	Resection
Solitary brain	SRS
Solitary brain	SRS
Solitary brain	SRS
Solitary brain	Radiotherapy
Solitary brain	SRS
Solitary brain	Radiotherapy
Solitary brain	Resection
Solitary heterolateral lung	Resection
Solitary left teres major muscle	Radiotherapy
Solitary lymph node ipsilateral axilla	Radiotherapy
Solitary lymph node left iliaca externa	Radiotherapy
Solitary ovary	Resection
Solitary pleura	Radiotherapy
Solitary pleura	Radiotherapy
Solitary pleura	Radiotherapy
Multiple metastases	
Two brain metastases	SRS
Three brain metastases	SRS
Three brain metastases	SRS
One in the left pectoral muscle and one in the right lung	Radiotherapy
Two bone metastases (right ilium, right pubis)	Radiotherapy

SRS, stereotactic radiosurgery.

Toxicity

Determined by the physician. The incidence of acute grade 3 oesophagitis was 15%, with only one patient still having grade 1 oesophagitis 3 months post-treatment. Three months after therapy, only three of /39 patients had grade 2 dyspnea (compared with 2 of 39 at baseline).

Grade 3 cough only occurred in one patient, but 3 months after therapy, no patient had cough of grade 2 or more (Table 5). After brain surgery, SRS, or other treatment of distant metastases, no toxicity of grade 3 or more was observed. One patient showed paresis grade 2, one seizures grade 2, two sensory neuropathy grade 2, two dizziness grade 1, and two headache grade 2. No side effects of grade 2 or more remained 2 months post-treatment.

Determined by the patient. Twenty-three percent reported transient grade 3 esophagitis with no severe esophagitis 3 months after therapy (Table 6). No grade 3 dyspnea or cough occurred. Three months after EGFR, 31% of the

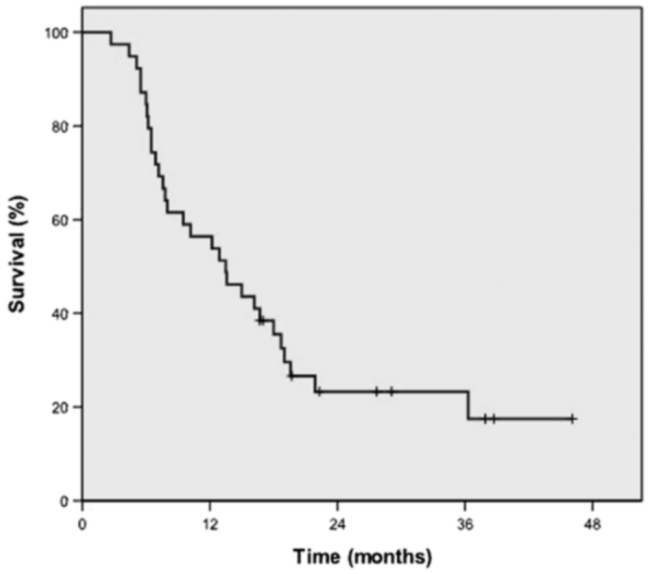

FIGURE 1. Overall survival (n = 39).

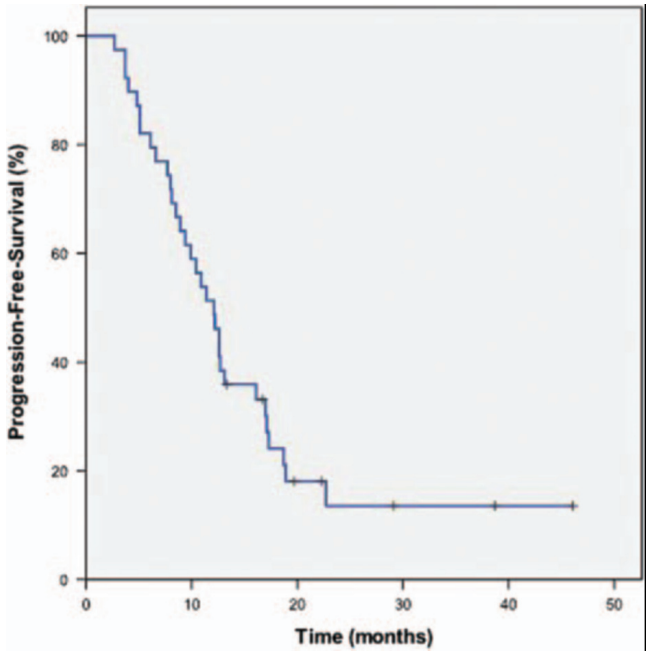

FIGURE 2. Progression-free survival.

patients reported having a better health status as opposed to baseline and 15% reported a worse health status. The proportion having a deterioration of health status after six months was 31%, correlating with cancer recurrence. There were no changes in mobility, self-care, activities of daily living, or mood over time.

Second-line treatment after recurrence. After a recurrence was diagnosed, nine patients (27.3%) only received best supportive care, mainly because of a bad general condition, seven (21.2%) were treated with chemotherapy only, and the rest received different treatments (Table 7).

TABLE 4. Patterns of Recurrence

Metastasis Location at Diagnosis	Site of First Progression
Adrenal	Peritoneum
Adrenal	In-field mediastinal lymph nodes
Adrenal	Bone
Adrenal	No recurrence
Bone	Bone
Bone	Bone
Bone	No recurrence
Bone	No recurrence
Bone	Bone
Bone	Bone
Bone	Bone
Brain	Bone
Brain	Brain
Brain	Bone
Brain	Bone
Brain	Bone
Brain	Brain
Brain	No recurrence
Brain	Brain
Brain	Brain
Brain	Brain
Brain	Leptomeningeal
Brain	Brain
Brain	Brain
Brain	Brain
Brain	Brain
Brain	Ovary
Brain	Brain
Brain	Bone
Node	In-field primary tumor
Node	Brain
Liver	Liver
Gastro-hepatic ligament	Brain
Lung	No recurrence
Ovary	Brain
Pleura	No recurrence
Pleura	Brain
Muscle	Brain
Muscle	Muscle, liver

Variables associated with OS and PFS. The following parameters were analyzed: volume of the primary tumor, volume of the nodes, volume of the metastases, total tumor volume, SUVmax of the primary tumor and of the nonbrain metastases, local stage, WHO performance status, comorbidity score, location of metastases, number of metastases, histological type, sex, age, and sequential versus concurrent chemoradiotherapy. None of these variables showed a correlation with OS or PFS, although a trend was noticed for the volume of the metastasis and OS (Table 8). The characteristics of the patients showing no disease progression are summarized in Table 9.

TABLE 5. Toxicity Scored by the Physician

Dysphagia	
Baseline	
G0	39 (100%)
Maximal	
G0	10 (25.6%)
G1	16 (41%)
G2	7 (17.9%)
G3	6 (15.4%)
3 mos post-treatment	
G0	38 (97.4%)
G1	1 (2.6%)
Dyspnea	
Baseline	
G0	27 (69.2%)
G1	10 (25.6%)
G2	2 (5.1%)
Maximal	
G0	21 (53.8%)
G1	13 (33.3%)
G2	5 (12.8%)
3 mos post-treatment	
G0	24 (61.5%)
G1	12 (30.8%)
G2	3 (7.7%)
Cough	
Baseline	
G0	18 (46.2%)
G1	20 (51.3%)
G2	1 (2.6%)
Maximal	
G0	10 (25.6%)
G1	25 (64.1%)
G2	3 (7.7%)
G3	1 (2.6%)
3 mos post-treatment	
G0	15 (38.5%)
G1	24 (61.5%)

DISCUSSION

Patients with distant metastases of NSCLC were deemed incurable and classified as having stage IV disease.[24] The observation that individuals with solitary lung or liver metastases may show long-term disease-free survival and even cure provided support for the concept of oligometastases[2,3,21,22] Patients with one to five distant metastases may be at a continuum between truly local disease and widely disseminated cancer. Radical local therapy may thus be able to cure a subset of these patients.

Data on patients with NSCLC are scarce. Most series are retrospective and the few prospective trials include synchronous and metachronous metastases that are amendable for SBRT or limited surgery.[13–15,23] Nevertheless, long-term survival was also observed in NSCLC.[13–16,23]

TABLE 6. Patient-Reported Outcome*

Dysphagia	
Baseline	
G0	13 (100%)
Maximal	
G0	3 (23.1%)
G1	4 (30.8%)
G2	3 (23.1 %)
G3	3 (23.1 %)
3 mos post-treatment	
G0	8 (61.5 %)
G1	1 (7.7 %)
Dyspnea	
Baseline	
G0	8 (61.5 %)
G1	4 (30.8 %)
G2	1 (7.7 %)
Maximal	
G0	8 (61.5 %)
G1	3 (23.1 %)
G2	2 (15.4 %)
3 mos post-treatment	
G0	7 (53.8%)
G1	5 (38.5%)
G2	1 (7.7%)
Cough	
Baseline	
G0	3 (23.1%)
G1	9 (69.2%)
G2	1 (7.7%)
Maximal	
G0	3 (23.1%)
G1	8 (61.5%)
G2	2 (15.4%)
3 mos post-treatment	
G0	4 (30.8%)
G1	9 (69.2%)
Health status versus baseline	
3 mos post-treatment	
Same	6 (46.2%)
Better	4 (30.8%)
Worse	2 (15.4%)
Missing	1 (7.7%)
6 mos post-treatment	
Same	5 (38.5%)
Better	3 (23.1%)
Worse	4 (30.8%)
Missing	1 (7.7%)
Mobility	
Baseline	
Minor problems	5 (38.5%)
No problems	7 (53.8%)
Missing	1 (7.7%)

(Continued)

TABLE 6. (*Continued*)

Mobility	
3 mos post-treatment	
Important problems	1 (7.7%)
Minor problems	4 (30.8%)
No problems	7 (53.8%)
Missing	1 (7.7%)
6 mos post-treatment	
Important problems	1 (7.7%)
Minor problems	4 (30.8%)
No problems	6 (46.2%)
Missing	2 (15.4%)
Self-care	
Baseline	
Minor problems	4 (30.8%)
No problems	8 (61.5%)
Missing	1 (7.7%)
3 mos post-treatment	
Severe problems	1 (7.7%)
Minor problems	3 (23.1%)
No problems	8 (61.5%)
Missing	1 (7.7%)
6 mos post-treatment	
Severe problems	1 (7.7%)
Minor problems	3 (23.1%)
No problems	8 (61.5%)
Missing	1 (7.7%)
Activities of daily living	
Baseline	
Minor problems	5 (38.5%)
No problems	7 (53.8%)
Missing	1 (7.7%)
3 mos post-treatment	
Severe problems	1 (7.7%)
Minor problems	4 (30.8%)
No problems	7 (53.8%)
Missing	1 (7.7%)
6 mos post-treatment	
Severe problems	1 (7.7%)
Minor problems	4 (30.8%)
No problems	7 (53.8%)
Missing	1 (7.7%)
Mood (fear and uncertainty)	
Baseline	
Minor problems	1 (7.7%)
No problems	8 (61.5%)
Missing	4 (30.8%)
3 mos post-treatment	
Minor problems	1 (7.7%)
No problems	9 (69.2%)
Missing	3 (23.1%)
6 mos post-treatment	
Minor problems	1 (7.7%)
No problems	8 (61.5%)
Missing	4 (30.8%)

*Most recent 13 patients, all treated with concurrent chemoradiotherapy.

TABLE 7. Second-Line Treatment after Recurrence

Radical treatment	
Resection left ovary (solitary recurrence)	1 (3%)
SRS for solitary brain recurrence	4 (12.1%)
Palliative treatment	
No anticancer treatment	9 (27.3%)
Chemotherapy only	7 (21.2%)
Erlotinib	1 (3%)
Palliative radiotherapy only	
Bone metastases	2 (6.1%)
Palliative radiotherapy to bone and chemotherapy	1 (3%)
WBRT only	1 (3%)
WBRT and chemotherapy	6 (18.2%)
SRS and chemotherapy	1 (3%)

SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

TABLE 8. Variables Associated with Overall Survival and Progression-Free Survival

	p	
Parameter	**Overall Survival**	**Progression-Free Survival**
Volume primary tumor	0.67	0.26
Volume nodes	0.14	0.42
Volume metastases	0.09	0.80
Total tumor volume	0.80	0.49
SUVmax primary tumor	0.99	0.79
SUVmax non brain metastases	0.78	0.95
Local stage	0.37	0.84
WHO performance status	0.93	0.49
Comorbidity score	0.49	0.92
Location metastases	0.52	0.51
Number metastases	0.44	0.60
Histological subtype	0.33	0.75
Sex	0.72	0.73
Age	0.37	0.72
Sequential versus concurrent	0.79	0.18
Chemoradiotherapy	—	—

SUVmax, mean maximal standardized uptake value; WHO, World Health Organization.

Because of these uncertainties, we started a prospective single-arm phase II trial in 2006 for patients with synchronous oligometastases from NSCLC. Although three quarters of the patients had local stage III disease, the 2- and 3-year OS was 23.3% and 17.5%, respectively. Even more important, both the 2- and 3-year PFS was 13.6%. Although a straightforward comparison with patients with stage IV NSCLC treated with chemotherapy only is not allowed, these results compare well with the latter group, in which a median PFS of typically 4 months is described.[35]

The present study has shortcomings. Because it was a nonrandomized trial, the real possible benefit of radical local therapy over chemotherapy alone remains uncertain although

TABLE 9. Characteristics of Patients Showing no Disease Progression after 2 Years

64-yr-old man with a T2N2 NSCLC with a solitary brain metastasis treated with resection followed by whole-brain radiotherapy (30 Gy/10 fractions), 3 cycles of cisplatin-gemcitabine, and thereafter radiotherapy to the primary tumor and lymph nodes (54 Gy/ 30 BID fractions).
62-yr-old man with a T3N3 large cell carcinoma with a solitary pleural metastasis, for which 3 cycles neoadjuvant cisplatin gemcitabine, followed by radiotherapy to the primary tumor and lymph nodes (54 Gy/ 30 BID fractions).
60-yr-old man with a T2N2 squamous cell carcinoma with a solitary metastasis in the sternum, all treated with concurrent cisplatin vinorelbine and radiotherapy (69 Gy/42 fractions).
52-yr-old woman with a T2N0 adenocarcinoma with a solitary metastasis in the sacrum, treated with concurrent cisplatin-vinorelbine and radiotherapy (70.2 Gy/39 fractions on the primary tumor and 54 Gy/ 30 BID fractions on the sacrum).
63-yr-old man with a T4N0 NSCLC with a solitary irresectable adrenal metastasis, treated with concurrent cisplatin-vinorelbine and radiotherapy (69 Gy/42 fractions on the primary tumor and 54 Gy/30 BID fractions on the adrenal metastasis).

the observation that six of 39 (15%) patients in our study did not show disease progression after 2 years is suggestive that a subgroup of these patients may be cured or enjoy a long-lasting PFS. The acute toxicity was as expected with these treatments,[28,29] but fortunately long-term side effects were rarely observed and not severe, even in the subgroup of patients with self-reported toxicity scores. This is in line with previous reports on chemoradiotherapy on the quality of life of lung cancer patients.[36]

Another caveat of the study is the obvious patient selection. Before embarking on this trial, we investigated the incidence of oligometastases in our referral region, covering 853 553 inhabitants on January 1, 2006. From the 450 newly diagnosed patients with lung cancer, about 50% had stage IV disease at diagnosis and 25 patients with NSCLC per year would have been eligible for our trial (data not shown). Nineteen of these 25 patients had local stage III NSCLC. In the 4 years' accrual period of this subsequent study, only 39 patients were enrolled, compared with the 100 who would theoretically be eligible. The included patients were much younger and in a better general condition with fewer comorbidities than the average NSCLC patient in our region.[37] The majority were women, which is also discordant with the population average with a preponderance of men.[37] Moreover, nearly all patients (34 of 39) had only one distant metastasis although according to the inclusion criteria up to four metastases could have been included. In some favorable subgroups of patients with brain metastases, long-term survival may indeed be achieved.[38,39]

Nevertheless, to the best of our knowledge this is the first prospective trial on NSCLC patients with synchronous distant metastases treated radically, and it does show a small but significant group of long-term survivors. Hasselle et al.[14] reported on a group of NSCLC patients that was more heterogeneous than ours because the possibility for hypofractionated radiotherapy was an inclusion criterion and both synchronous and metachronous metastases were allowed, like in the study of Cheruvu et al.[16] Our series come close to the inclusion criteria of Khan et al.,[5] although their series was retrospective. These differences may account for the diverging OS and PFS rates, but all support long-term PFS and OS.

The first site of progression is only in 5% of the patients in the high-dose radiotherapy volume or in radically resected sites. Most patients recur at distant sites. However, the brain represents a special case because nine of 17 patients with brain metastases had a cerebral recurrence at sites remote from the SRS field. Although randomized studies did not show a survival benefit of prophylactic WBRT after SRS over SRS alone,[32,40] WBRT may be worth investigating in selected subgroups.

We believe that the future is to identify specific genetic characteristics that underlie the oligometastastic feature and the combination of specific agents with local treatment of metastases. A recent example of the former is the identification of MiRNA 200c that is involved in the epithelial to mesenchymal transformation.[41] For the latter, the rational combination of targeted agents with radiotherapy[42,43] may well be a unique opportunity to eradicate distant metastases not only because of inhibition of driving mutations, but at the same time also because of the induction of specific antitumor immunity.[44] In conclusion, radical treatment of NSCLC patients with synchronous oligometastases is associated with long-term PFS.

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