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FULL PAPER

Outcome appraisal of patients with limited brain metastases (BMs) from non small cell lung cancer (NSCLC) treated with different local therapeutic strategies: a single institute evaluation

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Objective: To evaluate the outcome of patients with non-small-cell lung cancer (NSCLC) with limited brain metastases (BMs) treated with local approaches omitting whole-brain radiation therapy (WBRT).

Methods: Surgery was performed in case of a single, large BM, controlled extracranial disease and Karnofsky Performance Status (KPS) 90–100; stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiosurgery (HSRS) was performed in all other cases. The prescribed dose was 24 Gy/1 fraction for lesions <2.5 cm, and a median of 30 Gy (24–40 Gy) in 3–5 fractions for lesions >2.5 cm.

Results: 156 patients treated for 228 BMs were retrospectively evaluated. The median age was 62 years. The majority of patients had a KPS 90–100, recursive partitioning analysis Class II, diagnosis-specific graded prognostic assessment score 2.5–3 and 1–2 BMs. Surgical resection was performed in 18 cases, and SRS/HSRS was performed in 210 cases. The 1–2-year local control was $87.2 \pm 3.0\%$ and $72.8 \pm 5.0\%$; the 1.2-year brain distant

failure was $30.8 \pm 4.0\%$ and $58.1 \pm 6.0\%$; the 1–2-year overall survival was $60.9 \pm 3.9\%$ and $31.4 \pm 4.0\%$. On univariate and multivariate analysis, the following factors influenced survival: age ($p = 0.01$), the presence of lymph node involvement ($p = 0.03$), KPS ($p < 0.01$), the presence of extracranial metastases at the time of BM treatment ($p < 0.01$), the number of BMs ($p = 0.02$) and the treatment performed ($p < 0.01$).

Conclusion: The choice of an adequate local treatment can impact on survival in patients with limited BMs from NSCLC. A careful evaluation of prognostic and predictive factors is a pivotal additional aid.

Advances in knowledge: Radiosurgery or surgery followed by radiosurgery on the tumour bed in place of WBRT proved to be an effective treatment influencing outcome. Surgical resection followed by SRS on the tumour bed has to be considered for lesions ≥ 15 mm, in patients with good KPS, age ≤ 70 years, adenocarcinoma histology and oligometastatic disease.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the most common cause of brain metastases (BMs). About 10% of patients show BMs at diagnosis, and up to 45% patients will develop them during the course of their disease.^{1–3} For limited BMs, ≤ 4 lesions, several local approaches have been used: whole-brain radiotherapy (WBRT), single-dose stereotactic radiosurgery (SRS), hypofractionated stereotactic radiosurgery (HSRS) or surgery followed or not by radiation therapy (RT). For several years, WBRT has been considered the standard of care in patients with cancer;

but, considering the high risk of detrimental effects on neurocognitive functions, without an improvement of survival, it was not recommended in clinical practice anymore.^{4–9} Considering that the main cause of memory function decline is related to hippocampal damage, efforts to reduce the hippocampal dose during WBRT have been made.^{10,11} The Radiation Therapy Oncology Group 0933 Phase II clinical trial reported the outcome of patients with BM who were treated with hippocampus-sparing whole-brain radiation therapy. A better memory preservation compared with historical controls was recorded; but, these

data, albeit promising, deserve further confirmations.¹² A recent suggestion of the American Society for Radiation Oncology advises against the routine use of WBRT, encouraging the employment of SRS or HSRS, which are able to deliver selectively high ablative RT doses, in single or few fractions, without delay in the administration of systemic therapy. The role of surgical resection has evolved over time; but, to date, it is still reserved to few selected cases of larger BMs, in patients who are potentially long-term survivors or in case of invalidate neurologic symptoms.^{13–17} The open challenge question is which criteria have to be used for the treatment choice and whether an optimal local treatment, which is able to obtain an adequate brain control of disease, could influence patient survival. Recent data showed the intracranial efficacy of targeted drugs such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) or alkaline phosphatase (ALK) inhibitors compared with cytotoxic standard chemotherapy, justifying their use as first-line treatment in case of EGFR mutation or ALK rearrangement, but especially in case of disseminated brain disease.^{18–22} Based on this background, we evaluated patients with limited BMs from NSCLC treated in our institution using local approaches, surgery and/or radiosurgery omitting WBRT. The aim of this retrospective analysis was to evaluate the outcome in terms of local control (LC), brain distant failure (BDF) and overall survival (OS).

METHODS AND MATERIALS

Patients and procedures

The present study includes patients with limited BMs (up to four) from primary NSCLC treated with surgery plus HSRS or SRS/HSRS only, in relation to patient general condition (age, performance status and neurological symptoms) and disease status (other sites of extracranial metastases, number and size of BMs). Each patient was evaluated by a multidisciplinary team including a radiation oncologist, a neurosurgeon and a oncologist. In detail: (i) surgical resection followed by HSRS on the surgical cavity was performed in case of patients with Karnofsky Performance Status (KPS) 90–100, controlled extracranial disease, single brain lesion with diameter ≥ 30 mm, life expectancy longer than 6 months or progressive neurological deficits; (ii) SRS alone in case of small or multiple BMs; and (iii) HSRS alone in case of large BMs unsuitable for surgical resection. EGFR and ALK status was evaluated only in patients with adenocarcinoma histology and Stage IV at diagnosis, or in case of Stages I–III adenocarcinoma at disease recurrence, in patients not amenable for radical treatments. All patients were treated in agreement with the Helsinki Declaration. This study was based on a retrospective analysis of treatment charts and received approval from the local ethical committee.

Surgery

A “supramarginal resection”, defined as a microsurgical excision with an extension at least 5 mm larger than the enhancing T_1 weighted MRI sequence borders, was performed. In case of dural attachment, dura matter removal was carried out at least 2 cm in each direction from the stalk; when the skull base dura was involved if the anatomical features of major brain vessels and cranial nerves allowed, dural attachment has been engraved with a microscalpel, dressed and removed *en bloc*. Skull defects were

repaired with a dural synthetic substitute and fibrin glue to prevent cerebrospinal fluid fistula.

Radiation therapy

For SRS or HSRS, enhanced T_1 MRI sequences and post-contrast volumetric CT scan were used and co-registered to precisely delineate the target volume. A personalized thermoplastic mask was used for patient immobilization and repositioning. In case of surgical resection, the clinical target volume (CTV) corresponded to the surgical cavity, and the planning target volume (PTV) was defined as an isotropic expansion from CTV of 2 mm. In case of SRS/HSRS, the gross target volume consisted of the abnormality on contrast-enhanced T_1 MRI, CTV corresponded to gross target volume and no additional margins were used, and the PTV was generated by adding an isotropic margin of 2 mm from CTV. The delineated organs at risk (OARs) were the brain, brainstem, optic nerves, chiasm and lenses. No margins were added to OARs. The prescribed total dose and fractionation were chosen in relation to the size of BMs and/or to the close proximity of OARs: after surgical resection, all patients underwent 30 Gy in 3 fractions; in case of SRS or HSRS only, for lesions < 2.5 cm 24 Gy in single fraction and in case of lesions > 2.5 cm a median dose of 30 Gy (range 24–40 Gy) in 3–5 fractions. Plans were optimized aiming to achieve a PTV coverage with a dose delivered to more than 95% of the volume, $D_{95\%} > 95\%$ with a homogeneous dose distribution. Normalization was set in order to have 100% of the dose to target (PTV) mean. All plans were optimized using two partial coplanar or non-coplanar arcs, according to the lesion position. All patients were treated with the volumetric-modulated arc technique RapidArc (Varian Medical System, Palo Alto, CA) on three different Varian linear accelerators equipped with a four-dimensional couch. Exactrac (Brainlab) and cone-beam CT imaging were performed daily for patient setup and positioning verification.

Systemic therapy

Different regimens were used in relation to previous treatments received, patient age and KPS, EGFR and ALK status: platinum-based polychemotherapy, monochemotherapy consisted of vinorelbine, gemcitabine, taxane and pemetrexed or EGFR TKIs (gefitinib/erlotinib) and ALK inhibitors (crizotinib/ceritinib).

Outcome evaluation

Clinical outcome was evaluated by neurological examination, and brain MRI was performed 2 months after RT and then every 3 months. LC was defined as the absence of new radiographic enhancing abnormality in the treated areas on serial MRI, and BDF as the presence of new BMs or leptomeningeal enhancement outside the treated region. Radionecrosis was assessed using contrast-enhanced T_1 MRI, T_2 weighted MRI and perfusion MRI. Radionecrosis was considered as the presence of central hypodensity and peripheral enhancement on T_1 weighted post-contrast imaging, with oedema on T_2 weighted sequences and a clear lack of perfusion without any highly vascularized nodular area within the contrast-enhanced lesion on perfusion MRI. Histologic confirmation of radionecrosis was not required except for in patients in whom surgical resection has been needed. Systemic disease was evaluated by contrast-

Table 1. Patients and tumour characteristics

Parameter	Number of cases	%
Patients	156	100
Median age (range) [years]	62 (27–93)	
Gender		
Male	106	67.9
Female	50	32.1
Histology		
Adenocarcinoma	128	82.1
Squamous cell carcinoma	28	17.9
EGFR status (adenocarcinoma)	67	52.3
Mutated	17	25.4
Wild type	50	74.6
ALK status (adenocarcinoma)	60	46.9
Rearranged	8	13.3
Wild type	52	86.7
Primary tumour stage at diagnosis		
IA–IB	11	7
IIA–IIB	16	10.3
IIIA	29	18.7
IIIB	11	7
IV	89	57
Metastatic site at diagnosis		
Brain only	46	50.5
Extracranial only	25	27.5
Brain + extracranial	20	22
Treatment at diagnosis		
Surgery	15	9.6
Chemotherapy	60	38.4
Radiotherapy	15	9.6
Surgery + chemotherapy	27	17.3
Surgery + radiotherapy	2	1.3
Chemotherapy + radiotherapy	22	14.1
Surgery + chemotherapy + radiotherapy	11	7.1
No treatment	4	2.6
KPS		
90–100	104	66.7
80	40	25.6
70	12	7.7
RPA class		
I	18	11.5
II	137	87.8

(Continued)

Table 1. (Continued)

Parameter	Number of cases	%
III	1	0.6
DS-GPA score		
0.5–1	10	6.4
1.5–2	58	37.2
2.5–3	80	51.3
3.5–4	8	5.1
Extracranial metastases at BM diagnosis	56	35.9
Number of BMs treated	228	100
1	103	66
2	35	22.4
3	17	10.9
4	1	0.6

BM, brain metastasis; DS-GPA, diagnosis-specific graded prognostic assessment; KPS, Karnofsky Performance Status; RPA, recursive partitioning analysis.

enhanced total-body CT scan and fluorine-18 fludeoxyglucose positron emission tomography CT. Prognostic factors analyzed were age ($>$ or ≤ 70), gender, KPS, stage at diagnosis, recursive partitioning analysis classes (I–III), the updated diagnosis-specific graded prognostic assessment (DS-GPA),²³ tumour (T1–T4) and lymphonodal (N0–N3) staging, the presence of other extracranial metastatic sites at the time of BM, number of BMs (1 *vs* >1), BM volume, local treatment performed (surgery and/or radiosurgery) and administration of systemic or targeted therapies after local treatments of BMs.

Statistical analysis

Standard descriptive statistics were used to describe the general data behaviour. Actuarial survival and recurrence time observations were computed according to the method of Kaplan and Meier, starting from the date of BM diagnosis. In order to investigate the prognostic role of individual variables, the log-rank test or univariate Cox regression were used, respectively, for categorical and numerical data. Multivariate Cox model was used as a method to estimate the independent association of a variable set with OS, LC and BDF. Statistical software used was SPSS® v. 20 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL).

RESULTS

Patients and treatments

From January 2009 to December 2015, 156 patients treated for 228 BMs were included in this evaluation. The greater number of patients had a KPS 90–100 (66.7%), were in recursive partitioning analysis Class II (87.8%), had adenocarcinoma histology (82.1%) and a DS-GPA score 2.5–3 (53.8%). EGFR status was available in 67/128 (52.3%) patients with adenocarcinoma, of which 17 (25.4%) were mutated and 50 (74.6%) were wild type; ALK status was available in 60/128 (46.9%) patients, 8 (13.3%) were rearranged and 52 (86.7%) wild type. The median interval time between the diagnosis of primary NSCLC and the

appearance of BMs was 6.2 months (range 0–142 months). At the time of BMs, 56 (35.9%) patients had other extracranial metastases and 100 (64.1%) patients had BMs only. Most of the patients had 1–2 BMs (88.4%). Patient and tumour characteristics are shown in Table 1. The treatments performed were: surgery alone in 3 (1.9%) patients, surgical resection followed by HSRS on the tumour bed in 15 (10.3%) patients, SRS only in 103 (66.0%) patients and HSRS in 34 (21.8%) patients. Patients who underwent surgery alone were in Stage IV at the time of primary diagnosis, and they did not receive adjuvant HSRS for the need to start chemotherapy treatment. In one case, surgical resection was performed for progressive neurologic deficit or major neurologic symptoms uncontrolled by corticosteroid drugs. 80 (51.3%) patients received systemic therapy after BM treatment, consisting of platinum-based chemotherapy in 56 (70.0%) patients, monochemotherapy in 14 (17.5%) patients, EGFR TKIs in 10 (12.5%) patients and ALK inhibitors in 4 (5.0%) patients. Treatments performed in relation to patient and tumour characteristics are shown in Table 2.

Local control, distant brain failure and overall survival analysis

The median follow-up time for the entire cohort was 14.8 months (0.9–90.5 months) and 23.6 months (13.5–90.5 months) for patients who were alive. 29 (18.6%) patients had local recurrence at the site of treatment at a median time of 13.1 months (range 3.6–46.5 months). Among these, 5 patients received surgical resection followed by HSRS in patients, SRS in 15 patients and HSRS only in 9 patients; the median maximum tumour diameter of the relapse lesions was 23 mm (range 15–44 mm). At the time of local recurrence, BDF was present in 18 patients, and extracranial progression was present in 5 patients; 6 patients had local failure only. The 1- and 2-year LC rates were $87.2 \pm 3.0\%$ and $72.8 \pm 5.0\%$, respectively. The only factor statistically conditioning LC was the type of treatment performed; indeed, the 1- and 2-year LC rates were $75.0 \pm 2.2\%$

Table 2. Treatments performed in relation to patient and tumour characteristics

Total patients	Surgery in 18 patients		SRS/HSRS only in 138 patients		Total 156 patients
	<i>n</i>	%	<i>n</i>	%	<i>n</i>
Median age years (range years)	66 (50–79)		64 (27–93)		62 (27–93)
KPS					
90–100	18	100	86	62.3	104
80	0	0	40	29	40
70	0	0	12	8.7	12
RPA					
I	3	16.7	15	10.9	18
II	15	83.3	122	88.4	137
III	0		1	0.7	1
EGFR status (adenocarcinoma)	10	55.6	57	41.3	67
Mutated	1	10	16	28	17
Wild type	9	90	41	72	50
ALK status (adenocarcinoma)	8	44.4	52	37.7	60
Rearranged	1	12.5	7	13.5	8
Wild type	7	87.5	45	86.5	52
DS-GPA score					
0.5–1	0	0	10	7.2	10
1.5–2	1	5.6	57	41.3	58
2.5–3	16	88.8	64	46.4	80
3.5–4	1	5.6	7	5.1	8
Extracranial metastases at BM diagnosis					
Yes	2	11.2	53	38.4	55
No	16	88.8	85	61.6	101
Number of BMs					
1	16	88.8	86	62.3	102
2	2	11.2	36	26.1	38
3	0	0	15	10.9	15
4	0	0	1	0.7	1
Systemic therapies delivered	8	44.4	72	52.2	80
Chemotherapy	7	87.5	59	81.9	66
EGFR or ALK inhibitors	1	12.5	13	18.1	14

BM, brain metastasis; DS-GPA, diagnosis-specific graded prognostic assessment; HSRS, hypofractionated stereotactic radiosurgery; KPS, Karnofsky Performance Status; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery.

and 0.0% for patients who underwent surgery alone, $86.0 \pm 3.4\%$ and $75.7 \pm 5.0\%$ for patients who underwent SRS/HSRS only and 100.0% and $83.3\% \pm 1.5$ for patients who underwent surgery followed by HSRS, respectively ($p < 0.01$). BDF occurred in 57 (36.5%) patients. Among these, 6 (10.5%) patients had leptomeningeal disease progression. The median BDF time and the 1- and 2-year BDF rates were 21.7 months (95% confidence interval 17.6–25.9 months), $30.8 \pm 4.0\%$ and $58.1 \pm 6.0\%$. No factors were recorded as significantly affecting BDF. At the last

observation time, 38 (24.3%) patients are alive and 118 (75.7%) patients had died. The median OS time, the 1- and 2-year OS rates from BM diagnosis were 15 months (95% confidence interval 12.7–17.3 months), $60.9 \pm 3.9\%$ and $31.4 \pm 4.0\%$. Figure 1 shows LC rate, BDP and OS for all patients treated.

Toxicity

Grade I–II toxicity was observed in 23 patients and consisted of headache in 14 patients, hydrocephalus in 5 patients and

Figure 1. (a) Local control for patients with brain metastases (BM) from non-small-cell lung cancer (NSCLC); (b) brain distant failure for patients with BM from NSCLC; and (c) overall survival for patients with BM from NSCLC.

cerebrovascular ischaemia in 4 patients. No visual or motor sensory deficits were recorded for patients treated for lesions in close proximity to the optical nerves, chiasmata or brainstem. G2 radionecrosis occurred in 12 cases and G3 in 1 patient in whom surgical resection was performed. Histological data confirmed the presence of extensive radionecrosis that occurred at 13 months from SRS.

Prognostic factor analysis

On univariate analysis, factors recorded as influencing survival were age, KPS, lymphonodal status at diagnosis, the presence of extracranial metastases at BM diagnosis, the DS-GPA score, the number of BMs and the local treatment performed. On multivariate analysis, the only factors confirmed as affecting survival were the lymphonodal status, the presence of extracranial metastases, KPS and DS-GPA score. Details are shown in Table 3.

Salvage treatment for intracranial/local progression

Among 29 (18.6%) patients with local brain relapse, 21 (72.4%) patients received further treatment: 11 (52.4%) surgical resection and 10 (47.6%) HSRS or SRS. About 57 (36.5%) patients with BDF, of which 50 (87.7%) patients were treated: 13 (26%) patients underwent WBRT and 37 (74%) patients underwent HSRS or SRS. Systemic therapy was performed in 19 patients using different regimens in relation to previous treatment or EGFR/ALK status.

DISCUSSION

In the past years, many studies have focused on the treatment of BMs regardless of primary tumour, but still few studies are available for different single histologies.¹⁻¹⁶ Considering the different behaviour, the various tendencies to brain diffusion and the peculiar natural history of each primary tumour, defining the proper therapeutical approach could provide useful

Table 3. Factors evaluated as conditioning overall survival (OS) in univariate and multivariate analyses

Factors analyzed	Number of patients	Median OS months (95% CI)	1 year OS %	2 years OS %	Univariate <i>p</i> -value	Multivariate <i>p</i> -value	HR
Age (years)							
≤70	105	16.9 (13.5–20.3)	68.6 ± 4.5	35.5 ± 4.9	0.01	–	–
>70	51	10.5 (6.2–14.7)	45.1 ± 7	23.2 ± 6.5			
KPS							
70	12	5.3 (2.7–7.9)	16.7 ± 10.8	16.7 ± 10.8	<0.01	<0.01	0.95 (0.23–2.01)
80	40	7.6 (3.2–12)	35 ± 7.5	15.5 ± 6			
90–100	104	19 (13.8–24.1)	76 ± 4.2	39 ± 5.2			
DS-GPA score							
0.5–1	10	5.2 (3.1–7.2)	10 ± 9.5	10 ± 9.5	<0.01	0.01	3.50 (2.35–4.65)
1.5–2	58	9 (6.2–11.7)	39.7 ± 6.4	17.8 ± 5.2			
2.5–3	80	19 (12.8–25.1)	78.8 ± 4.6	42.5 ± 5.9			
3.5–4	8	15 (12.7–17.3)	100	35 ± 26.4			
EC metastases							
Yes	55	12.1 (9.7–14.5)	50.9 ± 6.7	17.9 ± 5.4	<0.01	0.03	1.10 (0.44–2.09)
No	101	18.6 (13.6–23.6)	66.3 ± 4.7	39.1 ± 5.2			
Lymphonodal status							
Positive	111	14.8 (12.5–17.1)	59.5 ± 4.7	25.7 ± 4.4	0.03	0.03	1.35 (1.25–2.65)
Negative	45	21.2 (11.7–30.8)	64.4 ± 7.1	46.3 ± 7.8			
Number of BMs							
1	103	15.8 (13–18.5)	64.1 ± 4.7	36 ± 4.9	0.02	–	–
>1	53	12.8 (8.7–17)	54.7 ± 6.8	21.5 ± 6.5			
Treatment							
Surgery ± HSRS	18	Not reached	92.9 ± 6.9	66.1 ± 14.3	<0.01	–	–
SRS/SHSRS	138	14.2 (11.9–16.5)	56.5 ± 4.2	26.5 ± 4			

BM, brain metastasis; CI, confidence interval; EC, extra cranial; DS-GPA, diagnosis-specific graded prognostic assessment; HR, hazard ratio; HSRS, hypofractionated stereotactic radiosurgery; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery.

information in clinical practice. The recent advent of molecularly targeted therapies and immunotherapies has led to a greater number of patients who are long-term NSCLC survivors, potentially at increased risk of developing BMs, making it essential a correct management.^{18–21} WBRT has been considered the treatment of choice for BMs, above all in case of multiple localizations or meningeal involvement. Published studies have shown a symptomatic improvement in 63% of patients, a gain in local, leptomeningeal and regional control following surgical resection and a significant reduction of intracranial failure (from 70–78% to 24–47%).^{4–6,23–26} Over the past decade, the use of SRS, in place of WBRT, is emerging as the first treatment choice, keeping WBRT as salvage treatment in case of widespread intracranial metastatic disease. This change has been mainly due to the potential risk of detrimental effect of WBRT on

neurocognitive function. Four randomized trials assessed stereotactic radiotherapy with or without WBRT for patients with four or less BMs. None of these trials have shown any survival improvement with WBRT, but showed improved intracranial control with the addition of WBRT.^{4–6,24} The recommendations have been to use SRS as an effective alternative.²⁵ However, to date, the optimal therapeutic strategy is not yet defined. Based on this background, we wanted to evaluate the outcome of patients with limited BMs from NSCLC treated in our institution with focalized treatment only, SRS, HSRS or surgery followed by HSRS, omitting WBRT. By use of this approach, LC at the site of treatment was obtained in 80% of patients, and BDF occurred in about 30% of patients at 1 year. Survival rate was also satisfactory, with an OS of 61% and 31% at 1 and 2 years, respectively. These results compare favourably with previous reports in which WBRT was employed.^{4–6} Indeed, at 1 year,

LC, BDF and OS rates recorded were 80–85%, 45–52% and 30–38.5%, respectively, in different series. Several issues deserve to be discussed. Ours is clearly a selected series in which the majority of patients had a good KPS, age ≤ 70 years, adenocarcinoma histology, controlled extracranial disease, mainly 1–2 BMs and then were potentially long-term survivors. These points have partially addressed the omission of WBRT, with the aim of maintaining a good quality of life, to reduce rapidly the corticosteroid therapy and to perform systemic therapy, if indicated, without delay. Although WBRT has shown an improved intracranial disease control, in our series, it was required only in 8% of cases at brain disease progression, avoiding it in $>90\%$ of patients. The majority of patients underwent SRS or HSRS, in case of larger lesions unsuitable for surgical resection; surgery was performed in very few selected cases: in patients with excellent KPS, progressive neurological deficits uncontrolled by corticosteroid drugs, controlled extracranial disease and a single, large BM. The results recorded have proven to have a significant impact on LC and OS of the treatment performed. Indeed, patients who underwent surgical resection followed by HSRS on the tumour bed have had a 2-year LC of 83% compared with 76% for patients who underwent SRS/HSRS ($p < 0.01$). Similarly, the 2-year OS was 66% vs 26% ($p < 0.01$), demonstrating a favourable trend of combined treatment also on survival. Surgical resection was performed at local progression in about 50% of patients, highlighting that in this group of patients, there was probably an assessment mistake in relation to the volume of BMs treated. Indeed, although SRS is recommended for BMs up to 3 cm maximum diameter, and it is usually preferred to surgery for its non-invasiveness, it achieves an LC of only 49% in BMs between 2.1 and 3 cm.²⁵ Literature data showed 12-month LC rates of 86% in tumours <1 cm in size and 56% in tumours ≥ 1 cm.^{27,28} In our series, all patients who relapsed and underwent surgical resection had BMs with maximum diameter ≥ 15 mm with important perilesional oedema. These findings coupled with literature data also suggest that in these patients, surgical resection has to be considered.^{29,30} Finally, it is well known that outcome of patients with NSCLC BM is mainly related to a series of prognostic and predictive factors, as widely detailed in the DS-GPA score, recently updated, including age, KPS, the presence of extracranial metastases

and number of BMs, and for adenocarcinoma histology, EGFR and/or ALK status.²⁰ Also, in our series, these factors have shown significant relevance, as detailed above. In addition, the locoregional lymphonodal status has also proven to be a factor significantly affecting survival. Indeed, the 2-year OS rate was 46% for patients with negative lymph nodes and 25.7% in case of positive lymph nodes ($p = 0.03$). On the other hand, survival was not conditioned by administration of chemotherapy, EGFR or ALK inhibitors after local treatment. These data could be due to the limited number of patients with EGFR mutation (10%) or ALK rearranged (5%) in our series. We are aware that our analyses have several limitations: the retrospective evaluation of our series including a heterogeneous patient cohort, patients treated in different ways and the lack of neurocognitive assessment with the resulting inability to compare our results with those in which WBRT was performed. In addition, although surgical resection followed by HSRS has proven to be a better treatment than SRS/HSRS, above all, for lesions ≥ 15 mm, the limited number of patients undergoing surgery does not allow providing definite conclusions, but only observations and partial suggestions. Nevertheless, considering the lack of literature data about the treatment of BMs for histology and the fair number of patients treated, our study could make a contribution to this topic.

CONCLUSION

Our analysis showed that, in patients with limited BMs from primary NSCLC, SRS/HSRS or surgery followed by HSRS is able to obtain an adequate LC with limited neurological morbidity. Surgical resection of BMs has to be considered in all cases of lesions >15 mm. The prognostic and predictive role of DS-GPA score was confirmed in addition to stage of primary tumour, above all in relation to lymphonodal status. From our experience, we believe that the discussion of each single case within a multidisciplinary team (oncologist, radiation oncologist and neurosurgeon) is of pivotal importance to drive the most appropriate therapeutic approach and so avoid to undertreating of patients who are potentially long-term survivors. Well-designed collaborative trials, including stratification of patients by histology, are necessary to draw final conclusions in this field.

REFERENCES

- Barnholtz-Sloan JS, Sloan AE, Davis FG, Vignea FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004; **22**: 2865–72.
- Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol* 2005; **75**: 5–14. doi: <https://doi.org/10.1007/s11060-004-8093-6>
- Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999; **43**: 795–803. doi: [https://doi.org/10.1016/s0360-3016\(98\)00442-8](https://doi.org/10.1016/s0360-3016(98)00442-8)
- Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; **295**: 2483–91. doi: <https://doi.org/10.1001/jama.295.21.2483>
- Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornuth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomized controlled trial. *Lancet Oncol* 2009; **10**: 1037–44. doi: [https://doi.org/10.1016/s1470-2045\(09\)70263-3](https://doi.org/10.1016/s1470-2045(09)70263-3)
- Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011; **29**: 134–41. doi: <https://doi.org/10.1016/j.ijrobp.2009.07.037>
- Kwon AK, Dibasi SJ, Wang B, Hughes SL, Milcarek B, Zhu Y. Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. *Cancer* 2009; **115**: 890–98. doi: <https://doi.org/10.1002/cncr.24082>

8. Rajakesari S, Arvold ND, Jimenez RB, Christianson LW, Horvath MC, Claus EB, et al. Local control after fractionated stereotactic radiation therapy for brain metastases. *J Neurooncol* 2014; **120**: 339–46. doi: <https://doi.org/10.1007/s11060-014-1556-5>
9. Navarria P, Pessina F, Cozzi L, Ascolese AM, De Rose F, Fogliata A, et al. Hypofractionated stereotactic radiotherapy alone using volumetric modulated arc therapy for patients with single, large brain metastases unsuitable for surgical resection. *Radiat Oncol* 2016; **6**: 76. doi: <https://doi.org/10.1186/s13014-016-0653-3>
10. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 2010; **97**: 370–76. doi: <https://doi.org/10.1016/j.radonc.2010.09.013>
11. Abayomi OK. Pathogenesis of irradiation-induced cognitive dysfunction. *Acta Oncol* 1996; **35**: 659–63. doi: <https://doi.org/10.3109/02841869609083995>
12. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014; **32**: 3810–16. doi: <https://doi.org/10.1200/jco.2014.57.2909>
13. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis: an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2012; **2**: 210–25. doi: <https://doi.org/10.1016/j.prro.2011.12.004>
14. Bhangoo SS, Linskey ME, Kalkanis SN; American Association of Neurologic Surgeons; Congress of Neurologic Surgeons. Evidence-based guidelines for the management of brain metastases. *Neurosurg Clin N Am* 2011; **22**: 97–104. doi: <https://doi.org/10.1016/j.nec.2010.09.001>
15. Pessina F, Navarria P, Cozzi L, Ascolese AM, Maggi G, Riva M, et al. Outcome evaluation of oligometastatic patients treated with surgical resection followed by hypofractionated stereotactic radiosurgery (HSRS) on the tumor bed, for single, large brain metastases. *PLoS One* 2016; **11**: e0157869. doi: <https://doi.org/10.1371/journal.pone.0157869>
16. Jagannathan J, Yen CP, Ray DK, Schlesinger D, Oskouian RJ, Pouratian N, et al. Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. *J Neurosurg* 2009; **111**: 431–38. doi: <https://doi.org/10.3171/2008.11.jns08818>
17. Wang CC, Floyd SR, Chang CH, Warnke PC, Chio CC, Kasper EM, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy × 3 daily fractions regimen. *J Neurooncol* 2012; **106**: 601–10. doi: <https://doi.org/10.1007/s11060-011-0697-z>
18. Shin DY, Na I, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. *J Thorac Oncol* 2014; **9**: 195–99. doi: <https://doi.org/10.1097/JTO.0000000000000069>
19. Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol* 2015; **33**: 1881–88. doi: <https://doi.org/10.1200/JCO.2014.59.0539>
20. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol* 2013; **8**: 654–57. doi: <https://doi.org/10.1097/jto.0b013e31828c28e7>
21. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012; **7**: 1807–14. doi: <https://doi.org/10.1097/jto.0b013e3182745948>
22. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended survival and prognostic factors for patients with alk-rearranged non-small-cell lung cancer and brain metastasis. *J Clin Oncol* 2016; **34**: 123–29. doi: <https://doi.org/10.1200/jco.2015.62.0138>
23. Sperduto PW, Yang JT, Beal K, Pan H, Brown PD, Bangdiwala S, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (lung-molGPA). *JAMA Oncol* 2016. doi: <https://doi.org/10.1001/jamaoncol.2016.3834>
24. Brown PD, Asher AL, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. NCCTG N0574 (alliance): a phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1–3 brain metastases. *J Clin Oncol* 2015; **33**: LBA4. doi: <https://doi.org/10.1093/neuonc/nov208.05>
25. Mehta MP. The controversy surrounding the use of whole-brain radiotherapy in brain metastases patients. *Neuro Oncol* 2015; **17**: 919–23. doi: <https://doi.org/10.1093/neuonc/nov089>
26. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Post-operative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1995; **280**: 1485–89. doi: <https://doi.org/10.1001/jama.280.17.1485>
27. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016; **22**: 2004–14. doi: [https://doi.org/10.1016/s0140-6736\(16\)30825-x](https://doi.org/10.1016/s0140-6736(16)30825-x)
28. Chang E, Hassenbusch S, Shiu A, Lang FF, Allen PK, Sawaya R, et al. The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery* 2003; **53**: 272–80. doi: <https://doi.org/10.1227/01.neu.0000073546.61154.9a>
29. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993; **33**: 583–90. doi: <https://doi.org/10.1002/ana.410330605>
30. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996; **78**: 1470–76. doi: [https://doi.org/10.1002/\(sici\)1097-0142\(19961001\)78:7<1470::aid-cnrc14>3.0.co;2-x](https://doi.org/10.1002/(sici)1097-0142(19961001)78:7<1470::aid-cnrc14>3.0.co;2-x)