Review Article on Radiotherapy for Brain Metastases from Lung Cancer

# WBRT for brain metastases from non-small cell lung cancer: for whom and when?—Contemporary point of view

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**Abstract:** The incidence of brain metastases (BM) is estimated between 20% and 40% of patients with solid cancer. The most common cause of this failure is lung cancer, and in locally advanced non-small cell lung cancer (NSCLC) BM represent a common site of relapse in 30–55% cases. The basic criteria of therapeutic decision-making are based on the significant prognostic factors which are components of prognostic scores. The standard approach to treatment of BM from NSCLC include whole brain radiotherapy (WBRT) which is used as adjuvant modality after local therapy (surgery or stereotactic radiosurgery) or as primary treatment and it remains the primary modality of treatment for patients with multiple metastases. WBRT is also used in combination with systemic therapy. The aim of presented review of literature is trying to answer which patients with BM from NSCLC should receive WBRT and when it could be omitted. There were presented the aspects of application of WBRT in relation to (I) choice between WBRT or the best supportive care and (II) employment of WBRT in combination with local treatment modalities [surgical resection or stereotactic radio-surgery (SRS)] and/or with systemic therapy. According to data from literature we concluded that the most important factor that needs to be considered when assessing the suitability of a patient for WBRT is the patient's prognosis based on the Lung-molGPA score. WBRT should be applied in treatment of multiple BM from lung cancer in patients with favourable prognosis and in in patients with presence of *EML4-ALK* translocation before therapy with crizotinib. Whereas WBRT could be omitted in patients with poor prognosis and after primary SRS.

**Keywords:** Whole brain radiotherapy (WBRT); brain metastases (BM); prognostic scores; non-small cell lung cancer (NSCLC)

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Brain metastases (BM) are the most common intracranial tumours in adults, representing over 50% of all lesions. Metastasizing into brain is a devastating failure associated with high morbidity and mortality. The incidence of BM is estimated between 20% and 40% of patients with solid cancer.

The steady increase in the incidence of BM is a consequence of technological progress in the treatment and diagnosis of tumours. On the one hand, this has resulted in more effective treatment, which has translated into longer survival. On the other, the application of advanced technology in image diagnostics has made early diagnosis of BM possible, including in clinically asymptomatic cases (1-5).

The most common cause of BM is lung cancer, which accounts more than 50% of all BM (6,7). BM developed in 22% of patients with non-small cell lung cancer

(NSCLC) at the time of initial diagnosis and they occur in approximately 40% of patients during disease (4,5,8-15). Whereas in locally advanced NSCLC after multimodality therapy BM represent a common site of relapse in 30–55% cases (9-11).

## Prognostic scores

The development of BM is an indicator of poor prognosis and predicts a short survival; median survival estimates from 4 to 7 months and it depends on patient factors (16-18). Otherwise, the presence of BM is the main factor in determining patient management; and the choice of treatment method depends on the number and size of BM and the presence of primary or metastatic extracranial tumor involvement (18-20).

The assessment of prognosis can help to identify which groups of patients might benefit from treatment and there are some scoring systems to predict outcomes for BM patients and in the most of popular using scores the age is the significant prognostic factor for survival (17,18,21-26).

An analysis of the results of clinical trials has provided the basis for a number of prognostic systems. The most commonly applied are the RPA classification (RPA-recursive partitioning analysis) and GPA (graded prognostic assessment) index, the classes or points of which, respectively, are associated with overall survival (OS) rate (27-29).

The RPA classification devised by Gaspar *et al.* in 1997 on the basis of 1,200 patients from three consecutive RTOG trials was the first scoring system developed for patients with BM who had received WBRT (23). This classification was developed to stratify patients in clinical trials and take treatment decision. This classification was validated for both NSCLC and SCLC and is based on the patient's age at the time of BM diagnosis, Karnofsky performance status (KPS), the status of the primary tumour, and the presence of extracranial disease. It divided patients with BM into three prognostic classes: RPA class 1 (age <65 years, KPS ≥70, primary tumour under control, no extracranial metastases), RPA class 3 (KPS <70), and RPA class 2, which covered all other patients. These classes corelate with median survival which is: 7.1 months in RPA class1, 4.2 months for RPA class2 and 2.3 months for RPA class3 (22-24).

In 2008, Sperduto *et al.* proposed a GPA index which based on comparison of other scores (RPA, Basic Score of Metastatic, Score Index for Radiosurgery) for 1960 patients from five randomized RTOG studies. The GPA index takes into account the following parameters—prognostic factors which include: age, KPS, number of BM and the presence of extracranial metastases. Each of these parameters scores with 0, 0.5 or 1.0 value. The patients with GPA 4.0 would have the best prognosis, whereas GPA 0.0 indicates the worst prognosis. The GPA performed stratifying patients into four prognostic groups: 0–1.0, 1.5–2.5, 3.0 and 3.5–4.0 (30). Henceforth, this index was validated using a specific diagnosis at the primary site and created disease-specific (DS-GPA) scores (17,18,30-34). These indexes were designed, similar to the original GPA. This score for patients with NSCLC and BM the value of 0.0 scoring criteria: age >60, KPS <70, the presence of extracranial metastases and >3 BM in DS-GPA, the value of 1.0 is assigned for age <50 years, KPS 90–100, absent of extracranial metastases and BM 1. The median survival in NSCLC and BM patients stratified by DS-GPA score was as following: of 3.02, 6.53, 11.33 and 14.78 months for DS-GPA score 0–1.0, 1.5–2.5, 3 and 3.5–4, respectively (30).

The clinical observations showed that patients with *EGFR* and *ALK* alterations had a markedly improved survival in comparison to those without these alterations. Therefore in 2017 the DS-GPA for patients with NSCLC and BM was updated by incorporating two new factors *EGFR* and *ALK* alterations into to original DS-GPA score and this new index is called the Lung-molGPA (35). The factors which had larger effect sizes were given a maximum score of 1.0 (higher scores corresponding to better prognosis) and they included KPS from 90 to 100 (*vs.* KPS ≤70), no extracranial metastases, and *EGFR* or *ALK* positivity (*vs. EGFR* and *ALK* negativity or unknown). The remaining 2 factors, age and number of BM, had smaller effect sizes and were given a maximum score of 0.5. Therefore, the same variable weighting used for the both nonadenocarcinoma and adenocarcinoma groups, although nonadenocarcinoma had a maximum score 3.0 (because patients could not receive point for gene alterations). The median survival of 5.3, 9.8 and 12.8 months for 0.0–1.0, 1.5–2.5 and 3 Lung-molGPA, respectively in patients with nonadenocarcinoma and 6.9, 13.7, 26.8 and 46.8 months for 0.0–1.0, 1.5–2.5, 3 and 3.5–4.0 Lung-molGPA, respectively in patients with adenocarcinoma (35).

The above prognostic scales have become the basic criteria employed in therapeutic decision-making. And thus, patients with a good prognosis are deemed eligible for local treatment, while the existence of numerous BM (disqualifying the patient from local treatment) are indications for WBRT. The prognosis should also be taken

 

into account in this case because there are some patients who will not benefit from WBRT when compared with best supportive care (16).

## Whole brain radiotherapy (WBRT)

The treatment options for BM in the past included surgical resection and/or WBRT (36-38). Surgery is of value for relieving the mass effect in symptomatic BM, as well as in case of single BM amenable to radical surgery in patients with controlled extracranial disease and good performance status. Surgery results in a high rate of relief symptoms in 60–90% of patients and improving the local control (39,40). The WBRT is used as adjuvant modality after surgery or as primary treatment to improve local control (41,42).

WBRT has been the standard approach to treatment of BM from NSCLC and it remains the primary modality of treatment for patients with multiple metastases. It leads to an improvement in symptoms with an overall response of 70–93% and provides in 60–80% cases local and distant brain control (43-48).

It should be noted that the prognostic scale/index rating is taken to account as a factor when first assessing a patient's eligibility for such treatment. Usually, the total dose administered is 30 Gy in 10 fractions, which results in a 59% radiographic response, including complete response rate of 24% (7,26,48).

Results of randomized trials assessing efficacy of other dose fractionation schedules and systematic reviews demonstrated that there is no advantage to modifying WBRT from either 30 Gy in 10 fractions or 20 Gy in 5 fractions and these schedules are considered standard of care (43). The results of the Cochran Library meta-analysis published in 2018 showed that a biological WBRT dose higher than the standard treatment does not ensure any greater benefits in terms of OS, improved neurological function or symptom control. On the other hand, the use of biological WBRT doses lower than the standard dosage of 30 Gy in 10 fractions yields poorer OS results and does not improve neurological function (49).

The rationale for WBRT is to destroying microscopic disease at original BM or at distant brain location, and this justifies necessity of WBRT application after locally therapies as surgical excision or stereotactic radio-surgery (SRS). The application of WBRT provides to improving local control but without benefit for survival, and moreover it accompanies by high risk of neurocognitive complications (42,50-52).

Recent published results of trials questioned the relevance of WBRT when radiosurgery or stereotactic radiotherapy is being used with increasing frequency and when targeted molecular compounds and immunotherapies have become available (7,27,28,32,53-59). Presently, the standard treatment for patients with BM consists of WBRT and/or SRS and/or surgery excision (7,15,16,26,38,47,60-67). The choice of therapeutic method is based on number of BM and performance status. Moreover, these factors are components of prognostic scale, especially in GPA index (DS-GPA) and Lung-mol GPA which are dedicated for lung cancer patients (17,18,35).

The aim of presented review is trying to answer who should receive WBRT and when it could be omitted in patients with BM from NSCLC. The aspects related to application of WBRT concern on (I) choice between WBRT or the best supportive care and (II) role of WBRT as in combination with local treatment modalities (surgical resection or SRS) and (III) employment of WBRT in combination with systemic therapy.

## WBRT *vs.* best supportive care

WBRT is the recommended treatment for patients with a good performance status if SRS is not suitable for BM, whereas WBRT should not be recommended for patients with a poor prognosis, a fact which has been confirmed by the results of clinical trials.

In the case of patients with a poor performance status or uncontrolled extracranial disease the therapeutic strategy also involves supportive care. Mulvena *et al.* published the results of the QUARTZ (Quality of Life after Treatment of Brain Metastases) trial, a phase III non-inferiority randomized trial, which try to answer whether WBRT improves survival in patients with BM from NSCLC (unsuitable for resection or stereotactic radiotherapy) in relation to prognosis (68). The authors compared optimal supportive care (OSC) and OSC plus WBRT (20 Gy given in 5 fractions). It was showed that (I) that WBRT did not improve OS (a median survival of 9.2 weeks for OSC plus WBRT *vs.* 8.5 weeks for OSC) and (II) unchanged QALY (Quality Adjusted Life Years)—the QALY difference in days between the two groups was only 4.7 (46.4 QALY days for OSC plus WBRT *vs.* 41.6 QALY days for OSC). These observations indicate that adding WBRT to OSC does not yield any advantages in terms of survival, quality of life or reduced steroid use. It is important to note that the patients who participated in the QUARTZ study had a poor

prognosis (37% of the patients who received WBRT were RPA class 3 and 42% had a GPA of 0–1 points). On the one hand, this suggests that they were not optimal candidates for WBRT, but on the other it may be a more accurate reflection of a typical clinical situation. Further analysis showed improved survival with WBRT in a subgroup of patients younger than 60 years, KPS ≥70, and a controlled primary tumour. However, no benefits from using WBRT were observed in patients with a poor prognosis (68). These observations confirm the importance of assessing a patient's prognosis at the time of evaluating his or her eligibility for treatment. It should be pointed out that the factors used to select patients are at the same time components of the GPA and RPA prognostic scales.

The usefulness of applying prognostic scales for patients with BM resulting from lung cancer is confirmed by the results of a study published in 2017 by Tsakonas *et al.* which purpose was to identify prognostic factors affecting survival in BM lung cancer patients treated with WBRT (29). A total of 280 patients with lung cancer were recruited to the study and divided into RPA classes and GPA groups according to age, KPS, control status of the primary tumour, the number of BM and the presence of extracranial metastases. Similarity to the QUARTZ study, majority of the patients had a poor prognosis (36.2% RPA class 3 and 60% GPA 0–1 points), and 76% had multiple BM. The study results indicate that (I) WBRT should be applied (if clinically indicated) in RPA class 1 patients and in RPA class 2 patients aged ≤70 years and with a GPA of ≥1.5 points, (II) WBRT should be not be applied in RPA class 3 patients and in RPA class 2 patients aged >70 years, (III) WBRT might be a reasonable option for RPA class 2 patients aged ≤70 years and with a GPA of <1.5 points.

The results of the Cochrane Library meta-analysis published in 2018 indicated that the use of OSC while omitting WBRT in NSCLC patients with multiple BM does not affect survival (49).

Summarizing, patients with poor prognosis are not optimal candidates for application of WBRT, while WBRT should be applied in patients with good prognosis, especially in a subgroup of patients younger than 60 years, KPS ≥70, and a controlled primary tumour.

## WBRT in combination with local therapy

The local therapy of BM includes surgical resection and SRS. Surgery is the oldest treatment method used in BM and it is still used in select patients with BM. Whereas SRS is highly conformal technique of radiotherapy as a result of improvement in technology and it has allowed more focused and higher dose delivery into tumour. SRS reduces dose received by surrounding brain tissue and therefore it causes fever side effects than WBRT.

## WBRT as adjuvant after local therapy

WBRT used in conjunction with neurosurgery or SRS for patients with single BM improves intracranial responses while having no positive effect on survival (45-47,52,64). Whereas omitting WBRT has negative impact of BM progression on neurologic and neurocognitive functions and these arguments favoured WBRT (50).

Soon *et al.* in the Cochrane Library analysis of surgery or SRS plus WBRT versus surgery or SRS alone which results confirmed that WBRT decreased relative risk of any intracranial progression at 1 year by 53% but there was no evidence in OS (69). Moreover, WBRT impact on neurocognitive function and has high risk of neurological adverse events (47,52,69).

### *WBRT after surgery*

Patchell *et al.* evaluated the role of WBRT given after surgical resection of BM (36). Their study was performed on a group of patients diagnosed with solitary brain lesions, who were randomized into two groups: surgical resection combined with WBRT *vs.* WBRT alone (the WBRT dose was 36 Gy in 12 fractions). The authors showed that surgical resection of BM combined with WBRT compared to WBRT alone provides better results in terms of local failures (crude 20% *vs.* 50%), median survival (40 *vs.* 15 weeks), time until neurological death (62 *vs.* 26 weeks) and the length of time a patient remains functionally independent (38 *vs.* 8 weeks). It is important to note that these results concerned patients with a single BM and were published in 1990 and thus before the SRS era, and indicate the prognostic role of local treatment, in this case surgery, performed before WBRT.

By way of contrast, the role of WBRT after postoperative treatment was assessed in a study in which patients (95 patients from which 60 with lung cancer) with a single BM were randomized into two groups: postoperative WBRT (50.4 Gy in 28 fractions) *vs.* observation (64). The authors reported that WBRT applied after surgical resection provided better treatment results than surgical resection alone in the case of the following parameters: local brain

 

recurrence at the original site (10% *vs.* 46%), distant brain recurrence (14% *vs.* 37%), frequency of neurologic death (14% *vs.* 44%), and time to failure (>57 *vs.* 27 weeks). On the other hand, it has no effect on either survival (median 48 *vs.* 43 weeks) or functional independence. This study was also conducted on patients with single BM and confirmed the positive effect of applying WBRT primarily with the aim of reducing overall brain failure (18% *vs.* 70%). However, it did not affect OS.

The comparison effectiveness of WBRT and SRS applied postoperatively was evaluated in multi-institutional randomised, phase 3 trial (NCCTG N107C/CEC 3) with 194 patients with 1–4 BM (one of them should be resected), from which 77% had single BM, and in 59% primary site was lung cancer (70). There was no survival differences between two analysed groups (SRS *vs.* WBRT) in survival (median survival: 12.2 *vs.* 11.6 months, respectively, P=0.70). Whereas in WBRT group higher cognitive deterioration was observed (85% *vs.* 52% after SRS, P=0.0003). Moreover, WBRT did provide higher overall intracranial tumour control (at 6 and 12 months: 90% and 78.6% after WBRT *vs.* 74% and 54.7% after SRS; P<0.0001). Whereas Lamba *et al.* in their review of literature confirmed no differences between WBRT and SRS given after surgical excision not only in survival abut also in local brain control. Additionally, authors noted that SRS was associated with lower risk of neurologic complications but in this group was higher risk of radiation necrosis (42).

### *WBRT after SRS*

SRS is common therapeutic modality used in patients with good prognosis and limited (i.e., small and well defined) BM. According to consecutive observations of Yamamoto *et al.* SRS alone as initial treatment in patients with 5–10 BM and ≥10 BM (with summary volume not greater than 15 mL) did not seem to fare worse than those respectively with 2–4 BM and 2–9 BM in OS, intracranial tumor control, neurologic deterioration, neurotoxicity or necessity of salvage therapy (71,72).

Whereas Mizuno *et al.* conducted study of comparison of efficacy of SRS and WBRT in patients with 10–20 BM from NSCLC (73). They noted there was not significant differences in survival (7.3 months in SRS group and 7.2 months in WBRT group) and in neurological survival (14.5 *vs.* 12.9 months. Whereas time to intracranial progression was significantly shorter in the SRS group than in WBRT group (7.1 *vs.* 19.1 months, P=0.009). Author concluded that SRS may be a useful as alternative treatment for 10–20 BM from NSCLC, but these results should be confirmed in prospective trials which evaluate neurocognitive functions and complications.

By way of contrast, the role of WBRT as an adjuvant following SRS was assessed in the following randomized studies: a retrospective review of a multi-institutional study (Snned *et al.*, 1999), and in phase III randomized clinical trials: JROSG 99-1(Aoyama *et al.*, 2006), NCT00548756 (Chang *et al.*, 2009), EORTC 22952-26001 (Kocher *et al.*, 2011), NCCTG N0574 (Brown *et al.* 2016) (45-47,52,74). Patients with BM from lung cancer constituted 52–72% of all included patients. Authors of above trials observed that SRS alone was associated with high rates of brain failures (50–76% *vs.* 15–47% after WBRT addition). Although benefit of WBRT for local control these results did not translate into an improvement of OS, moreover in two studies showed trend toward inferior survival in WBRT group was shown (47,52).

The addition of WBRT to SRS reduces the rate of distant brain recurrence by approximately half while local control is improved by an absolute value of approximately 15–30%. This improvement in local control without an associated survival benefit has been attributed to the efficacy of salvage therapy (47).

WBRT given after local therapy reduces both local and distant brain recurrences and in this way, WBRT is favourable for local control. However as showed Chang *et al.* and Brown *et al.* WBRT added to SRS was responsible for worsening of neurocognitive function (47,52).

Brown *et al.* performed randomized trial in 213 patients (from which 68% with lung cancer) with 1–3 BM, who were randomized into SRS plus WBRT *vs.* SRS alone (47). Authors noted less cognitive deterioration in SRS whereas intracranial tumor control was increased in addition of WBRT (85% *vs.* 50% at 12 months).

The largest prospective randomized study (performed by Kocher *et al.*, 2011) assessing the effect of WBRT after local treatment (surgical resection or SRS) of 1-3 BM was the EORTC 22952-26001 study (46). Following local treatment, the patients were randomized into two groups: WBRT (30 Gy in 10 fractions) *vs.* observation. The study results indicated the positive impact of WBRT on the reduction of the following parameters: 2-year brain failure (27% *vs.* 59%), neurologic death (28% *vs.* 44%) and local failure (23% *vs.* 42% in a surgery group and 33% *vs.* 48% in an SRS group). However, no differences of survival and the preservation of performance status was observed.

 

The results of the Cochrane Library meta-analysis confirmed that the application of WBRT after SRS improves local and distant brain control, but it does not affect survival (49). On the other hand, such a procedure is negatively associated with a poorer neurocognitive outcome.

The fact that WBRT following SRS has been shown to have no benefits in terms of survival and failure rates calls into question the very legitimacy of this approach, especially as it is also associated with an increased risk of neurocognitive complications. The adverse effect of WBRT on cognitive function has been confirmed by the results of a randomized multi-institutional study NCCTG N0574 conducted on a group of 194 patients with 1–3 BM, most of whom had a single BM (77%) and in whom 59% of all BM originated from lung cancer (47). The results indicate that independent SRS results in reduced cognitive decline (at both 3 and 12 months) and better quality of life, without having any impact on local control and OS. The rate of cognitive deterioration at 3 months was in SRS arm compared to SRS and adjuvant WBRT arm 63.5% *vs.* 91.7%.

Results of above trials indicate necessity of defining patients who may benefit from adjuvant WBRT added to SRS. The secondary analysis of trials: JROSG 99-1, EORTC 22952-26001, and NCCTG N0574 were performed to assess the impact of WBRT on survival in relation to prognosis in patients with NSCLC (75-77).

A re-analysis of several studies (75-77) and individual patient data meta-analysis (59,78) of patients with NSCLC produced varying results regarding the effect of WBRT following SRS on the treatment outcome.

Aoyama *et al.* in a re-analysis of the JROSG 99-1 study which investigated the feasibility of SRS alone (because the current trend of using SRS alone) for patients with different prognoses determined by DS-GPA (75). New analysis was conducted on a group of patients with 1–4 BM from NSCLC; they constituted 67% of all initial participants in the study. The results showed that WBRT performed after SRS had a more positive effect on survival than SRS alone in a subgroup of patients with a favourable prognosis (DS-GPA 2.5–4.0), while it had a positive impact on the frequency of brain tumour recurrence in both patients with a favourable prognosis (DS-GPA 2.5–4.0) and those with an unfavourable prognosis (DS-GPA 0.5–2.0). These results suggest improved survival with addition WBRT to SRS among NSCLC patients with favourable diagnostic-specific graded prognostic assessment scores at baseline (median survival of 16.7 *vs.* 10.6 months respectively for SRS and WBRT *vs.* SRS alone). Authors noted that the important role of WBRT for NSCLC patients with a favourable prognosis should be considered, but they pointed out that their findings should be validated in prospective studies.

Whereas results of secondary analysis of EORTC 22952-26001, and NCCTG N0574 demonstrated that there is no significant survival benefit to addition of WBRT after SRS in NSCLC patients with favourable prognosis in GPA index and in patients with limited [1–3] BM undergoing SRS (76,77).

On the other hand, Sahgal *et al.* (78) published the results of an individual patient data meta-analysis of randomized Phase III studies comparing SRS (18–25 Gy) with SRS plus WBRT (30 Gy in 10 fractions). In total, 364 patients with 1–4 BM were included in the analysis, of whom 59% were patients with NSCLC. Most of the patients (59%) were RPA class 2, and 56% had distant metastases. This analysis assessed the impact of applying WBRT after SRS depending on the age of the patients (the cut-off point was 50 years). Authors pointed that for patients ≤50 years of age, SRS alone favoured survival, and the initial omission of WBRT did not impact distant brain relapse rates. They concluded that SRS alone may be preferred treatment for this group.

Summarizing the above, the WBRT could be omitted in patients with favourable prognosis who received primary SRS.

### *WBRT with SRS boost*

The impact on treatment outcomes of an SRS boost after WBRT was shown in a randomized RTOG 9508 study (62). The use of an SRS boost improved local control and increased the likelihood of a stable or improved performance status at 6 months, while improved survival was only observed in patients with a single BM and an RPA class1 prognosis.

The effects of an SRS boost after WBRT have been assessed in randomized trials (62,63,79). A post-WBRT SRS boost results in increased 1-year local control without affecting survival compared to WBRT alone (63).

A RTOG 95-08 study, which only included patients with 1–3 BM and where the largest lesion had a maximum diameter of 4 cm, revealed no significant difference in survival (median survival 6.5 months in the case of WBRT plus a SRS boost and 5.7 months for WBRT alone), although an SRS boost resulted in improved survival in a subset of patients with a single BM (62). In addition, the

 

higher 1-year local control rate observed in patients who received an SRS boost did not translate into a lower death rate from neurologic progression. An originally unplanned analysis of subgroups revealed the positive effects of OS with an SRS boost in patients with NSCLC (median survival: 5.9 months for WBRT plus SRS boost and 3.9 months for WBRT alone).

Sperduto *et al.* re-analysed this study, focusing on a subgroup of patients with lung cancer, who accounted for 84% of all the original participants in the study (79). To assess the application of a SRS boost the patients were restratified by their DS-GPA score. The results revealed the benefits of OS when WBRT is used in combination with SRS boost compared with WBRT alone in patients with DS-GPA 3.5–4.0 points (21 *vs.* 10.3 months, respectively). However, this difference was close to borderline statistical significance, and no benefits were observed in the case of DS-GPA <3.5. The authors stressed that these results should be interpreted with caution, especially as they were obtained from a small sample without random selection.

The Cochrane Library meta-analysis, which assessed the effects of supplementing WBRT with SRS in patients with BM, indicates that this method does not significantly improve survival compared to WBRT alone (80). The WBRT and SRS boost only improved survival in RPA class1 patients as well as patients with a single BM.

## WBRT and systemic therapy

Study with using radiosensitizing agents added to WBRT showed no difference in OS and no improvement in response rate. Radiosensitizing agents should not be used in a standard clinical practice (81-85). The results of study performed in NSCLC patients which compared motexan gadolinium (MGd) used with WBRT and WBRT alone showed a trend toward improved time to neurological progression and time to neurocognitive destroying with use of MGd. These trends were not statistically significant and there was no difference in OS (85).

Combination cytotoxic agents with WBRT evaluated in meta-analysis showed that no improved in OS and in increase of toxicity (48). Topotecan in combination with WBRT for metastatic NSCLC did not improved OS, furthermore adverse events were increased (86).

Patients with subtypes of NSCLC which are molecularly defining included epidermal growth factor receptor (EGFR) mutation [sensitive to therapy with EGFR tyrosine kinase inhibitors (TKI)] may be candidates for combination therapy. Since 2012 when the phase III EURTAC trial with erlotinib showed a survival benefit in EGFR mutation-positive NSCLC patients in comparison to chemotherapy, several trials have suggested an increased survival also in situation of brain metastasis (87,88). Study with erlotinib resulted in response rate of 86% and improving survival with minimal toxicity. Welsh *et al.* in phase II trial reported longer OS compared to historical controls when erlotinib was added to WBRT for patients with EGFR mutations (89). Zhuang *et al.* showed that erlotinib used together with WBRT prolonged OS and PFS with a tolerable toxicity (90). Wu *et al.* in patients with asymptomatic BM from lung cancer with EGFR mutation observed higher intracranial progression-free survival (15.2 *vs.* 4.4 months). But some other authors did not notice in their trials any benefit of combination erlotinib with WBRT, however there were a lot of patients with EGFR wild-type tumors (91-93).

The efficacy of addition temozolamid or erlotinib to WBRT with SRS for NSCLC patients with 1–3 BM was evaluated in RTOG study 0320. Unfortunately results showed no trend toward improved median survival with the addition of either temozolamid or erlotinib (89,93).

Some NSCLC are subtypes with echinoderm microtubule-associated protein-like 4—anaplstic lymphoma kinase—EMK4-ALK translocation (responders to crizotinib). It's known that ALK inhibitors improve PFS as compared to chemotherapy (94). Crizotinib does not pass the blood-brain barrier well and therefore WBRT or SRS possibly should be considered as initial treatment for BM from NSCLC with presence of *EML4-ALK* translocation (95,96). Costa *et al.* in a retrospective analysis demonstrated that time to intracranial progression was longer in group with combination crizotinib/WBRT (95).

There are a lot of ongoing trials of radiation therapy and targeted therapies and we should wait for their results. People have to be very careful because combination of radiation and targeted agents could bring unexpected side effects.

## Conclusions

WBRT should be carefully considered in the case of NSCLC patients with BM, because achieving intracranial disease control may be associated with worse cognitive decline. According to the data from the literature, the most important factor that needs to be considered when assessing the suitability of a patient for WBRT is the patient's prognosis based on the Lung-molGPA score. WBRT

 

should be applied in treatment of multiple BM from lung cancer: in patients with favourable prognosis and in in patients with presence of *EML4-ALK* translocation before therapy with crizotinib. Whereas WBRT could be omitted in patients with poor prognosis and after primary SRS.

This rule applies both when WBRT is used as the sole method of radiotherapy as well as when it is combined with local treatment (surgery, SRS), which is the approach adopted in the case of patients with 1–4 BM. However, it should be noted that the use of WBRT in combination with SRS (primary management plus an SRS boost) is associated with an increased risk of neurocognitive complications, which justifies caution when assessing the suitability of patients for such treatment.

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