Editorial

Oligometastatic non-small cell lung cancer: is there a role for locoregional therapy?

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Jianjun Qin (Division of Thoracic Surgery, Henan Cancer Hospital, Zhengzhou University, Zhengzhou, China).

Comment on: Barton MK. Local consolidative therapy may be beneficial in patients with oligometastatic non-small cell lung cancer. CA Cancer J Clin 2017;67:89-90.

Submitted Jun 11, 2017. Accepted for publication Jun 12, 2017.
doi: 10.21037/jtd.2017.06.108
View this article at: http://dx.doi.org/10.21037/jtd.2017.06.108

Until recently, distant metastatic involvement was considered to be a generalized state of disseminated disease with a very poor prognosis, in clear contrast to those patients without any evidence of metastatic spread. Some years ago, the concept of oligometastatic disease emerged representing patients with only a few or "oligo" metastases (1). At major lung cancer conferences this remains a hotly debated topic focused on the question whether there really exists an intermediate state in-between patients without distant metastases and those with multiple metastatic involvement in one or more distant organs (2).

The International Association for the Study of Lung Cancer (IASLC) picked up this concept and in the 8th tumor-node-metastasis (TNM) edition a new category was introduced representing those patients with a single metastasis in a single distant organ, currently M1b involvement (3). In contrast, patients with more than one metastasis in a single or multiple distant organs, are currently described as M1c disease. Many fascinating questions remain. Are distant metastases completely independent from the primary tumor or does some kind of interaction exist which may stimulate further growth and increase metastatic potential? In this way, may better control of the primary tumor reduce further development and growth of distant metastases? May combined modality therapy including locoregional treatment improve prognosis in this patient category? Might aggressive therapy of remaining primary tumor by a local ablative therapy, consisting of surgery, radiotherapy or a combination of these, improve disease-free or even overall survival? These are intriguing questions to which no definite answer exists at the present time (4).

There have been a number of studies that have analysed treatment failure after first-line systemic therapy for metastatic non-small cell lung cancer (NSCLC). According to these studies, progressive disease is more likely to occur at sites of disease present at baseline, rather than in new sites (5). Therefore, patients with stage IV NSCLC but with limited number of metastases could benefit from ablation of these metastases as a means of reduction of tumor volume or prevention of future growth (6,7). Studies have suggested that local ablative therapy such as surgery or radiotherapy could be beneficial in oligometastatic disease for consolidation (2,8-10). However, this hypothesis was not based on randomised, controlled studies.

A recent landmark trial investigated the role of local ablative therapy in patients with stage IV NSCLC with three or fewer metastases remaining after first-line systemic therapy, and provided some provocative results (11). In this multicentre, randomised, controlled phase II study patients from three hospitals were included with following criteria: pathologically confirmed diagnosis of stage IV NSCLC, presence of three or fewer metastatic disease lesions after first-line systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, age of 18 years or older, and standard first-line systemic

therapy as initial treatment (11). None of the patients had evidence of progressive disease at randomisation. The standard therapy consisted of four or more cycles of platinum doublet chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) rearrangements received EGFR or ALK inhibitors respectively for 3 months or longer. Patients were enrolled after completing their first-line systemic therapy. Disease progression was assessed by systemic and also brain imaging. Patients without progression after first-line systemic therapy were randomly assigned to either the local consolidative therapy group or the maintenance treatment group. The randomisation of patients and data was not masked in this study. The following five prognostic covariates were used for balancing the randomisation: number of disease sites, response to first-line systemic therapy, central nervous system metastases, intrathoracic nodal status, and EGFR or ALK mutation.

Patients in the local consolidative therapy group received surgery, radiotherapy or a combination with the aim of ablating all residual disease. The decision to apply a specific therapeutic regimen was determined in a multi-disciplinary thoracic oncological team. Maintenance treatment was chosen from a predefined list of approved regimens that was set up by the Food and Drug Administration (FDA). The latter included pemetrexed and bevacizumab, erlotinib (EGFR mutation), crizotinib (ALK rearrangement), and observation without cytotoxic treatment. Adverse events and progressive disease were followed in both groups with imaging studies every six weeks in the first year. Systemic imaging was performed with either computed tomography (CT) or positron emission tomography (PET)-CT and/or brain imaging [magnetic resonance imaging (MRI) or CT] in the case of intracranial metastases. The primary endpoint was progression-free survival which was measured from the time of randomisation until the time of disease progression or death. Secondary outcomes were overall survival, safety and tolerability, time to progression of previous metastatic lesions, time to appearance of new metastatic lesions, and quality of life.

Between November 28, 2012 and January 19, 2016, 74 patients were enrolled in this study. Twenty-five patients were not eligible for randomization. A total of 49 patients were randomly assigned to the local consolidative therapy group (25 patients) and to the maintenance group (24 patients). The median follow-up time for all randomised patients was 12.4 months (13.4 in the local consolidative therapy group and 11.3 in the maintenance treatment group). A significantly longer progression-free survival was noted in the local consolidative therapy group than in the maintenance treatment group. Median progression-free survival was 11.9 months in the local consolidative therapy group versus 3.9 months in the maintenance treatment group [hazard ratio 0.35 (90% CI, 0.18–0.66), log-rank P=0.0054]. Furthermore, an excellent one-year progression-free survival of 48% (90% CI, 28.7–65.7) was obtained in the local consolidative group versus 20% (90% CI, 7.1–38.0) in the maintenance treatment group. Six patients in the local consolidative therapy group and eight patients in the maintenance group died in this study. All deaths were related to lung cancer except for one in the local consolidative therapy group which was due to a sudden cardiac death which most likely, was not treatment-related. Time to the appearance of a new lesion was longer among patients in the local consolidative therapy group than among patients in the maintenance treatment group (11.9 *vs.* 5.7 months; P=0.0497). No grade 4 adverse events or deaths due to treatment occurred in either groups. Five patients had grade 3 events in the local consolidative therapy group: two patients had radiation-induced oesophagitis, one patient had anemia, one patient had a pneumothorax and one patient had abdominal pain (gallstones, not related to disease). Two patients had grade 3 events in the maintenance therapy group: one patient had anemia and one patient had fatigue.

This represents an important trial as it is the first randomised, controlled trial of aggressive local consolidative therapy to all sites followed by standard maintenance treatment versus maintenance treatment or observation for patients with oligometastatic NSCLC with no progression after initial systemic therapy. As might be expected, progression-free survival was longer for patients in the local consolidative treatment group than in the maintenance / observation group. A number of retrospective studies with different selection criteria related to lymph node status, tumor histology, tumor volume, performance status, number of metastatic lesions and number of metastatic sites, have pointed at a role for local consolidative therapy in oligometastatic NSCLC (8). In the present study, progression-free survival for the maintenance treatment group was similar to hypotheses in previous studies (3.9 *vs.* 4 months anticipated). However, progression-free survival in the consolidative treatment group was considerably longer than in other studies (11.9 *vs.* 7 months anticipated). This could be due to the fact that the hypothesis was based on retrospective data. Furthermore, time to appearance of

a new lesion was longer in the local consolidative therapy group than in the maintenance treatment group. The precise reason for this finding has not been established but this could possibly be due to changes in the natural history of the disease or due to changes in anticancer immune responses.

A number of limitations and concerns limit the scientific validity of this trial. Due to a recommendation by the Data Safety Monitoring Committee this study was stopped earlier than initially scheduled after an interim analysis showed that local consolidative therapy extended progression-free survival when compared to the maintenance treatment group. This resulted in a relatively small number of patients in the treatment groups which limits the overall statistical power. Furthermore, depending on insurance approval, physicians chose the imaging method for disease staging which could possibly affect the final outcome (CT or PET-CT for body imaging, and CT or MRI for brain imaging). In order to increase the inclusion rate no distinction was made between different histological and molecular subtypes of NSCLC. For this reason, the treatment effect on different subtypes of NSCLC could not be determined. Lastly, quality of life could not be precisely assessed as follow-up questionnaires were only partially filled-out precluding a final analysis (11).

Long-term survival after treatment of oligometastatic disease may be observed. We recently reported a 50-year-old patient who presented with a painful femoral bone metastasis which was found to be a single distant metastasis from a right upper lobe lung cancer (12). The bone metastasis was treated by osteosynthesis for stabilization followed by local radiotherapy. Sequential chemoradiation was administered for the right lung cancer. Initially, local control was obtained on both sites but 17 months later the upper lobe cancer started growing and was clearly positive on PET scanning. After discussion within our multidisciplinary tumor board, salvage surgery was applied and a right upper lobectomy performed. Long-term survival was obtained in this particular case with no evidence of disease 8 years after lobectomy.

Regarding treatment strategy of oligometastatic disease of NSCLC some similarities can be found with isolated lung perfusion which is a specific technique to deliver high-dose locoregional chemotherapy in patients with a limited number of lung metastases to obtain better local control and prevent early recurrent disease in the lung parenchyma (13). In the experimental basic research setting isolated lung perfusion was found to be a highly effective treatment for metastases from adenocarcinoma and sarcoma tumors (14). Several clinical research studies followed and together with a center in the Netherlands we combined resection of all lung metastases with isolated lung perfusion in a phase I study to determine the maximum tolerated dose (15,16). In this way isolated lung perfusion can be considered to be a kind of adjuvant therapy in patients with oligometastatic pulmonary disease to improve local control. To explore this further, we initiated a phase II study together with three centers in the Netherlands (17). In the first part comprising 50 patients we could demonstrate that time to local progression was not reached, although metastases outside the perfused lung still occurred determining the ultimate prognosis. The second part expanding this phase II study to 100 patients was recently completed and results will become available in a few months.

In conclusion, patients with oligometastatic disease are a newly defined category and evidence is growing that multimodality therapy consisting of systemic therapy and local ablative therapy consisting of surgery, radiotherapy or a combination of both, may improve prognosis in specific subsets. However, many questions remain and further studies incorporating new therapeutic strategies are necessary to define the best patient category that will benefit from a more aggressive therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Berzenji L, Van Schil PE. Oligometastatic non-small cell lung cancer: is there a role for locoregional therapy? J Thorac Dis 2017;9(7):1814-1817. doi: 10.21037/jtd.2017.06.108

