

# Stereotactic Ablative Body Radiotherapy (SABR) in Pulmonary Oligometastatic/Oligorecurrent Non-small Cell Lung Cancer Patients: A New Therapeutic Approach

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**Abstract.** *Aim: Stage IV non-small cell lung cancer (NSCLC) is characterized by poor prognosis. Palliative chemotherapy and/or best supportive care are considered standard treatment. Nevertheless, for patients with limited distant metastases (1-5 metastases), called oligometastatic disease, better prognosis has been observed. We evaluated response rate, survival, time to progression and toxicity in oligometastatic/oligorecurrent NSCLC patients treated with stereotactic body radiotherapy (SBRT) delivered to all active sites in the lung. Patients and Methods: Twenty-nine lung metastases in 22 patients affected by oligometastatic/oligorecurrent NSCLC were treated with SBRT to all active sites of disease. Inclusion criteria were: controlled primary tumor with complete response or stable disease after surgery/radiotherapy/combined therapy;  $\leq 4$  synchronous or metachronous lung metastases at the time of treatment; no other active sites of distant metastases. Results: Response to treatment was as follows: complete response in 21% of lesions, partial response in 69% of metastases, stable disease in 10%. Ninety-one percent of patients had complete metabolic response, and 9% had a partial metabolic response. Median follow-up was 18 months. The 1-year and 2-year OS was 86% and 49%, respectively. The 1-year and 2-year PFS was 79% and 40%, respectively. Median time to progression and median OS were 18 months and 24 months, respectively. Local control was 93% at 1 year and 64% at 2 years. Overall, acute toxicity occurred in 18% (4/22) of patients; two patients experienced grade 2 pneumonitis. Grade  $\leq 2$  late toxicity occurred in 50% of patients. No grade  $\geq 3$  toxicities were recorded. Conclusion: Aggressive*

*stereotactic radiotherapy is a feasible and well-tolerated treatment for oligometastatic/oligorecurrent NSCLC patients with lung metastases offering longer survival. Ablative radio therapy has a potential role in the management of well-selected stage IV NSCLC patients while increasing their quality of life and survival.*

Stage IV non-small cell lung cancer (NSCLC) is characterized by poor prognosis with median survival from 8 to 11 months (1). Palliative chemotherapy and/or best supportive care are considered standard treatment offering a median survival of 12 months (2). Nevertheless, in patients with limited distant metastases (1-5 metastases), called oligometastatic disease (3), better prognosis has been observed. The local control of the oligometastases may improve survival (4). The state of oligorecurrence is defined as oligometastases with a controlled primary tumor (5).

Oligometastatic NSCLC is not really defined as a separate disease entity, as outcomes are significantly poorer than other malignancies. Selected NSCLC patients with low-volume metastatic disease have been reported to be long-survivors, but the adequate treatment remains controversial. A recent review (6) demonstrated an oligometastatic state in NSCLC patients, mostly with controlled primary and brain metastases only. Outcomes were heterogeneous; median time to progression was 12 months (range= 4.5-23.7 months) and the median overall survival was 19 months. Definitive treatment to primary, N-stage and disease-free interval were found to be prognostic factors to survival.

Emerging data on the use of stereotactic ablative radiotherapy (SABR) in oligometastatic patients from any primary site demonstrated high rates of local control for lung metastases (7), as well as for liver and adrenal gland metastases (8), and in selected patients, even long survival. Current recommendations support the use of aggressive local radiotherapy for patients with 1-3 brain metastases or solitary metastasis from NSCLC without other active sites of disease (9, 10). Resection or stereotactic radiosurgery (SRS) of intra-

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cranial lesions improve survival rates mainly in patients without mediastinal node involvement and with lower T-stage. Surgical studies have shown that metastasectomy of extra-cranial extra-adrenal solitary metastases in selected patients could also achieve long-term survival, in particular for those with stage I-II NSCLC (11).

We evaluated the use of stereotactic body radiotherapy (SBRT) delivered to all active sites in the lung in patients with oligometastatic/oligorecurrent NSCLC. Response, survival, time to progression, and toxicity were assessed. To our knowledge, this is the first study to evaluate SBRT treatment considering only active lung metastases in NSCLC patients with controlled primary tumor and previous complete response or stable disease to other metastases obtained from radical local treatment (SBRT/surgery).

## Patients and Methods

**Patients.** Twenty-nine lung metastases in 22 patients affected by oligometastatic/oligorecurrent NSCLC were treated with SBRT to all active sites of disease in our Department of Radiation Oncology. Patients were carefully reviewed and data were retrospectively analyzed. A performance status ECOG (Eastern Cooperative Oncology Group Criteria)  $\leq 2$  was required for all patients to participate in the study. Inclusion criteria were: controlled primary tumor (oligorecurrent/oligometastatic NSCLC) with complete response or stable disease/metabolic complete response after surgery/radiotherapy/combined therapy;  $\leq 4$  synchronous or metachronous lung metastases at the time of treatment; no other active sites of distant metastasis (complete response/stable disease/metabolic complete response after local treatment).

Pre-treatment evaluation included clinical examination, complete blood count, total body computed tomography (CT) scan, lung function tests, and 18-fluorodeoxyglucose-positron emission tomography (FDG-PET/CT) for all patients. The current study was carried-out according to the Declaration of Helsinki and the Internal Review Board of our Institution has approved the study. Written informed consent was obtained by all patients.

**Treatment.** All patients underwent a 4-dimensional CT pre-treatment planning in the supine position. The maximum intensity projection (MIP) image constituted a visualization of the maximum extent of the target movement in free breathing. An internal tumor volume (ITV) method was used to define the target volume including the tumor position in all phases of the normal respiratory cycle. Planning CT images were matched with diagnostic PET-CT for the ITV delineation. The planning target volume (PTV) was determined by adding 4 mm in all directions to the ITV.

Total prescribed dose to the PTV encompassed the 90-95% isodose, with normalization to the maximal dose. Position before treatment was checked using cone-beam (Kilo-Voltage) CT scan. Stereotactic body radiation therapy was delivered with a Varian Linear Accelerator (Varian, Palo Alto, CA), using 7 to 9 static non-opposing coplanar fields, with 6-MV photons.

The choice of radiation schedule was based on the target volume, the site of metastases and the number of the treated lesions. The prescribed dose was 23 Gy in a single fraction (minimal biologically-effective dose 10 [BED10] 76 Gy) for multiple

synchronous lesions. The total dose was 30 Gy in single fraction (minimal BED10 120 Gy) for peripheral or small tumors ( $<30$  cc). The total dose was 45 Gy in 3 fractions (minimal BED10 112.5 Gy) for centrally located or large tumors ( $\geq 30$  cc).

**Follow-up and statistics.** A total body CT with contrast medium was performed at 1 month after RT completion and every 6 months afterward. A post-treatment FDG/PET-CT was performed at 4 months after RT and for suspected progressive disease. Treatment-related adverse effects were assessed at each follow-up and were graded according to CTCAE v 4.0.

The Response Evaluation Criteria in Solid Tumors (RECIST) measurement were used to determine response; also, metabolic response was evaluated. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 22.0 (IBM Corp., Armonk, NY). The overall survival (OS) was defined as the time from the date of ablative therapy for the lung metastases to the date of death from any cause or last follow-up. The progression-free survival (PFS) was defined as the time from the date of ablative therapy for the lung metastases to the date of local/distant progression. Local recurrence after SBRT was defined as in-field or marginal regrowth of the disease. Metastases-free survival (MFS) was defined as any site of distant progression (including the ipsilateral lung). Cancer-specific survival (CSS) was calculated as the date of the death due to progression from NSCLC. Survivals were estimated using the Kaplan–Meier method.

## Results

**Patients' characteristics.** Between March 2010 and July 2014, 22 patients affected by oligometastatic/oligorecurrent NSCLC with 29 lung metastases were treated with SBRT to all active sites of disease. All patients presented controlled primary tumor after primary treatment with surgery +/- radiotherapy/chemotherapy (13/22), definitive chemoradiotherapy (3/22), chemotherapy alone (IV stage NSCLC: 5/22), stereotactic ablative radiotherapy (1/22).

Most patients had metastases to the lungs only (59%). Nine of the 22 patients (41%) presented also other distant locations of disease involving the lung, adrenal gland, brain and bone: 3 patients had two metastases, 3 patients three metastases, 1 patient four metastases, 2 patients five metastases. All patients presented with synchronous/metachronous oligometastatic disease and only lung metastases were active before SBRT. They have had previous complete response or stable disease and/or metabolic complete response on the other metastatic locations after aggressive therapy with surgery/SBRT. Maintenance chemotherapy with erlotinib (6 patients) or pemetrexed (3 patients) was administered in 9 patients. Thirteen patients were not receiving chemotherapy for: co-morbidities (8 patients), complete response after radical treatment (4 patients), or rejection (1 patient).

At the time of SBRT, most patients with lung disease alone presented one active metastasis only (18 patients) and only 4 patients had 2-4 metastases. Patients' and tumor characteristics are summarized in Tables I and II.

Table I. *Patients' characteristics (N=22).*

|   | N (%)     |
|---|-----------|
| Mean age (years)                                  | 66        |
| Range (years)                                     | 52-85     |
| Gender  |           |
| Male  | 15 (68)   |
| Female  | 7 (32)    |
| Co-morbid conditions                              |           |
| COPD  | 8 (36)    |
| Other   | 7(32)     |
| Histology   |           |
| Adenocarcinoma                                    | 14 (63.7) |
| Squamous cell carcinoma                           | 7 (31.8)  |
| NOS   | 1 (4.5)   |
| Stage   |           |
| IB  | 7         |
| IIA   | 2         |
| IIB   | 1         |
| IIIA  | 6         |
| IIIB  | 1         |
| IV  | 5         |
| Number of metastases<br>(Oligometastatic disease) |           |
| 1 site  | 13 (59)   |
| 2 sites   | 3 (13.5)  |
| 3 sites   | 3 (13.5)  |
| 4 sites   | 1 (5)     |
| 5 sites   | 2(9)      |
| Previous metastatic organs                        |           |
| Lung  | 4 (18)    |
| Brain   | 3 (15.5)  |
| Adrenal gland                                     | 2 (9)     |
| Bone  | 1 (5)     |
| Maintenance chemotherapy                          |           |
| Yes   | 9 (41)    |
| No  | 13 (59)   |

\*COPD, Chronic Obstructive Pulmonary Disease; AJCC, American Joint Committee on Cancer. NOS, Not otherwise specified.

**Response and disease progression.** Response to treatment occurred as follows: complete response in 21% of lesions (6/29), partial response in 69% of metastases (20/29), and stable disease in 10% (3/29). Twenty-six/out of twenty nine (91%) of the irradiated lung lesions had complete metabolic response and 9% (3/29) had a partial metabolic response.

In-field local progression was observed in 4 patients (4 lesions): 3 of them presented previous PR and 1 patient presented initial SD, respectively. Distant progression occurred in 11 (38%) patients. Seven (7/11) patients had distant lung progression alone without other organs involved and three of them (3/7) presented associated local progression of the irradiated lung metastases with SBRT. These patients received palliative chemotherapy (3/7) with erlotinib, supportive care (3/7), or new SBRT treatment (1/7). Two (2/11) patients had diffuse distant progression. One (1/11) patient had brain and

Table II. *Tumor and treatment characteristics (N=29).*

|   | N (%)    |
|---|----------|
| Number of lung metastases<br>(Active disease) |          |
| 1 metastasis                                  | 18 (82)  |
| 2-4 metastases                                | 4 (18)   |
| Location of lung metastases                   |          |
| Central                                       | 6 (21)   |
| Peripheral                                    | 23 (79)  |
| Diameter of lung metastases                   |          |
| ≤2 cm   | 10 (34)  |
| >2 cm   | 19 (66)  |
| Maximal tumor diameter (cm)                   |          |
| Median  | 1.7      |
| Range   | 0.9-4.5  |
| PTV volume (cc)                               |          |
| Median  | 10.1     |
| Range   | 3.4-75.2 |
| SBRT scheme                                   |          |
| 30 Gy/1 fr                                    | 12 (42)  |
| 45 Gy/3 fr                                    | 7 (24)   |
| 23 Gy/1 fr                                    | 10 (34)  |

\*PTV, planning treatment volume; SBRT, stereotactic body radiotherapy.

lung progression combined to local progression, he underwent palliative total brain radiotherapy. One (1/11) patient had mediastinal lymph node progression and subsequently chemotherapy was administered.

**Survival and tolerance.** Median follow-up was 18 months (range=4-53 months). The 1-year and 2-years OS were 86% and 49%, respectively. The 1-year and 2-years PFS were 79% and 40%, respectively. Median time to progression and median OS were 18 months and 24 months, respectively (Figure 1). Local control was 93% at 1 year and 64% at 2 years (median time not reached - NR). The CSS was 93% at 1 year and 60% at 2 years, respectively (median time NR). The 1- year and 2-years MFS were 87% and 42%, respectively (median time 18 months).

At the time of analysis, 14 patients were alive. Three patients were alive with PD (2 in the lung and 1 in mediastinal lymph nodes) and received palliative chemotherapy, while 11 patients had no evidence of disease or SD. The median follow-up of the survivors was 17 months (range= 6-46 months). Death occurred in 8 patients: 5 died from systemic progression of disease and 3 died from other causes.

Acute toxicity occurred in 18% of patients; two patients experienced grade 2 pneumonitis. Late toxicity occurred in 50% of patients: 8 patients presented grade 1 lung fibrosis, 2 patients presented grade 1 chest wall pain, 2 patients

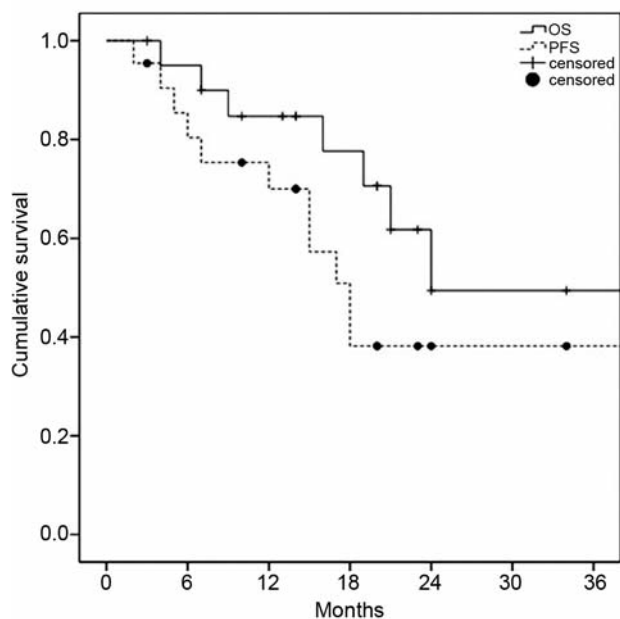


Figure 1. Overall survival (OS) and progressive-free survival (PFS).

presented grade 2 lung fibrosis, 1 patient experienced grade 2 pneumonitis, 1 patient experienced grade 2 esophagitis. No grade  $\geq 3$  toxicities were recorded.

## Discussion

Non-small cell lung cancer has generally a poor prognosis in advanced stages (12). Approximately 30–50% of patients are diagnosed with metastatic disease and about 40% will develop metastatic progression (13).

In selected NSCLC patients who received radical treatment to the primary tumor in combination to resection of limited- volume for metastatic disease a longer survival was noticed (14, 15). Usually, these patients presented with synchronous solitary brain metastases, good performance status, controlled intra-thoracic disease, and/or node-negative disease (16).

In recent years, NSCLC patients with slow progression and controlled primary tumors may be considered oligometastatic and may benefit from aggressive treatment to the distant active disease. However, only few studies with adequate follow-up raise the possibility that long-term survival might not be due to the treatment alone, but rather to the selection of patients based on favorable inclusion criteria (17).

Surgical series suggest that oligometastatic NSCLC with brain metastases can be successfully treated when also an aggressive treatment is administered to control the primary tumor (18). Resection or SRS are both feasible and efficient in patients with solitary brain metastasis obtaining high rates

of local control and survival (19); in these patients a combined approach of systemic therapy should be considered (20). Small surgical series regarding oligometastatic/oligorecurrent NSCLC patients with (21) isolated adrenal gland metastases reported 1- and 2-year OS rates of 45-80% or 30-52%, respectively for metachronous or synchronous metastases. Retrospective studies examining aggressive treatment to the primary and all oligometastatic sites of disease (brain, adrenal gland, axillary nodes, and contralateral lung metastases) with surgery or radiation have shown OS rates of 20.4-28.3%, with improved survival for node- negative status (22).

We selected a population of oligometastatic/oligorecurrent NSCLC patients with controlled primary tumors and active sites of disease only in the lung. These patients were submitted to SABR to all active synchronous/metachronous lung metastases. Most of them had solitary lung metastasis (59%). Forty-one percent of the patients also presented other previous distant locations of disease, but they have had previous complete response or stable disease and/or metabolic complete response after aggressive therapy. Maintenance chemotherapy was administered in 9 patients.

A prospective study by Parkih *et al.* enrolled 186 patients with oligometastatic NSCLC treated with definitive therapy to the primary tumor and surgery/SBRT to the metastases. Definitive therapy to the primary tumor was associated with prolonged survival ( $p=0.043$ ) (23). Our series was selected based on primary tumor control, submitting to SBRT of lung metastases, only patients with controlled primary, supposing potential long survival in this sub-group.

Therefore, patients with lung metastases from NSCLC are not included in oligometastatic studies using SBRT since they are principally submitted to systemic chemotherapy. Evidence from the literature is inhomogeneous reporting only mixed primary series with small numbers of patients treated with SBRT for oligometastatic lung tumors and the demonstrated median survival is around 19 months, but outcomes are not distinguished for histology (24). These studies frequently include oligometastatic tumors with higher survival compared to stage IV NSCLC. A retrospective study by Inoue *et al.* evaluated the clinical outcomes of patients with oligometastatic lung tumors from any primary who underwent SBRT. The 3- and 5-year OS and PFS rates were 72% and 54%, respectively, but only 9/22 patients had NSCLC diagnosis (25).

Only few studies had evaluated oligometastatic/oligorecurrent NSCLC patients treating the active sites with SBRT. Principally, patients with brain metastases have been analyzed. SRS is an efficient therapy in oligometastatic brain NSCLC patients obtaining high rates of local control (26). Although, adjuvant SRS to the surgical cavity is indicated after large brain metastases resection to improve local control (27).

Patients affected by oligometastatic NSCLC submitted to SBRT are analyzed in small series including patients with active extra-cranial disease. Most series enrolled patients with metastases located in the adrenal gland, bone and lymph nodes. A recent phase II study (28) was conducted on 39 NSCLC patients having <5 metastases at diagnosis principally in the brain, but also in the bone and adrenal gland, treated with surgery or SBRT or standard radiotherapy. Thirty-seven (95%) of the patients received chemotherapy. Median OS was 13.5 months and median PFS was 12.1 months. Only two patients had a local recurrence. Another phase II study (12) evaluated NSCLC patients with  $\leq 5$  metastatic lesions treated with consolidative SBRT (50 Gy/10 fractions) to the metastases located in the pleura/lung (30% of the patients; 15/26), lymph nodes, adrenal gland and bone, after induction chemotherapy. After a median follow-up of 16 months, the metabolic response rate was 90%, and the median PFS and OS were 11.2 and 23 months, respectively. The pulmonary grade 3 toxicity rates were 8%.

The evidence of efficient aggressive local therapy in oligometastatic NSCLC with associated lung metastases is due to retrospective surgical series. Even in these cases it is difficult to distinguish between a T4-stage, a second primary tumor or a metastatic lesion. Votolini *et al.* (29) showed a median survival of 32 months and a 5-year survival of 34% in patients with synchronous lung cancers, demonstrating better prognosis for node-negative disease. The postoperative mortality was 7%.

In clinical practice, patients with advanced NSCLC present with co-morbid conditions, advanced age and related symptoms, and often they are unfit to chemotherapy or second resection. In our series, 13 patients were not receiving chemotherapy for co-morbidities, and had complete response after radical treatment or rejection.

A meta-analysis by Ashwort *et al.* (30) described a median OS of 26 months (1-year 70.2%, 5-years 29.4%) in oligometastatic NSCLC patients treated commonly with surgery to the primary tumor (83.9%) and metastases (62.3%), but also with SABR or standard radiotherapy. Factors predictive to survival were: synchronous *versus* metachronous metastases ( $p < 0.001$ ), lymph nodes stage ( $p = 0.002$ ), and adenocarcinoma histology ( $p = 0.036$ ). The presence of lung metastases was found to be a worse prognostic factor to OS ( $p = 0.022$ ).

We enrolled selected patients with potential long survival. The current study described a complete response in 21% of lesions, partial response in 69% of metastases, and stable disease in 10%. Twenty-six/out of twenty nine of the lung lesions had complete metabolic response. The 1-year and 2-year OS was 86% and 49%, respectively. The 1-year and 2-year PFS was 79% and 40%, respectively. Median time to progression and median OS were 18 months and 24 months,

respectively. Local control was 93% at 1 year and 64% at 2 years. Our outcomes are in accordance to those of other (12, 23, 24, 28, 29) studies. The high rates of distant progression support an oligometastatic state rather than a second primary tumor, and the time to progression is slow, suggesting long-term survival and slow-growth disease.

Aggressive local therapy may have an important role to disease control and survival but also systemic therapy can improve outcomes. The present study indicated that this particular sub-group of oligometastatic NSCLC has long survival (median=2 years) and disease tends to metastasize mostly in the lung (40% of the patients): 7 patients had distant lung progression alone without other organs involved and 2 patients had diffuse distant progression involving the lung. These outcomes suggest that IV NSCLC has a high propensity to progress in distant locations. Randomized trials have demonstrated response rates >60% and median survival around 24 months for advanced NSCLC with activated mutations of the epidermal growth factor receptor (EGFR) (31), unfortunately, only about 10% of the non-Asiatic population present the active mutations. Chemotherapy should always be considered in fit patients.

Our study suffers some limits such as the small sample of patients and the retrospective nature. On the other hand, patients were carefully selected and the series is homogeneous. Our data suggest that the oligometastatic state exists in NSCLC and lung metastases should be considered for local treatment with ablative radiotherapy. The treatment was well-tolerated and no grade  $\geq 3$  toxicities were recorded. A long survival and time to progression were observed in this selected sub-group.

The recent literature suggests an oligometastatic/oligorecurrent state for NSCLC patients (6, 32-35). Even lung metastases are considered an unfavorable prognostic factor for survival, patients presenting limited disease and no other distant active sites may benefit from SBRT.

## Conclusion

NSCLC patients with slow progressive disease and controlled primary tumor may be considered oligometastatic and may have long-term survival. Principally, patients with good performance status, node-negative disease, good response to primary therapy may benefit from aggressive local therapy to all oligometastatic/oligorecurrent sites of active disease compared to those with widespread distant metastases. SABR may be used as an aggressive therapy to active metastatic disease. Indeed, the most important criterion to select candidates for ablative therapy is to identify who might benefit from intensified management strategies. Randomized controlled trials are required to evaluate the benefit of aggressive therapies in this sub-group and all predictive factors useful to patient selection.

## Conflicts of Interest

None.

## References

- Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Ganti AK, Govindan R, Grannis FW Jr, Jahan T, Jahanzeb M, Johnson DH, Kessinger A, Komaki R, Kong FM, Kris MG, Krug LM, Le QT, Lennes IT, Martins R, O'Malley J, Osarogiagbon RU, Otterson GA, Patel JD, Pisters KM, Reckamp K, Riely GJ, Rohren E, Simon GR, Swanson SJ, Wood DE, and Yang SC; NCCN Non-Small Cell Lung Cancer Panel Members. NCCN Non-Small Cell Lung Cancer Panel Members: Non-small cell lung cancer. *J Natl Cancer Netw* 8: 740-801, 2010.
- Non-Small Cell Lung Cancer collaborative Group: Chemotherapy and supportive care *versus* supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst Rev* 5: CD007309, 2010.
- Lopez Guerra JL, Gomez D, Zhuang Y, Hong DS, Heymach JV, Swisher SG, Lin SH, Komaki R, Cox JD and Liao Z: Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. *Int J Radiat Oncol Biol Phys* 84: 61-67, 2012.
- Milano MT, Zhang H, Metcalfe SK, Muhs AG and Okunieff P: Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat* 115: 601-608, 2009.
- Niibe Y, Kuranami M, Matsunaga K, Takaya M, Kakita S, Hara T, Sekiguchi K, Watanabe M and Hayakawa K: Value of high dose radiation therapy for isolated osseous metastasis in breast cancer in terms of oligo-recurrence. *Anticancer Res* 28: 3929-3931, 2008.
- Ashworth A, Rodrigues G, Boldt G and Palma D: Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung Cancer* 82: 197-203, 2013.
- Siva S, MacManus M, and Ball D: Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol* 5: 1091-1099, 2010.
- Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, and Okunieff P: Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys* 67: 793-798, 2007.
- Hu C, Chang EL, Hassenbusch SJ 3rd, Allen PK, Woo SY, Mahajan A, Komaki R, and Liao Z: Non-small cell lung cancer presenting with synchronous solitary brain metastasis. *Cancer* 106: 1998-2004, 2006.
- Bonnette P, Puyo P, Gabriel C, Giudicelli R, Regnard JF, Riquet M, Bricchon and PY; Groupe Thorax: Surgical management of non-small cell lung cancer with synchronous brain metastases. *Chest* 119: 1469-1475, 2001.
- Salah S, Tanvetyanon T, and Abbasi S: Metastectomy for extra-cranial extra-adrenal non-small cell solitary metastases: systematic review and analysis of reported cases. *Lung Cancer* 75: 9-14, 2012.
- Collen C, Christian N, Schallier D, Meysman M, Duchateau M, Storme G, and De Ridder M: Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic non small-cell lung cancer patients. *Ann Oncol* 25: 1954-1959, 2014.
- Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, and Pignon JP: Meta-analysis of concomitant *versus* sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 28: 2181-2190, 2010.
- Burt M, Wronski M, Arbit E, and Galicich JH: Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. *J Thorac Cardiovasc Surg* 103: 399-410, 1992.
- Luketich JD, and Burt ME: Does resection of adrenal metastases from non-small cell lung cancer improve survival? *Ann Thorac Surg* 62: 1614-1616, 1996.
- Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R and Weichselbaum R: The oligometastatic state-separating truth from wishful thinking. *Nat Rev Clin Oncol* 11: 549-557, 2014.
- Wronski M, Arbit E, Burt M, and Galicich JH: Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. *J Neurosurg* 83: 605-616, 1995.
- Mussi A, Pistolesi M, Lucchi M, Janni A, Chella A, Parenti G, Rossi G, and Angeletti CA: Resection of single brain metastasis in non-small-cell lung cancer: prognostic factors. *J Thorac Cardiovasc Surg* 112: 146-153, 1996.
- Niibe Y, Nishimura T, Inoue T, Kakita S, Hara T, Sekiguchi K, Watanabe M and Hayakawa K: Oligometastases of brain only in patients with non-small cell lung cancer (NSCLC) treated with stereotactic irradiation (STI): a multiinstitutional study. *Int J Radiat Oncol Biol Phys* 78: S497, 2010.
- Gomez DR, Niibe Y, and Chang JY: Oligometastatic disease at presentation or recurrence for non small cell lung cancer. *Pulm Med* 2012: 396592, 2012.
- Tanvetyanon T, Robinson LA, Schell MJ, Strong VE, Kapoor R, Coit DG and Bepler G: Outcomes of adrenalectomy for isolated synchronous *versus* metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol* 26: 1142-1147, 2008.
- Hanagiri T, Takenaka M, Oka S, Shigematsu Y, Nagata Y, Shimokawa H, Uramoto H and Tanaka F: Results of a surgical resection for patients with stage IV non-small-cell lung cancer. *Clin Lung Cancer* 13: 220-224, 2012.
- Parikh RB, Cronin AM, Kozono DE, Oxnard GR, Mak RH, Jackman DM, Lo PC, Baldini EH, Johnson BE and Chen AB: Definitive primary therapy in patients presenting with oligometastatic non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 89: 880-887, 2014.
- Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenas H, Chidel MA, Pugh TJ, Kane M, Gaspar LE and Scheffer TE: Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases. *J Clin Oncol* 27: 1579-1584, 2009.
- Inoue T, Katoh N, Onimaru R and Shirato H: Clinical outcomes of stereotactic body radiotherapy for patients with lung tumors in the state of oligo-recurrence. *Pulm Med* 2012: 369820, 2012.
- Vogelbaum MA, Angelov L, Lee SY, Li L, Barnett GH and Suh JH: Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. *J Neurosurg* 104: 907-912, 2006.

- 27 Minniti G, Esposito V, Clarke E, Scaringi C, Lanzetta G, Salvati M, Raco A, Bozzao A and Maurizi Enrici R: Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys* 86: 623-629, 2013.
- 28 De Ruyscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, Bootsma G, Pitz C, van Eijnsden L, Geraedts W, Baumert BG and Lambin P: Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases long-Term results of a prospective phase II Trial. *J Thorac Oncol* 7: 1547-1555, 2012.
- 29 Voltolini L, Rapicetta C, Luzzi L, Ghiribelli C, Paladini P, Granato F, Gallazzi M and Gotti G: Surgical treatment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node-negative subgroup. *Eur J Cardiothorac Surg* 37: 1198-1204, 2010.
- 30 Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, Congedo MT, Gomez DR, Wright GM, Melloni G, Milano MT, Sole CV, De Pas TM, Carter DL, Warner AJ and Rodrigues GB: An individual patient data meta-analysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 15: 346-355, 2014.
- 31 Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA and Fukuoka M: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 361: 947-957, 2009.
- 32 Dahele M and Senan S: The role of stereotactic ablative radiotherapy for early-stage and oligometastatic non-small cell lung cancer: evidence for changing paradigms. *Cancer Res Treat* 43: 75-82, 2011.
- 33 Jabbour SK, Daroui P, Moore D, Licitra E, Gabel M and Aisner J: A novel paradigm in the treatment of oligometastatic non-small cell lung cancer. *J Thorac Dis* 3: 4-9, 2011.
- 34 Gomez DR, Niibe Y and Chang JY: Oligometastatic disease at presentation or recurrence for non small cell lung cancer. *Pulm Med* 2012: 396592, 2012.
- 35 Patel PR, Yoo DS, Niibe Y, Urbanic JJ and Salama JK: A call for the aggressive treatment of oligometastatic and oligorecurrent non-small cell lung cancer. *Pulm Med* 2012: 480961, 2012.

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