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Case Report

Evaluation of Potential Predictive Biomarkers for Defining Brain Radiotherapy Efficacy in NSCLC Patients with Brain Me-Tastases: A Case Report and Review of Literature

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Abstract: Non-small-cell lung cancer (NSCLC) is the second most common cancer worldwide, resulting in 1.8 million deaths/year. Most of the patients are diagnosed with a metastatic disease. Central Nervous System is one of the major metastatic sites. Brain metastases are associated with severe neurological symptoms, shorter survival and worst clinical outcomes. Brain radiotherapy and systemic oncological therapies are currently used for controlling both cancer progression and neurological symptoms. Brain radiotherapy includes stereotactic brain ablative radiotherapy (SBRT) or whole brain radiotherapy (WBRT). SBRT is applied for single or multiple (≤ 4) small lesions (< 3 cm), while WBRT represents the best treatment choice in case of multiple and large brain metastases. In both cases radiotherapy application can represent an overtreatment causing severe toxicities without achieving a significant clinical benefit. So far, some scores have been proposed to define the potential clinical benefits derived from brain radiotherapy. However, most of them are not well validated into clinical practice. In this article, by presenting a clinical case of a patient with advanced NSCLC carrying a BRAF^{V600E} mutation and brain metastases, we review the variables as well as the potential applicable scores to be considered in order to predict clinical outcomes and benefits from brain radiotherapy in patients with NSCLC and brain metastases.

Keywords: brain metastases; NSCLC; predictive biomarkers for radiotherapy; radiotherapy; prognostic scores; WBRT; BRAF mutation

1. Introduction

Non-small-cell lung cancer (NSCLC) is the second most common cancer worldwide, resulting in 2 million diagnoses and 1.8 million deaths per year [1,2]. The most important risk factor for NSCLC is cigarette smoke because of its carcinogenic chemicals [3]. This risk increases to the number of cigarettes smoked per day as well as per years spent in smoking; other well-known risk factors are asbestos, radon and silica exposure [3]. There are different histologic subtypes of NSCLC including squamous cell carcinoma, adenocarcinoma, adeno-squamous carcinoma, large-cell carcinoma and NSCLC not otherwise specified (NOS) [4]. Types of NSCLC are also classified in oncogene or non-oncogene addicted based on the presence/absence of specific tumor alterations [5,6]. The former includes tumors carrying KRAS (20-30%), EGFR (10-15%), ALK (3-7%), BRAF (2-4%), cMET (2-4%), ROS1 (1-2%), RET (1-2%), HER2 (1-2%) and NTRK (0.5-1%) alterations [5,6]. Treatment of NSCLC includes surgery, chemotherapy, targeted therapy, immunotherapy and radiotherapy. Surgery with tumor resection represents the primary treatment for stage I and II NSCLC [3,7,8] while for stage III

disease it is an important component of the multimodality approach in association with radiotherapy and chemotherapy [3,9]. Chemotherapy can include the combination of platinum derivatives (cisplatin or carboplatin) with other cytotoxic agents such as gemcitabine, paclitaxel, pemetrexed, nab-paclitaxel and vinorelbine as well as use of single chemotherapeutic agents both in early and advanced disease [3,10–13]. Targeted therapy with tyrosine kinase inhibitors is only applicable to small subset of patients carrying oncogene alterations. It currently includes KRAS^{G12C} inhibitors (sotorasib and adagrasib [14,15]), EGFR inhibitors (first-generation: erlotinib and gefitinib; second-generation: afatinib and dacomitinib; third-generation: osimertinib) [16–22], ALK inhibitors (first-generation: crizotinib; second-generation: alectinib, brigatinib, ceritinib, and ensartinib; third-generation: lorlatinib) [23–28], BRAF inhibitors (dabrafenib) [29], cMET inhibitors (capmatinib and tepotinib) [30,31], ROS1 inhibitors (first-generation: crizotinib; second-generation: entrectinib) [32,33], RET inhibitors (pralsetinib and selpercatinib) [34,35], HER 2 targeting agents (trastuzumab deruxtecan) [36] and NTRK inhibitors (entrectinib and larotrectinib) [37,38]. Immunotherapy with immune checkpoint inhibitors (ICIs) such as anti-programmed cell death-1 (PD-1) (cemiplimab, nivolumab and pembrolizumab) [39–46], anti-programmed death-ligand 1 (PD-L1) (atezolizumab and durvalumab) [47–49] and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) (ipilimumab) [42] is revolutionizing the treatment landscape of non-oncogene addicted NSCLC, being utilized as a single agent or in combination with chemotherapy in both early and advanced stage of the disease [39–53]. Lastly, radiotherapy is currently used either with a radical intent, in combination with chemotherapy for treatment of primary tumors, or as a single agent with palliative intent, for treatment of bone or brain metastases [3,9,54–58]. The latter represent a major site of the metastatic disease [59–61] and are consequence of a complex process that includes induction of angiogenesis, malignant cell blood dissemination, extravasation, proliferation and survival [62]. Brain radiotherapy is administrated either as stereotactic ablative radiotherapy (SBRT) or as whole brain radiotherapy (WBRT), based on patient and tumor characteristics [56,58,63–66]. SBRT delivers a high dose to limited size targets, representing a reasonable strategy for patients not candidate to surgery in presence of 1 to 4 brain metastases < 3 cm. On the other hand, WBRT is the best choice in case of multiple and large brain metastases [56,58,63–66]. In both cases, radiotherapy is utilized both to relieve neurological symptoms and to inhibit tumor progression but its limited efficacy and derived neurotoxicity can lead to select best supportive care as a valid alternative option [58,67–69]. As a result, there is the need to define potential biomarkers which can help to identify patients who can really benefit from brain radiotherapy, avoiding useless treatments. So far, some scoring systems have been proposed [70–72]. Here, by presenting the clinical outcomes obtained from WBRT in a patient with brain metastases from an advanced NSCLC carrying a BRAF^{V600E} mutation, we analysed the potential variables as well as the available scoring systems useful to predict clinical outcomes and benefits from brain radiotherapy in patients with NSCLC and brain metastases.

2. Case Presentation

In January 2023, a 62-year-old Caucasian male, no smoker, went to first aid of University Hospital "San Giovanni di Dio e Ruggi d'Aragona" because of dyspnea, visual impairments and dizziness. His neurological syndrome got worse in a few hours. Radiological evaluation with CT scan demonstrated presence of multiple brain metastases localized in the left frontal, right frontoparietal and occipital lobes as well as in the right cerebellar hemisphere. Massive edema, compression of cerebellum, right lateral ventricle and subfalcine herniation were also described (Figure 1a,b). Other tumor localizations included presence of a large mass in the right-upper lung lobe and multiple lymph nodal, liver (10mm) and spleen (30 mm) metastases (Figure 1c,d).

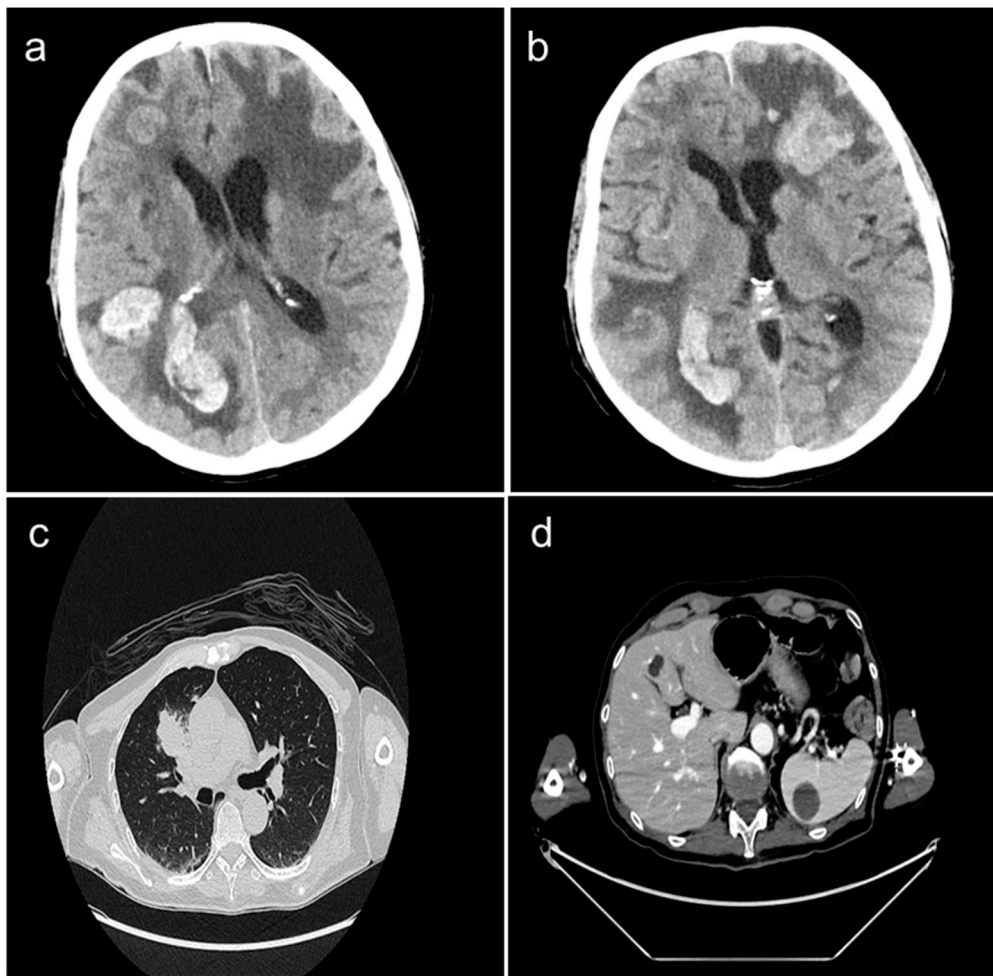


Figure 1. Whole body CT-scan performed at diagnosis in January 2023 showing the presence of multiple brain metastases localized in the right frontoparietal, occipital (panel a) and left frontal lobes (panel b). Large mass in the right-upper lung lobe (panel c), liver metastasis (10mm) and spleen metastasis (30 mm) (panel d) are also presented. .

Basal tumoral markers were in normal range, except neuron-specific enolase (NSE) (14.9 ng/ml). Baseline ECG showed sinus rhythm at 82 bpm and a QTc of 425 ms. Blood pressure was 125/80 mmHg and SpO₂ was 98%. According to brain metastasis localization, the patient had pyramidal syndrome, numbness, ocular ptosis, spastic paraplegia and aphasia, neurocognitive decline and loss of self-care. Analysis of biohumoral parameters demonstrated a significant increase of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), iron, ferritin, bilirubin (especially non-direct index), blood urea and glycemic levels while those of albumin, transferrin, sodium, potassium and calcium were reduced. Blood count was normal. Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 3. Karnofsky performance status (KPS) was 40%. Supportive care was immediately started with administration of dexamethasone 8 mg every 8 hours, mannitol 18% every 6 hours and levetiracetam 500 mg bid. Following 4 days of treatment support, the patient gained a little benefit in neurological symptomatology and a percutaneous CT-assisted lung biopsy was performed. Following 7 days, tumor histopathological analysis confirmed the diagnosis of lung adenocarcinoma with PD-L1 tumor proportion score (TPS) between 1 and 49%. Based on better neurological symptoms and clinical conditions WBRT was immediately started (30 Gy in 10 fractions). During the following 7 days from the end of radiotherapy, molecular analysis of tumor biopsy demonstrated the presence of BRAF^{V600E} mutation. Based on this result, the patient was candidate to BRAF and MEK inhibitor combination with dabrafenib and trametinib. However, at same time, neurological symptoms got worse with development of pyramidal syndrome, ocular ptosis, spastic paraplegia, aphasia, neurocognitive decline and inability to swallow. As a result,

dabrafenib and trametinib were not started. Comparison of biohumoral parameters with those of pre-radiotherapy treatment demonstrated a decrease in hemoglobin (HGB) levels, red blood cell (RBC) and platelet (PLT) count (11.4 g/dl vs 14.1 g/dl for HGB; $7.42 \times 10^6/\mu\text{l}$ vs $6.02 \times 10^6/\mu\text{l}$ for RBC and $282 \times 10^3/\mu\text{l}$ vs $161 \times 10^3/\mu\text{l}$ for PLT), while white blood cell (WBC), neutrophil (NEU) count and NEU-to-lymphocyte ratio (NLR) were increased ($25.3 \times 10^3/\mu\text{l}$ vs $17.14 \times 10^3/\mu\text{l}$ for WBC, $24.14 \times 10^3/\mu\text{l}$ vs $16.02 \times 10^3/\mu\text{l}$ for NEU and 34 vs 54 for NLR). Cardiac evaluation showed a progressive elevation of heart rate (maximum value of 179 bpm), atrial flutter development and alterations in ST trait. Tumoral markers were higher than basal (Ca 125 was 49.9 U/ml vs 26.6 U/ml and Ca 19.9 was 36.6 U/ml vs 19 U/ml). Unfortunately, following 6 days, despite of specific cardiologic treatment, clinical conditions got worse, and patient died.

3. Discussion

SBRT and WBRT play a major role in the treatment of brain metastases. WBRT represents the best choice of treatment in case of multiple and large brain metastases, regardless of tumor type. In NSCLC, WBRT has been shown to improve both neurological symptoms and disease control [60,63,73]. Nevertheless, WBRT is also associated to temporary or persistent toxicity [58,64,74]. The former includes alopecia, dermatitis, fatigue, otitis, nausea and alterations in both memory and executive functions [63,64,75]. Persistent toxicity includes impaired physiological function of hippocampus, ataxia, insomnia, dysphasia and dementia [64,74,76–79]. WBRT toxicity can be reduced by exclusion of selective brain areas such as the hippocampus, leading to an improvement of neurocognitive function, functional autonomy and quality of life [64,75,80]. In the case we have described, WBRT included the hippocampus area, severe toxicities were reported, and no clinical benefit was achieved. Brain metastases were derived from a NSCLC carrying a BRAF^{V600E} mutation. In this type of tumor, administration of BRAF and MEK inhibitors has demonstrated to improve both overall survival and response rate, even in presence of brain metastases [29]. However, to the best of our knowledge, no clinical study has evaluated the intracranial efficacy of BRAF and MEK inhibitor combination in BRAF^{V600E} NSCLC patients with multiple symptomatic brain metastases. In contrast, several preclinical and clinical studies have been investigating the combination of BRAF inhibitor and radiotherapy as well as of BRAF and MEK inhibitors in melanoma patients carrying similar alterations in BRAF, even in presence of multiple brain metastases. [81–86]. It has been shown that aberrant activation of RAS/BRAF pathway in melanoma cells increases the resistance to radiations while its inhibition restores the radio-sensitization of cancer cells [84,87,88]. In addition, Sambade et al. have demonstrated a synergistic effect of BRAF inhibitor and radiation in melanoma cell death through an increase in G1 arrest of cancer cells, laying the basis for combinatorial therapeutic approach [89]. Unfortunately, even in melanoma patients, the combination of BRAF inhibitor and radiation has been limited by a significantly increase of severe toxicities [90–98]. As a result, BRAF inhibitors are administered before or later WBRT. On the other hand, several lines of evidence have demonstrated a relevant clinical benefit obtained by BRAF and MEK inhibitors in melanoma patients carrying BRAF^{V600E} [82,99,100]. In this setting, BRAF and MEK inhibitor combination induces 68% of intracranial disease control rate (stable disease, partial response and complete response of 37%, 26% and 5%, respectively) [101]. Further studies are needed to validate the efficacy of the combination of BRAF and MEK inhibitors in NSCLC patients carrying BRAF^{V600E} mutation with brain metastases.

Besides BRAF and MEK inhibitors, in our case, the combination of chemotherapy and anti-PD-1-based immunotherapy could represent an alternative therapeutic approach. In the definition of the best therapeutic algorithm, one should take into account that besides oncogene alterations PD-L1 tumor expression plays a major role for treatment choice in advanced NSCLC patients [42,45,46]. As a result, in the patient we have described, according to PD-L1 tumor expression, platinum-based chemotherapy and anti-PD-based immunotherapy could represent an alternative therapeutic option. This therapeutic approach has clearly demonstrated to improve both response rate and survival outcomes of treated patients as compared to standard platinum-based chemotherapy [45,46]. However, so far, no study has compared which is the most effective therapeutic approach in NSCLC patients and no study testing sequential strategies such as BRAF and MEK inhibitor combination as

compared to the combination of immunotherapy and chemotherapy in NSCLC patients carrying BRAF^{V600E} is available. In BRAF^{V600E} melanoma patients, two recent clinical studies have shown that presence of BRAF^{V600E} mutation may influence the best therapeutic sequence in advanced melanoma. Specifically, a major benefit is achieved from an up-front immunotherapy as compared to up-front BRAF and MEK inhibitor combination [102,103]. In the clinical case we have described administration of chemotherapy and anti-PD-1-based immunotherapy was limited by i) availability of clinical data in the setting of patients carrying BRAF^{V600E} with symptomatic brain metastases; ii) detrimental effect of high dose steroids on the efficacy of anti-PD-1 therapy; iii) the clinical conditions of the patient (PS ECOG 3, KPS 3); and iv) Italian guideline indications that limits administration of platinum-based chemotherapy and anti-PD-1 therapy following failure to prior BRAF and MEK inhibitor combination. One could expect that based on the faster activity the combination of BRAF and MEK inhibitors should represent the best therapeutic option in this specific subgroup of patients. Further prospective studies are needed to clarify this specific aspect.

In our case, we did not promptly start BRAF and MEK inhibitor combination since tumor oncogene analysis was still pending. We promptly started WBRT just following histological tumor analysis because of neurological symptoms. As a result, we were unable to assess the potential tumor brain response and clinical benefit deriving from sequential strategies of targeting agents and radiotherapy. In any case, WBRT alone did not provide any clinical benefit, severe toxicities were developed and BRAF and MEK inhibitors were not then administrated. Based on the obtained results, one might suppose that best supportive care could be a valid alternative option to WBRT. So far, some score systems have been proposed to predict clinical outcomes from WBRT in patients with brain metastases. They include the Radiation Therapy Oncology Group–Recursive Partitioning Analysis (RTOG-RPA) and the WBRT-30-NSCLC scores [71,104]. The RTOG-RPA score is a statistical methodology which creates a regression tree according to prognostic significance. For its validation, both pre-treatment and treatment-related variables were analyzed [104] (Table 1).

Table 1. List of pre-treatment and treatment-related variables analyzed for the identification of RTOG-RPA scoring system.

Variable	Description
Brain metastases	Alone
	With other brain metastases
Primary lesion	Controlled
	Uncontrolled
Primary lesion site	Lung
	Breast
	Other
Histology	Squamous
	Adenocarcinoma
	Large cell
	Small cell
	Melanoma
	NSC
Prior brain surgery	Other
	None
Time interval from diagnosis of primary to brain metastases	Yes
	≤ 2 years
	> 2 years
Headache	Absent
	Present

Seizure	Absent Present
Visual disturbance	Absent Present
Neurologic function	None Minor Moderate Major
Midline shift	No Yes
Mass effect	No Yes
Location of lesions	Frontal Temporal Parietal Occipital Basal ganglia/thalamus Cerebellum Brainstem
Sentinel location of lesions	Frontal Temporal Parietal Occipital Basal ganglia/thalamus Cerebellum Brainstem
Sentinel lesion side	Left Right Midline
Necrotic center	No Yes
Number of lesions	Single Multiple
Tumor response	Complete Partial Stable Progression
KPS	30-40 50-60 70-80 90-100
Area (mm ²)	0-400 401-900 901-1600 > 1601

	< 40
	40-44
	45-49
Age (years)	50-54
	55-59
	60-64
	65-69
	> 70
	2400-3499
	3500-4000
Total dose (cGy)	4001-5279
	5280-6079
	6080-6719
	6720-9000

Abbreviations: cGy: centigray; KPS: Karnofsky performance status and NSC: non-small-cell.

Among all the prognostic variables identified (Table 2), three RPA classes were defined.

Table 2. Univariate analysis of pre-treatment and treatment-related variables tested for the identification of RTOG-RPA scoring system.

Variable	Comparison	p-Value
Brain metastases	alone vs with other metastases	< 0.0001
KPS	≥ 70 vs < 70	< 0.0001
Age (years)	< 65 vs ≥ 65	< 0.0001
Prior surgery	no vs yes	0.005
Histology	squamous vs small cell vs others	< 0.0001
Primary lesion	controlled vs uncontrolled	< 0.0001
Primary site	breast vs lung and others	0.001
Time interval	< 2 years vs > 2 years	0.004
Number of lesions	single vs multiple	0.021
Sentinel lesion side	left and/or right vs midline	0.038
Sentinel location	frontal, temporal, parietal, occipital and basal ganglia/thalamus vs cerebellum and brainstem	0.033
Neurologic function	no vs yes	< 0.0001
Headache	no vs yes	0.003
Total dose (cGy)	≥ 5200 vs < 5200	< 0.0001
Tumor response	complete or partial vs stable or progressive	0.019

Abbreviations: cGy: centigray and KPS: Karnofsky performance status.

In the first class were included patients who had KPS ≥ 70 , age < 65 years and no extracranial disease. In the second were included patients with a KPS ≥ 70 and at least one unfavorable prognostic factor. The last group included patients with a KPS < 70. According to this score, an increased survival from WBRT for brain metastases was obtained only patients in first class [104]. In contrast no benefit was achieved in patients with a KPS ≤ 70 and higher tumor burden.

The second score system, the WBRT-30-NSCLC score was developed for patients with intracerebral metastases from NSCLC. Eight factors were investigated in NSCLC patients receiving WBRT including age, gender, KPS, interval from diagnosis of NSCLC to WBRT, pre-WBRT systemic treatment, primary tumor control, number of intracerebral metastases, and metastasis outside the brain (Table 3) [71]. Among the variables analyzed, age, KPS, systemic treatment and metastasis outside the brain were found to correlate with 6-month patient survival.

Table 3. List of variables analyzed for the identification of WBRT-30-NSCLC scoring system.

Variable	Description
Age (years)	≤ 62
	≥ 63
Gender	Male
	Female
KPS	< 70
	70
	> 70
Interval from diagnosis of NSCLC to WBRT	≤ 1 months
	≥ 2 months
Pre-WBRT systemic treatment	No
	Yes
Control of the primary tumor	No
	Yes
Number of intracerebral metastases	1-3
	≥ 4
Metastasis outside the brain	No
	Yes

Abbreviations: KPS: Karnofsky performance status; NSCLC: Non-small-cell lung cancer and WBRT: whole brain radiotherapy.

Then for each identified prognostic variable a score was assigned (Table 4) and 4 groups of patients were identified with 6-month survival rates of 3, 26, 65, and 100% [71].

Table 4. WBRT-30-NSCLC score.

Variable	Factor Score
Age (years)	
≤ 62	4
≥ 63	2
KPS	
< 70	1
70	3
> 70	5
Pre-WBRT systemic treatment	
No	2
Yes	4
Number of intracerebral metastases	
1-3	4
≥ 4	2
Metastasis outside the brain	
No	5
Yes	2

Abbreviations: KPS: Karnofsky performance status and WBRT: whole brain radiotherapy.

Patients with a score of 9–10 points were proposed to be treated with a short-course WBRT because their survival was poor, while NSCLC patients with a score of 17–18 points should receive long-course WBRT, being their survival longer [71]. Whether we compare these scores the WBRT-30-NSCLC score appears to be more accurate for NSCLC as it identifies patients with intracerebral metastases from NSCLC who will die within 6 months or survive longer. However, both scoring systems display some limitations. First, they both do not distinguish between WBRT with hippocampal inclusion from that with hippocampal exclusion. Second, both scores do not consider the biological and molecular features of tumors as well as evaluation of biohumoral parameters of NSCLC patients. Exclusion of hippocampal area from radiotherapy field has a lower impact on neurological declines and preserves memory and concentration. On the other hand, evaluation of biohumoral parameters can help to identify patients with short lifespan. In our case, we did not apply any of the scoring systems available. Analysis of class risk score by both scoring systems shows a poor risk class for both RTOG-RPA and WBRT-30-NSCLC. As a result, although the patient was affected from a BRAF^{V600E} NSCLC with multiple sites of metastasis (brain, spleen, and liver), both scoring systems were efficient in predicting no clinical benefit from WBRT. Currently no scoring systems are available for this type of patient as well as for other types of oncogene addicted tumors. Further studies are needed to grant personalized radiotherapy treatment for this patient population. In our case, besides the clinical features analyzed in both scoring systems, we also detected a progressive heart failure, an elevation of tumoral markers, a lowering of serum hemoglobin levels, an increasing of platelet count and a worsening of liver and renal function. These parameters should also be considered since they may help to identify an imminent exitus of the patient and therefore no benefit from WBRT. Among these parameters, NLR might be one of the best candidates as prognostic and/or predictive factor. Indeed, two studies have already demonstrated that high values of both pre-treatment and post-treatment NLR predict for poor survival in NSCLC patients brain metastases treated with SBRT or WBRT [105,106]. In our patient both pre-treatment and post-treatment NLRs were extremely high and correlated with poor prognosis and with no benefits from WBRT. However, to validate the prognostic/predictive role of these parameters including NLR, further studies in the specific subset of NSCLC patients with brain metastases carrying BRAF^{V600E} mutation treated with WBRT are needed. Lastly, beyond the value of the specific parameters, our case report seems to suggest that a rapid worsening of these parameters may be the best factor to predict which patients have the worst prognosis. In these conditions as well as for poor risk classes from RTOG-RPA and WBRT-30-NSCLC scores, best supportive care should lead to select best supportive care as a valid alternative option in order to avoid a useless treatment.

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