Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450)

BRIEF REPORT

Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450)

Dirk De Ruysscher, MD, PhD,[a,*] Rinus Wanders, MD,[b] Lizza E. Hendriks, MD, PhD,[c] Angela van Baardwijk, MD, PhD,[b] Bart Reymen, MD,[b] Ruud Houben, MSc,[b] Gerben Bootsma, MD, PhD,[d] Cordula Pitz,[e] Linda van Eijsden, MD,[f] Anne-Marie C. Dingemans, MD, PhD[c]

[a]*Department of Radiation Oncology (Maastro Clinic), GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands*
[b]*Maastro Clinic, Maastricht, The Netherlands*
[c]*Department of Pulmonology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands*
[d]*Department of Pulmonology, Zuyderland Hospital, Geleen, The Netherlands*
[e]*Department of Pulmonology, Laurentius Hospital, Roermond, The Netherlands*
[f]*Department of Pulmonology, Sint Jans Gasthuis, Weert, The Netherlands*

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ABSTRACT

Introduction: Two randomized studies have shown an increased progression-free survival (PFS) by adding a radical local treatment to systemic therapy in responding patients with oligometastatic NSCLC, but long-term data are lacking. We updated the results of our previous phase II trial with a minimal follow-up exceeding 7 years.

Methods: This is a prospective single-arm phase II trial. 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). No previous response to systemic treatment was needed.

Results: Forty patients were enrolled, 39 of whom were evaluable (18 men, 21 women); mean age was 62.1 ± 9.2 years (range, 44 to 81 years). Twenty-nine (74%) had N2 or N3 disease; 17 (44%) brain, 7 (18%) bone, and 4 (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 months); 1-, 2-, 3-, 5-, and 6- year OS was 56.4%, 23.3%,12.8%, 10.3%, 7.7%, and 5.1%, respectively. Median PFS was 12.1 months (95% confidence interval: 9.6–14.3 months); 1-, 2-, 3-, 5-, and 6- year OS was 51.3%, 13.6%, %,12.8%, 7.7%, 7.7%, and 2.5%, respectively. Only three patients (7.7%) had a local recurrence.

Conclusions: In patients who were not selected according to response to systemic treatment, the PFS at 5 years was 8%. Entering patients in trials combining local therapy with novel systemic agents (e.g., immunotherapy) remains mandatory.

Keywords: Non-small cell lung cancer; oligometastases; long-term survival; phase II trial

***Corresponding author.**

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Address for correspondence: Dirk De Ruysscher, MD, PhD, Maastro Clinic, Dr. Tanslaan 12, 6229ET Maastricht, The Netherlands. E-mail: dirk.deruysscher@maastro.nl

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Introduction

Since the seminal paper of Hellman and Weichselbaum[1] describing an intermediate state between patients with localized cancer and those with overt distant metastases, there is increasing interest in the treatment of synchronous oligometastases, also of patients with NSCLC. Many retrospective series suggested that a substantial proportion of highly selected patients are alive after 5 years, in subgroups nearly exceeding the overall survival (OS) of unselected patients with localized disease.[2,3] Prospective trials, including ours, also suggested that long-term progression-free survival (PFS) would be possible by treating patients with a few metastases with systemic therapy and radical local treatment with merely acute, reversible side effects.[4-6] In our trial, we reported after a median follow-up of 27.7 ± 10.5 months (mean, 28.3 months; minimum 16.7 months, maximum 46.1 months), a median OS of 13.5 months (95% confidence interval [CI]: 7.6–19.4 months), with a 1-year OS of 56.4%, a 2-year OS of 23.3%, and a 3-year OS of 17.5%. The median PFS was 12.1 months (95% CI: 9.6–14.3 months) with a 1-year PFS of 51.3%, and a 2- and 3-year PFS of 13.6%.[4]

Two randomized phase II studies with as primary endpoint PFS showed an increased PFS by adding a radical local treatment to systemic therapy in patients responding to systemic therapy, but long-term PFS and OS data are lacking.[5,6]

As we have now reached a minimum follow-up of 7 years of patients included in our previously published phase II study, we here report the long-term PFS and OS.

Patients and Methods

The details have been published previously.[4] This was a prospective single-arm phase II trial (NCT 01282450). The main inclusion criteria were pathologically proven NSCLC stage IV with less than five metastases at primary diagnosis, eligible for radical local treatment (surgery or radiotherapy). No previous response to systemic treatment was required.

Patients were staged with a whole body ^{18}F-deoxyglucose–positron-emission tomography–computed tomography (CT) scan and a CT with intravenous contrast or a contrast-enhanced magnetic resonance image of the brain. Pathologic confirmation of at least one distant metastasis was mandatory, unless for brain metastases only when the multidisciplinary team considered this diagnosis as “most likely.”

Both surgery and radiotherapy for the primary tumor and for distant metastases were allowed in the same patient. The radiotherapy biologic dose was at least 60 Gy (except for brain metastases). Systemic treatment was not mandatory.

The primary endpoint was OS at 2- and 3-years, the secondary endpoints PFS, dyspnea, dysphagia, and patterns of recurrence.

Results

Patients

The details of the patients and the primary and secondary endpoints have been published previously.[4]

Between July 27, 2006, and July 23, 2010, 40 patients were enrolled, 39 of whom were evaluable (18 men, 21 women), with a mean age of 62.1 ± 9.2 years (range, 44 to 81 years). Twenty-nine (74%) had N2 or N3 disease. Seventeen patients (44%) had brain metastases, 7 (18%) bone, and 4 (10%) adrenal gland metastases. Thirty-five (87%) had only a single metastatic lesion. Thirty-seven (95%) of the patients received chemotherapy as part of their primary treatment. The current analysis was performed on May 5, 2018.

From the 17 patients with brain metastases, 4 received resection, and the rest received stereotactic radiosurgery. All patients with bone or solitary pleural metastases or the patient with a solitary adrenal metastasis that was irradiated were treated with twice-daily 1.8 Gy fractions, mostly to a dose of 54 Gy, again reflecting the era of the trial, when stereotactic radiotherapy for bone or adrenal metastases had not yet been implemented. Extrathoracic lymph node metastases and the patient with a metastasis in the left teres major was treated for the metastasis with the same fractionation schedule.

Reflecting the period in which this study was performed, only three patients were tested for an EGFR mutation. One of these patients was treated with gefitinib. One patient received erlotinib as second-line therapy without mutation testing.

Overall and PFS

The median OS was 13.5 months (95% CI: 7.6–19.4 months). The 1-, 2-, 3-, 4-, 5, and 6-year OS rates were 56.4%, 23.3%, 12.8%, 10.3%, 7.7%, and 5.1% (95% CI: 0% – 11.9%; two patients), respectively. The median PFS was 12.1 months (95% CI: 9.6–14.3 months). The 1-, 2-, 3-, 4-, 5, and 6-year PFS rates were 51.3%, 13.6%,12.8%, 7.7%, 7.7%, and 2.5% (95% CI: 0% – 7.4%; one patient), respectively (Fig. 1).

Characteristics of Patients With a PFS at 5 Years

From the 3 of 39 patients with a PFS after 5 years, one had initially a squamous cell cancer cT2N2 with a single pathologically proven bone metastasis in the sternum. He developed an adenocarcinoma in the contralateral lung 71 months after the first diagnosis. One patient had a NSCLC-NOS cT4N0 with a single

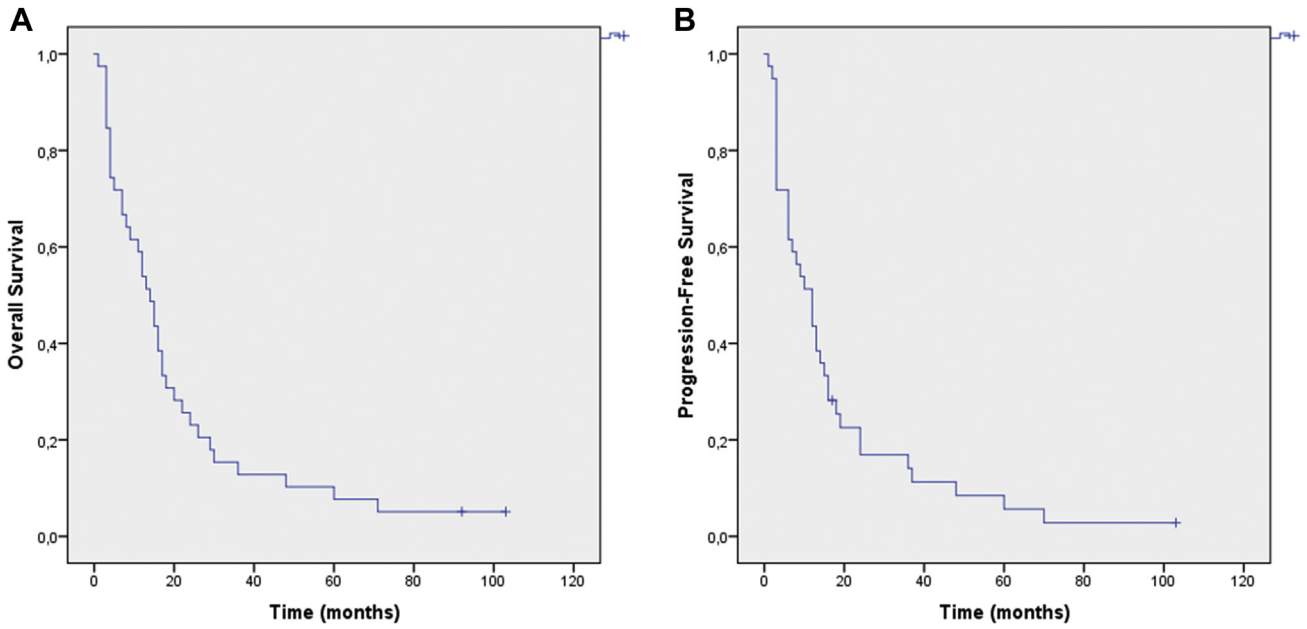

Figure 1. (*A*) Overall survival. (*B*) Progression-free survival.

adrenal metastasis that was removed by surgery and developed a squamous cell cancer of the tongue after 70 months, and one a cT1N2 adenocarcinoma with a pathologically proven contralateral lung adenocarcinoma with a similar morphological appearance, however, without genetic comparison. The latter patient is still free of disease.

Patterns of Recurrence

Despite the fact that no extracranial metastases were treated with stereotactic radiotherapy, only three patients (7.7%) had a local recurrence, all in the planning target volume ("in field") of their primary tumor. One of these patients received gefitinib, one chemotherapy, and one best supportive care. No local recurrence occurred in the involved lymph nodes. All other recurrences appeared at previously identified distant metastatic sites.

Second Primary Cancers

Two patients developed a second primary cancer: one patient a tongue carcinoma after 70 months and one developed an adenocarcinoma in the contralateral lung 71 months after the first diagnosis. Both patients died of their second cancer.

Treatment at First Relapse

Two patients were treated with an EGFR-tyrosine kinase inhibitor (TKI) (one gefitinib and one erlotinib) at first progression. Ten patients received only best supportive care (including palliative radiotherapy) because of a poor performance status, nine patients received platinum-based chemotherapy, five stereotactic radiosurgery for brain relapse (one with chemotherapy) and seven whole brain radiotherapy (one whole brain radiotherapy alone and six with chemotherapy). None received immune therapy.

Conclusions

To the best of our knowledge, this is the first report of a prospective study on the PFS and OS beyond 5 years in NSCLC patients with oligometastases. These data are important because the major aim of adding a radical local treatment to systemic therapy is to prolong the PFS and to achieve a long-term OS in some patients. In our study, approximately 8% of the patients achieved a PFS after 5 years. We believe that the OS results at 5 years were not affected by the second-line treatment. Reflecting the period in which the trial was open (2006–2010), only two patients received a TKI and none immune therapy. Most patients had treatment failure at distant sites, indicating the need to optimize the systemic treatment. Because of the promising results of immune treatment on long-term OS and the synergy between chemotherapy and radiotherapy and immune therapy, trials with combined modality treatment are obvious.[7-10] Entering patients in trials designed for oligometastases is therefore essential.

Offering a radical treatment to patients with synchronous oligometastases outside of a clinical study is reasonable when there are no trial options, provided that the patient is in a good general condition and is aware of the still generally dismal results, although a prolonged

PFS may be envisaged.[5,6] Although there is no consensus on the definition of oligometastases, nearly all our patients had only a single metastasis. Even then, a 5-year PFS of only 8% could be obtained; this underscores the need for cautious patient selection. Selection for radical local therapy could be improved by selecting only oligometastatic patients responding to induction treatment (chemotherapy or a TKI), as was done in the two randomized phase II trials.[5,6]

In conclusion, a radical approach to patients with oligometastases leads to a definite, but small proportion of 5-year survivors. Improvements in systemic therapy to decrease distant failures are needed.

Acknowledgments

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