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Case Report

Unexpected long survival of brain oligometastatic non-small cell lung cancer (NSCLC) treated with multimodal treatment: a single-center experience and review of the literature

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Abstract: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide. Fifty percent of the cases are metastatic at diagnosis and about 20% develop brain metastasis. The brain involvement represents a negative prognostic factor. However, some patients could benefit from locoregional treatments of metastatic foci and experience an unexpected long survival or healing. In the previous years some classifications were proposed to identify patients' prognostic category, according to stage of the primary tumor, the timing of metastases occurrence (synchronous or metachronous) and the number of metastatic sites. Several data show a benefit in patients receiving resection of both the primary tumor and brain metastases. Whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) are the selected options in most cases. Overall, literature data showed highly variable outcome, with an overall survival (OS) ranging from 5.9 to 68 months. No data from randomized and homogeneous trials are currently available. Therefore, a growing interest in this field is observed. Different trials investigating the effectiveness of local treatments and studies analyzing biological mechanisms are ongoing. In this report we analyze literature data and we explore the current field of study. Furthermore, we show a single institutional experience of multimodal management of stage IV NSCLC with brain metastases, experiencing an unexpected long survival. We conclude that a better knowledge of this subpopulation of patients and new studies in this field can lead to distinguish the patients who can benefit from local treatment from those with poor prognosis.

Keywords: Lung neoplasm; oligometastatic disease; survival

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death across the world (1). Over 50% of these patients present metastatic disease at diagnosis, while many others develop metastatic dissemination during their course of disease and about 20% of these patients develop brain metastases.

Median survival for patients with stage IV NSCLC treated with chemotherapy alone is between 8 and 11 months (2). Brain metastases development represents a negative prognostic factor and median survival in this subgroup of patients is 7 months (3,4).

Hellman and Weichselbaum defined the oligometastatic state as an intermediate clinical state between locoregionally confined and widespread cancer (5). Since 1995 it has been hypothesized that these patients with limited metastatic foci may experience longer survival and, in rare cases, potential cure following comprehensive tumor ablation.

In the last two decades a number of studies evaluating the role of locally ablative therapies [i.e., surgical resection

Table 1 Clinical-pathological characteristics of the patients

# of case	Sex, age at diagnosis	Smoking history	Diagnosis (month, year)	Histology	Stage	Number, localization of mets at diagnosis	Number and synchronous (s) or metachronous (m) mets	Treatment		Systemic treatment	Ashowrth risk group	N.O.C. classification	Survival (months)	
								Primary tumor	Mets				PFS	OS
#1	M, 58	Heavy	Apr 2013	Adk NSCLC	IV	1, brain	1 s	–	Surgery	CT	Intermediate	Intermediate	36	36
#2	M, 59	Heavy	Mar 2012	Adk NSCLC	IV	1, brain	1 s	Surgery	Surgery	CT	Intermediate	Intermediate	49	49
#3	F, 38	Never	Mar 2012	Adk NSCLC	IV	2, brain	2 s and 4 m	Surgery	SRS and WBRT	CT	High	Intermediate	3	49
#4	F, 49	Heavy	Dec 2010	Sarcomatoid LC	IV	3, brain	3 s	Surgery	Surgery and SRS	CT	Intermediate	Intermediate	65	65
#5	F, 64	Never	May 2010	Adk NSCLC	IV	1, brain	1 m	Surgery	SRS	None	Intermediate	Low	74	83

Table 1 shows the clinical-pathological characteristics of the patients, patients' risk group according to Ashworth and Niibe-Onishi-Chang criteria and survival data (PFS, OS) of the patients. Mets, metastases; N.O.C., Niibe-Onishi-Chang classification; PFS, progression-free survival; OS, overall survival; M, male; F, female; heavy smoker, ≥20 pack-years; never smoker, adult who has never smoked, or smoked less than 100 cigarettes in his or her lifetime; Adk: adenocarcinoma; NSCLC, non-small cell lung cancer; LC, lung cancer; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; CT, chemotherapy.

(SR), and stereotactic radiosurgery, (SRS)] for limited metastatic foci have been performed (6,7). Patients with synchronous brain oligometastases represent a population that can benefit from aggressive locoregional treatments. SR, SRS and whole-brain radiotherapy (WBRT) are the main therapeutic options (8-10).

The treatment of single metastases with different localization than brain is controversial but several reports have shown longer survivals in this subgroup of patients treated with aggressive locoregional treatments (11-15).

We present in this report five cases of oligometastatic NSCLC patients experiencing unexpected long survival after aggressive locoregional treatment of their metastatic districts.

Case presentations

The median age of the patients at diagnosis was 53.6 years (range, 38–64 years). Clinical and pathological features of the patients are reported in *Table 1*.

These patients have been treated at Sant'Andrea Hospital of Rome between May 2009 and April 2016. For three of them, cancer was diagnosed during the hospitalization at the Emergency Department (ED) for symptoms caused by brain metastases. These cases were immediately treated with neurosurgical intervention.

All patients had brain metastases. We defined synchronous if the metastases occurred within 2 months from the diagnosis of the primary tumor. The disease of this subgroup of patient was considered biologically more aggressive. We chose 2 months for the definition of "synchronous metastases" according to previous published data and also because of logistical concerns relative to the SEER registry process.

Cancer staging was done according to TNM 7th edition. All the patients still undergo clinical and radiological [Computed Tomography (CT) scan, brain magnetic resonance imaging (MRI)] follow-up every 6 months.

All patients are still alive, and the median overall survival (OS) is 49 months (range, 36–83 months).

Progression-free survival (PFS) was defined as the time from the first SR to the first radiological evidence of disease progression.

OS was defined as the time from diagnosis until death from any cause.

Survival data were calculated from the day of first treatment of either the primary tumor or metastatic lesions for patients with synchronous metastases, and from the day

of first treatment of oligometastatic disease for patients with metachronous metastases.

Written informed consent was obtained from all the patients for publication of this case series.

Case 1

A 58-year-old, heavy smoker (45 pack-years), Caucasian male was admitted to the ED for speech impairment and tonic-clonic seizures on April 2013. A brain MRI revealed a 12 mm left fronto-subcortical lesion with associated edema. A total body CT scan showed a 10 mm nodule in the right lung. An urgent SR of the brain mass was performed. An atypical resection of the middle lobe of the right lung was performed three weeks later. The histological examinations showed a brain metastasis of lung adenocarcinoma (ADK) [TTF-1+, CK7+, EGFR wild type (wt) and rearrangement of ALK] and a chondroid hamartoma of the lung, respectively. From August 2013 to January 2015 the patient received a first line treatment with platinum and pemetrexed for 6 cycles followed by maintenance pemetrexed for a further 6 months. Since subsequent total body CT scan didn't show evidence of disease, the patient started the follow-up with an OS of 36 months.

Case 2

On March 2012, a 59-year-old Caucasian male, heavy smoker (42 pack-years) was admitted to the ED for balance disorder. A brain MRI showed a 15 mm cerebellar lesion. An urgent cerebral surgery was performed and the histological and immunohistochemistry features suggested a metastasis of NSCLC ADK TTF-1+. A CT scan revealed a mass in the right lung and in April 2012 the patient underwent a right upper lobectomy with systematic lymphadenectomy for stage IV grade 3 lung ADK (pT2a pN0 M1b, EGFR wt, no ALK rearrangement). There was no radiological evidence of disease after surgery. From July 2012 to October 2012 the patient received 4 cycles of platinum-based chemotherapy. There is no clinical and radiological evidence of disease recurrence so far, with an OS of 49 months.

Case 3

A 38-year-old, never smoker, Caucasian female underwent a left lower lobectomy and systematic lymphadenectomy on March 2012 for stage IIIA NSCLC ADK (pT3 pN2 Mx, EGFR wt, no rearrangement of ALK and ROS-1). On April 2012 she came for a visit at our department and we decided to complete the staging with a brain MRI. The exam showed the presence of two brain metastases. Between May and September 2012, she received 6 cycles of platinum based chemotherapy and she underwent SRS of the brain metastases. On March 2013 brain MRI showed new metastases and the patient underwent SRS and whole brain radiotherapy (WBRT). At April 2016 the disease is still under control and the OS is 49 months.

Case 4

A 49-year-old Caucasian female, heavy smoker (36 pack-years) was admitted to the ED with seizures and hypoesthesia of the right arm on December 2010. A total body CT scan showed a brain lesion and a left lung mass. The patient underwent craniotomy with total excision of the brain lesion first: the histological exam revealed a metastatic NSCLC TTF-1+ CK7+. The patient subsequently underwent left upper lobectomy with systematic lymphadenectomy. Histological analysis showed a sarcomatoid lung cancer (pT2 pN0 M1b). On February 2011, a brain MRI showed three new lesions, and so she performed SRSs. From March to July 2011, she received 6 cycles of platinum based chemotherapy. On February 2012, a total body CT scan revealed an increase in dimension of the frontal brain lesion so she underwent a second cerebral surgery for mass removal. The histological examination showed necrosis and inflammations, with no evidence of cancer tissue. Afterwards, she continued the radiological and clinical follow-up. The patient is still alive and the OS is 65 months.

Case 5

A 64-year-old Caucasian female, never smoker, underwent a left lower lobectomy on May 2009 for stage IA lung ADK (pT1 pN0 G3, EGFR wt). A PET scan performed after surgery was negative. According to the stage of disease the patient did not undergo adjuvant treatment. On February 2010 a total body CT scan and a brain MRI showed the presence of one left frontal brain metastasis. The patient underwent a SRS and then she started radiological and clinical follow-up. At April 2016 the patient is still alive with no evidences of disease and the OS is 83 months.

Discussion

An increasing interest in oligometastatic condition has

been observed in scientific literature since this condition for NSCLC has been defined in 1995 by Hellman and Weichselbaum (5). Many reports demonstrate that this subgroup of patients may experience a long survival or even healing (16,17). Nevertheless, only one clinical randomized trial has been published so far, and the management remains controversial. However, local therapies aimed to eradicate the disease seem to be the most reliable strategies (16).

A recent systematic review published by Ashworth and colleagues, analyzing 49 reports and 2,176 oligometastatic NSCLC patients, showed highly variable results in terms of survival (18). In fact, in this report, OS ranges between 5.9 and 52 months (median 14.8 months) and time to progression (TTP) from 4.5 to 23.7 months (median 12 months). In particular, they observed a longer survival (19 months) in patients with the primary tumor controlled by local treatments. The longest survival has been reported in patients with mixed metastatic sites, while patients with adrenal gland metastases showed the shortest survival (18).

The same group of researchers published in 2014 an individual patient data metanalysis, on 757 NSCLC patients with 1–5 metastases (19). Both primary tumor and metastatic sites were treated with surgery. Twenty six months of median OS and 11 months of median PFS were observed. The authors divided the patients into three classes of prognosis: low risk, including patients with metachronous metastases; intermediate risk, including patients with synchronous metastases and no nodal involvement; high risk, including patients with synchronous metastases and nodal involvement (N1–N2). The 5-year OS were 47.8%, 36.2% and 13.8%, respectively. Other prognostic factors were: primary tumor (T) stage; histology (better prognosis for ADK); presence of brain or lung metastases and surgical treatment of the T (19).

Niibe and colleagues proposed another classification (Niibe-Onishi-Chang classification) for oligometastatic patients in 2013. This classification divided the patients in favorable, intermediate and unfavorable prognosis, according to the timing of metastases occurrence (synchronous or metachronous), the number and the location of metastatic sites (20).

Although the traditional management for metastatic NSCLC contemplates only palliative treatments, recent data show that surgery of the primary tumor leads to a better survival in patients with NSCLC and brain metastases (8,17,21,22).

Iwasaki and colleagues demonstrated that patients that underwent lung and brain surgery experience a longer survival than patients who underwent resection of the lung lesion only (23). American College of Chest Physicians (ACCP) Guidelines suggest SR of the brain metastasis followed by WBRT and adjuvant chemotherapy as standard of care for patients with a single brain metastatic focus (24).

The management of multiple brain metastases is more controversial. SRS may be the preferable option in these cases (25).

Interestingly, recent data, mainly reported as case reports, showed a tumor regression at non-irradiated sites. This effect, called “abscopal”, could be mediated by immune system, by enhancing T cells function, inducing immunogenic cells’ death and improving antigen expression and presentation (26,27).

The concern in understanding the biology of oligometastatic cancer is lately increasing. It is commonly accepted that metastatic progression is a multi-step process. Two hypotheses to explain the differences between oligometastases and polymetastases have been proposed. According to the first hypothesis oligometastases and polymetastases may have different phenotypes, determined by clonal populations with different metastatic potential. The second hypothesis suggests that metastatic process may be a continuum and oligometastatic disease is an early phase that can evolve in polymetastatic stage (28).

In this report we present five cases of oligometastatic lung cancer, showing a long survival, after a multimodal treatment. In our cases the PFS ranges between 3 to 65 months. All patients are still alive and progression free, with an OS ranging between 36 and 84 months. All patients underwent surgery for the primary tumor.

Brain metastases were synchronous in four cases and in three of these were symptomatic (i.e., seizure, speech impairments, arm hypoesthesia and balance disorders). SR was performed in these three cases in order to relieve symptoms, while SRS alone or in association with WBRT was the selected therapeutic option for asymptomatic lesions. Only one patient with multiple symptomatic brain metastases received both surgical and radiation treatment. None received WBRT after surgery. The PFS and OS observed are surprisingly longer than those reported in the literature. These data are showed not only in patients with single metastasis and despite the classification of risk and prognosis according to Ashworth and Niibe-Onishi-Chang. In fact, only one of the cases we report is classified as poor risk or favorable prognosis (*Table 1*).

We performed a review of the last 5 years’ literature published on Medline (via PubMed—last search performed

Table 2 Review of studies for oligometastatic lung cancer

Author	Type of study	Pts (N)	Smoker	Histology	Metastases site (pts)	Number of metastases	Treatment		Survival (months)		Publication year
							Primary tumor	Metastases	PFS	OS	
Collen *et al*. (13)	Phase II	26	NR	ADK =17; SC =2; other =7	Brain =6; bone =8; adrenal =6; lung =15; other =13	1–5	CRT =17; SBRT =9	SBRT	11.2	23.0	2014
De Ruysscher *et al*. (29)	Phase II	40	NR	ADK =13; SC =9; other =18	Brain =17; bone =7; adrenal =4; lung =1; other =19	1–3	CRT =36; SBRT =2	SUR =9; SRS =11; SBRT =17	12.1	13.5; OS brain: 13.6	2012
Gomez *et al*. (32)	Phase II R	49	NR	NSCLC	NR	1–3	CT =49	RT =13; CRT =7; SUR + RT =3; SUR =1	14.4	Not reached	2016
Arrieta *et al*. (12)	Retrospective	30	23 (76.7%)	ADK =24; SC =4; other =2	Brain	1–5	CRT	WBRT	8.4	31.8	2011
Griffioen *et al*. (11)	Retrospective	61	56 (91.8%)	ADK =48; SC =5; other =8	Brain =36; bone =11; adrenal =4; lung =4; other =6	1–3	SUR =3; SUR + CT =3; SUR + CRT =3; CRT =40; RT =2; SBRT =10	SRS =18; SBRT =6; RT =13; WBRT =2; SUR =6; SUR + RT =16	6.6	13.5	2013
Enders *et al*. (30)	Retrospective	114	93 (81.5%)	NR	Brain	>1	SUR; CT	SUR; WBRT	NR	11.2	2016
Fleckenstein *et al*. (33)	Retrospective	75	NR	ADK =50; SC =17; other =8	Brain =51; bone =7; adrenal =34; lung =9; other =12	1–5	SUR =55; CRT =18; SBRT =2	SUR =12; SBRT/SRS/ hSRT =19; SUR + RT =49; RT =4	13.0	21.8	2016
Lamm *et al*. (31)	Case report	1	NR	ADK	Brain; brainstem; lung	2 brain; 1 crbl; 1 brainstem; 1 lung	CRT	SRS; SUR	5.0	>68.0	2012
Leduc *et al*. (34)	Case report	1	Yes	ADK	Brain; adrenal	2 brain; 1 adrenal	SBRT	SBRT	12.0	>30.0	2015
Yarchoan *et al*. (27)	Case report	1	Yes	ADK	Crbl; brain; adrenal; liver; lung	1 crbl; 2 brain; 1 adrenal; 1 liver; 1 lung	SUR + CT	WBRT; SRS; SUR	5.0	>60.0	2015

Table 2 shows results of our published literature search on Medline (via PubMed) about the management of oligometastatic lung cancer in the last 5 years. Pts, patients; R, randomized; NR, not reported; ADK, adenocarcinoma; SC, squamous cell carcinoma; crbl, cerebellum; SUR, surgery; SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy; CRT, chemoradiotherapy; CT, chemotharapy; RT, radiotherapy; WBRT, whole brain radiotherapy; hSRT, hypofractionated stereotactic radiosurgery; PFS, progression free survival; OS, overall survival.

on June 2016). We considered all the reports presenting data about oligometastatic NSCLC patients with brain metastases. We excluded the studies enrolling patients with various tumor types (8,11-13,27,29-34). As reported in *Table 2*, literature data are available from case reports, retrospective series and phase II trials. Very heterogeneous

Table 3 Ongoing trials

ClinicalTrials.gov identifier	Phase	Intervention	Status
NCT01781741	Pilot study	SBRT after surgery	Ongoing, not recruiting
NCT02450591	Pilot study	Erlotinib followed by local treatment	Recruiting
NCT01941654	II	Local ablative therapy after EGFR TKI	Recruiting
NCT01185639	II	SBRT after CT	Ongoing, not recruiting
NCT02054819	II	CT and concurrent radiation to primary plus radiation therapy to metastatic site	Recruiting
NCT02316002	II	Pembrolizumab after curative intent treatment	Recruiting
NCT01725165	II R	Local treatment *vs*. maintenance CT after induction chemotherapy	Ongoing, not recruiting
NCT00887315	II R	CT *vs*. CT and hypofractionated image guided radiotherapy	Terminated for slow accrual
NCT01796288	II R	Second line erlotinib *vs*. erlotinib plus RT	Recruiting
NCT00776100	II R	Observation *vs*. radiation therapy after induction CT	Completed
NCT01446744	II R	SABR *vs*. palliative standard of care (CT or RT)	Recruiting
NCT02417662	III	CT *vs*. CT plus SABR	Not yet open
NCT02076477	III	CRT followed by CT *vs*. CT followed by CRT	Recruiting

Table 3 shows all the completed, ongoing and not planned studies on the effectiveness of local treatments for oligometastatic lung cancer (source: clinicaltrials.gov—last search performed on June 2016). R, randomized; SBRT, stereotactic body radiation therapy; CT, chemotherapy; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; CRT, chemoradiotherapy.

outcomes are reported, with OS ranging from 11.2 to over 68 months. As expected, the better outcomes were described in case reports than in larger studies. Two retrospective series enrolled only patients with brain metastases. Nevertheless, they shown conflicting results, with a long OS of 31.8 months in Arrieta and colleagues' series and a shorter OS (11.2 months) in Enders and colleagues' report (12,30). A retrospective series published by Fleckenstein and colleagues addresses the relevance of synchronous *vs*. metachronous metastasis, not founding a prognostic relevance in this characteristic (33).

Interestingly, during the 2016 ASCO annual meeting the first randomized trial on oligometastatic NSCLC was presented. In this phase II study patients randomized to receive locoregional treatments showed a better PFS (14.4 months) than the control group (PFS 3.9 months) (32). Furthermore, treatment options are very heterogeneous, both for primary tumor and metastatic sites.

Since few data from randomized or homogeneous trials are currently available in literature, a growing interest in oligometastatic disease is observed. An increasing number of trials designed in order to study the effectiveness of local treatments (radiotherapy or surgery) are ongoing (*Table 3*). In particular, a phase III trial studying the best timing for chemotherapy and chemoradiotherapy (CRT) is ongoing (NCT02076477), and another phase III trial comparing chemotherapy alone *vs*. chemotherapy and stereotactic ablative radiotherapy (SABR) is open, but is not yet recruiting (NCT02417662).

Recent advances demonstrate a correlation between microRNA expression and oligometastatic stage (28,35,36). Lussier and colleagues identified certain microRNAs associated with a high rate of progression (HRP) and others with a low rate of progression (LRP) in NSCLC patients (36). Circulating tumor cells in oligometastatic patients are under investigation as well (NCT02949837). Further analyses are required. In fact, a better knowledge of tumor biology can help oncologists to identify patients with indolent disease, who could benefit from local treatment.

Conclusions

This case series confirms that oligometastatic NSCLC patients treated with locoregional aggressive therapies experience better outcomes and longer survivals. In fact, despite the evidence that stage IV NSCLC can benefit only from palliative oncologic therapies, curative radiotherapy and surgery of the metastatic loci turned out to be a potential better therapeutic option for this subgroup of patients.

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Footnote

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

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