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Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases

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ABSTRACT

Objectives: Patients with stage IV non-small cell lung cancer (NSCLC) are considered incurable and are mainly treated with palliative intent. This patient group has a poor overall survival (OS) and progression free survival (PFS). The purpose of this study was to investigate PFS and OS of NSCLC patients diagnosed with synchronous oligometastatic disease who underwent radical treatment of both intrathoracic disease and metastases.

Materials and methods: Patients with NSCLC and oligometastatic disease at diagnosis, who were treated with radical intent between 2008 and 2016, were included in this observational study. Treatment consisted of systemic treatment and radical radiotherapy or resection of the intrathoracic disease. Treatment of the metastases consisted of radical or stereotactic radiotherapy, surgical resection or radiofrequency ablation.

Results and conclusions: Ninety-one patients (52% men, mean age 60 years) in good performance status were included. Thirty-eight patients (42%) died during follow-up (median follow-up 35 months). The cause of dead was lung cancer in all patients, except one. Sixty-three (69%) patients developed recurrent disease. Eleven recurrences (17%) occurred within the irradiated area. For the whole group, the median PFS was 14 months (range 2–89, 95%CI 12–16) and the median OS was 32 months (range 3–89, 95%CI 25–39). The 1- and 2-year OS rates were 85% and 58% and the 1- and 2-year PFS rates were 55% and 27%, respectively.

Radical local treatment of a selected group of NSCLC patients with good performance status presenting with synchronous oligometastatic disease resulted in favorable long-term PFS and OS.

1. Introduction

Lung cancer is the leading cause of cancer death, with 1.59 million deaths annually worldwide [1]. More than half of the patients with non-small cell lung cancer (NSCLC) are diagnosed with metastatic disease [2].

According to current treatment guidelines, stage IV NSCLC patients are considered incurable and are mainly treated with palliative intent [3]. Nonetheless, the treatment options of stage IV NSCLC patients have increased with a tendency towards a more personalized treatment approach. When a patient has a limited number of metastases (also called 'oligo metastasis' [4,5]), a more radical treatment regime instead of palliative treatment may be beneficial with respect to progression free and/or overall survival [6].

Hellman and Weichselbaum first described the term 'oligometastasis' in 1995 [4,5]. According to this concept, radical/aggressive local cancer treatments might be curative in a proportion of patients with a limited amount of metastases. However, the existing literature is seriously flawed by the lack of a general consensus on the definition of oligometastatic disease. A commonly used definition in the literature is 'metastases limited in number and destination organ'. However, the specific number is not consistently formulated. Often a maximum of 2 metastases are referred to as oligometastatic disease, and treated accordingly [7,8]. In contrast, ≤5 metastases are also mentioned as oligometastatic disease and considered for radical treatment [7]. Considering the lack of a proper definition for oligometastatic disease, there is a need to investigate the association between the number of metastases and survival in stage IV NSCLC patients. Limited retrospective data are available in literature on oligometastatic NSCLC, both on synchronous and metachronous metastases and on heterogeneous treatments including surgery, stereotactic ablative radiotherapy and radical radiotherapy [7–27]. In a recent systematic review on the evidence for the oligometastatic theory in NSCLC, Ashworth et al. [7] concluded that: "Long-term survivors do exist. Radical treatment of the

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primary lung tumor and metastases are strongly associated with improved long-term survival". Gomez et al. [14] reported the outcome of a prematurely terminated phase II randomized trial. In this trial, patients with oligometastatic NSCLC without progression after first line systemic therapy were randomized between local consolidative therapy versus maintenance therapy or observation. The outcome showed improved progression free survival for those patients treated with local consolidative therapy.

Hence, radical local treatment on the primary tumor and the metastases seems to improve survival in oligometastatic NSCLC disease [7,8,11,13–15,18–20]. Since a radical treatment approach for synchronous oligometastatic NSCLC is not standard of care according to current treatment guidelines, more evidence is needed to confirm the benefit of this therapeutic approach.

Therefore, the purpose of this observational study was to determine the progression free survival (PFS) and overall survival (OS) of NSCLC patients with good performance, diagnosed with synchronous oligometastatic (< 5 metastases) disease treated with curative intent of the intrathoracic disease and the metastases.

2. Materials and methods

Patients diagnosed with synchronous oligometastatic NSCLC who were treated between July 2008 and August 2016 were included in this observational study. Patients were selected during the multidisciplinary tumor board meeting for thoracic cancer in our institute. When radical local treatment for oligometastatic disease was considered, patients were registered in a database between 2008 and 2016. Details of all patients were retrospectively retrieved using this registration database, with subsequent review of all the patients' charts. Patients who had progressive disease before they finished their radical local treatment were not registered in the database. The Institutional Review Board of our institute waived review because of the retrospective nature of the study.

Inclusion criteria for this analysis included histological or cytological proven NSCLC and less than 5 synchronous metastases at the time of diagnosis. Patients were excluded if they had other uncontrolled malignancies. Staging was done for all patients by fluorodeoxyglucose-positron-emission-tomography-(FDG-PET)-scan, CT-thorax and for the brain a contrast-enhanced magnetic resonance imaging (CE-MRI) or a CT of the brain with intravenous contrast. Ideally, metastatic disease was pathologically proven but this was not mandatory. Different types of local therapies were allowed. Systemic therapy was not mandatory.

For the primary tumor, treatment was considered radical if the patient underwent surgery or if a radical radiotherapy dose was given (≥55 Gy biological equivalent dose (EQD2)/α/ß = 10). For the treatment of the metastases, sometimes a lower radiation dose was prescribed (stereotactic radiation for brain metastasis: 1 × 15 up to 1 × 24 Gy (N = 25), adrenal gland: 3 × 8 up to 3 × 12.5 Gy (N = 11), or bone: 3 × 8 Gy up to 3 × 15 Gy or 5 × 7 Gy (N = 9)). Other treatment modalities such as radiofrequency ablation (RFA (N = 1)) were considered radical as well.

In general, the clinical outcome of the treatment was evaluated 8 weeks after treatment by clinical consultation and repeat CT. Subsequently, follow-up was performed every 3 months by the pulmonologist and radiation oncologist or surgeon. After 2 years, follow-up was performed every 6 months. In case of brain metastases, a MRI-brain was performed every 3 months.

Primary endpoints were progression free survival (PFS) and overall survival (OS). Survival was calculated from date of pathologically proven diagnosis until the last date of follow-up or death. PFS was calculated from date of pathologically proven NSCLC until the date of first progression (local, regional, distant) or death. Progressive disease was scored based on available clinical data or imaging report of tumor progression.

Table 1
Patients and tumor characteristics.

Patient and tumor characteristics	N (%)
Sex	
Male	48 (52.7%)
Female	43 (47.3%)
WHO performance status	
0	44 (48.4%)
1	45 (49.5%)
2	2 (2.2%)
Stage (ignoring M- status)	
1A	10 (11.0%)
1B	3 (3.3%)
2A	11 (12.1%)
2B	10 (11.0%)
3A	33 (36.3%)
3B	24 (26.4%)
T-stage	
T0-Tx	2 (2.2%)
T1	24 (26.4%)
T2	33 (36.3%)
T3	14 (15.4%)
T4	18 (19.8%)
Nodal stage	
N0	32 (35.2%)
N1	10 (11.0%)
N2	33 (36.3%)
N3	16 (17.6%)
Pathology	
Adenocarcinoma	58 (63.7%)
Squamouscellcarcinoma	9 (9.9%)
Large cell neuro-endocrine carcinoma	6 (6.6%)
Non-small-cell lung cancer NOS	18 (19.8%)
Number metastases	
1	77 (84.6%)
2	9 (9.9%)
3	2 (2.2%)
4	3 (3.3%)
Location metastases	
Brain (1)[a]	29 (31.9%)
Brain (2)	3 (3.3%)
Brain (3)	1 (1.1%)
Brain (4)	3 (3.3%)
Bone	23 (25.3%)
Bone (2)	1 (1.1%)
Adrenal gland	13 (14.3%)
Lymph node	6 (6.6%)
Liver	2 (2.2%)
Soft tissue	1 (1.1%)
Pulmonary	1 (1.1%)
Thyroid Gland	1 (1.1%)
Breast	1 (1.1%)
Liver and bone	1 (1.1%)
Pleural and bone	1 (1.1%)
Brain and bone	1 (1.1%)
Adrenal gland and pulmonary	1 (1.1%)
Adrenal gland and brain	1 (1.1%)
Adrenal gland (2) and lymph node	1(1.1%)

WHO = world health organization, NOS: not otherwise specified. TNM 7th edition was used for staging.
[a] Within brackets number of metastasis.

2.1. Statistical analysis

Descriptive statistics were used for patient, tumor and treatment characteristics. Median OS and PFS were calculated using the Kaplan-Meier method. Median follow-up was calculated using the reverse Kaplan-Meier method. Univariate Cox regression analysis was done on patient, tumor and treatment characteristics to identify predictors of OS and PFS. P-Values were used to quantify degree of association between each of the factors and the survival-based endpoints. Multivariate Cox regression analysis was performed for OS and PFS, based on selected variables from univariate analysis ($p < 0.10$). Multivariate analysis was done by backward selection, based on p-value with a removal