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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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.