e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(8); 930-935

Original Research Article

# A Comparison between Two Radiation Dose Regimes of Whole Brain Radiation with Temozolomide in a Resource Constraints Setting: A Real World Experience

**Ghosh S.[1], Das A.[2], Chowdhury K.B.[3]**

[1]Assistant Professor Department of Clinical Oncology, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospital (SRIMS & SH) Durgapur, West Bengal, India.
[2]Assistant Professor Department of Clinical Oncology, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospital (SRIMS & SH) Durgapur, West Bengal, India.
[3]Associate Professor Department of Radiotherapy, Maldah Medical College and Hospital (MMC & H), Maldah, West Bengal, India.

**Received: 09-06-2023 / Revised: 13-07-2023 / Accepted: 08-08-2023**
**Corresponding author: Dr. Ghosh S.**
**Conflict of interest: Nil**

**Abstract:**

**Background:** Brain metastasis is considered as one of the worst prognostic factors of any carcinoma. Treatment aims at symptom palliation and intra cerebral disease control. Despite the introduction of SRS, neurosurgery, FSRT, whole brain radiation still remains the most practiced treatment. For ineligible patients for advanced treatments, higher dose WBRT is often discussed along with chemotherapy.

**Methods:** In this study two separate radiotherapy regimes (Standard 30 Gy in 10Fr vs Protracted 40 Gy in 20 Fr) along with Temozolomide have been compared in terms of Efficacy and Survival in a resource constrained setting.

**Results:** Irrespective of radiation dose used, no added advantage of a protracted regime was found in terms of survival (p=0.837), however it achieves better objective response rate. In terms of 6 months follow up there was no incidence in PS1 whereas only 31 % patients with PS 2 survived at the end of 6 months. Similarly, 70% patients with "some response" in MRI survived compared to only 14.5% with "stable intracranial disease" (p=0.002).

**Conclusion:** Despite of no survival advantage, higher dose regime with Temozolomide is a safe and efficacious option and may be more suitable to carefully selected performance status 1 patients. Multi institutional study with more number of patients can give insights about using higher dose regime.

**Keywords:** Temozolomide, radiation dose, Biological Effective Dose (BED), radiotherapy.



## Introduction

Brain metastasis is most common intracranial neoplasm that occurs in 10-30% of all diagnosed cancer cases in its disease course.[1] Most common primary sites are of lungs, breast, and melanoma.[2] Symptom palliation and stopping the intra-cerebral progression are often achieved through whole brain radiation (WBRT). It also helps in breakdown of blood brain barrier so that subsequent systemic therapy can penetrate better into brain parenchyma. Yet results are often dismal with a median survival of 1- 7 months.[3] For certain patient populations with limited disease burden, new approaches combine intracranial surgery, stereotactic radiation, and fractionated radiation.

Targeted therapies with better CNS penetration also benefit this population for systemic disease control. These developments have shown better progression free survival data. The performance status and presence of extra cranial disease remain the most important poor prognostic factors in spite of guidelines promoting advanced algorithms.[4] NCDB data analysis from 2010 to 2015 showed increasing trend for SRS use (12.7%) but WBRT was provided as first radiation treatment for brain mets in nearly 26.8% patients.[5] So in real world, as data suggests patients are often ineligible for intense therapeutic approaches and WBRT still holds a niche for treatment of brain metastasis.

To improve efficacy of WBRT, Series of trials have utilized principles like use of higher Biological Effective Dose (BED) and addition of concurrent agents. Higher BED use is justified as its radio biologically transforms into better response. Evidence suggests that protracted radiotherapy regimen can be used in selected patients with better performance status.[6] Regarding use of concurrent agents, radio sensitizers or chemotherapy have been useful as it causes more cellular damage by interacting with DNA repair pathways.

Temozolomide (TMZ) is widely investigated as it has shown effective CNS penetration and a manageable toxicity profile with an advantage of oral dosing. Trials has reported higher response rate when TMZ is used along with WBRT.[7, 8]

**Aim**

This study aims at studying efficacy of two different radiation dose regimes along with use of Temozolomide in resource constraint setting in carcinoma of Lungs and breast.

**Materials and Methods**

From March 2019 to January 2020, this study was conducted in the department of Oncology, R G Kar Hospital and Medical College, West Bengal. Patients with age <70 years and histological proof of carcinoma lung and carcinoma breast having been diagnosed of brain metastasis at any point of their treatment were prospectively included in the study. Decision of WBRT is taken through multidisciplinary meetings. After obtaining preliminary informed consent, patients were randomized by 1:1 allocations into two arms namely ARM A & ARM B. A total of 51 patients have been included in the study. Arm A used a fractionated schedule of 30 Gy in 10 Fr (3Gy/Fr @5 days a week) whereas Arm B used a more protracted schedule of 40 Gy in 20 Fr (2Gy/Fr @ 5 days a week). Patients having a worse PS (3 or more) were started with dexamethasone (8 milligram twice daily after food with proton pump inhibitor cover and later tapered down as required as per physician's discretion). Patients on dexamethasone having no improvement of performance status were excluded from the study. Whole brain RT was planned with a 2D conventional simulator and treated with bilateral pair portal with standard GERMAN HELMET technique using blocks for eye and oral cavity. As per department protocol, all patients were treated in Theratron 780E cobalt 60 machine. In both arms, concurrent Temozolomide was prescribed at a dose of @ 75 mg /m2 on the days of radiation with weekly complete blood count review. After completion of radiation all patients were followed up with an MRI brain using RANO BM criteria [9] at an interval of 1 month, 3 months and 6 months respectively. Survival was calculated from the date of start of Radiation to the event. Further palliative systemic treatment was at physicians' discretion.

**Table 1: Demography details**

| | 30 Gy/10 Fractions ARM A (26) | 40 Gy/ 20 Fractions ARM B (24) |
|---|---|---|
| **AGE (IN YEARS)** | | |
| MEDIAN (Year) | 55 (37 -65) | 51 (30-69) |
| **SEX** | | |
| MALE | 07 (26.9%) | 10 (41.67%) |
| FEMALE | 19 (73.1%) | 14 (58.34%) |
| **PS AT THE START OF WBRT** | | |
| PS 1 | 04 (15.4%) | 02 (8.34%) |
| PS 2 | 22 (56.6%) | 22 (91.6%) |
| **PRIMARY** | | |
| LUNG | 14 (54.4%) | 15 (62.5%) |
| BREAST | 12 (45.6%) | 09 (37.5%) |
| **SITES OF METS** | | |
| SINGLE | 18 (69.2%) | 12 (50%) |
| MULTIPLE | 08 (30.7%) | 12 (50%) |
| **NUMBER OF BRAIN METASTASIS** | | |
| ONE | 06 (23%) | 04 (16.7%) |
| TWO | 08 (30.7%) | 01 (4%) |
| THREE OR MORE | 12 (46.3%) | 19 (79.3%) |
| **RT DURATION (DAYS)** | | |
| MEDIAN | 14 (11-31) | 28 (26-52) |

**Results**

A total of 51 patients were included in this study and one patient has withdrawn consent from the study. Demographic details are given in table 1. Arm A, 26 (52%) and ARM B, 24 (48%) patients. Median follow up period is around 137 days (19 days to 436 days). Median age in both groups was 55 years (37-65 years) and 51 years (30-69 years). Overall more female patients (33, 66%) were enrolled. Among 29 patients (58 %) of lung patients, the majority (52%) belonged to NSCLC and only 20.6 % had EGFR mutations. (Table 2) Among 21 (42%) carcinoma breast patients 19 % and 28.5 % belonged to poor prognostic Her 2 neu rich and TNBC group respectively. (Table 3) Majority 44 patients (88%) distributed in both arms belong to PS 2 at the time of start of treatment of brain metastasis. Though during diagnosis of brain metastasis around 8 (16%) patients presented in PS 3 who were improved after high dose steroids and supportive care. In ARM A, 18 (69%)

patients presented with Single sites of metastasis (brain only) whereas 50% of patients enrolled in Arm B had both extra-cranial and brain mets. In ARM A 14 patients (53.8%) in arm A had 2 or less brain metastases whereas 12 (46.2 %) patients had 3 or more brain metastases. Similarly arm B had the majority 19 (79%) patients with 3 or more brain lesions. All patients completed radiation and median time to complete is 11 days (11-31 days) in ARM A and 28 days (26-52 days) in ARM B.

Regarding response measurement at 1 month, 4 patients died early before any MRI was done. So 4 patients have been excluded from final analysis. In 30Gy arm Partial response @ 1 month, 3 month, 6 months was found in 9 patients, 10 patients and 9 patients respectively. In 40 Gy arm, response @ 1 month, 3 months, 6 months was found in 10 patients, 11 patients and 6 patients respectively. Altogether some responses were seen over the follow up period in 10 patients (38.5%) in arm A, and 13 patients (54.2%) in Arm B (statistically not significant p=0.47). Nobody has encountered any grade 3 hematological or gastrointestinal toxicity due to Temozolomide.

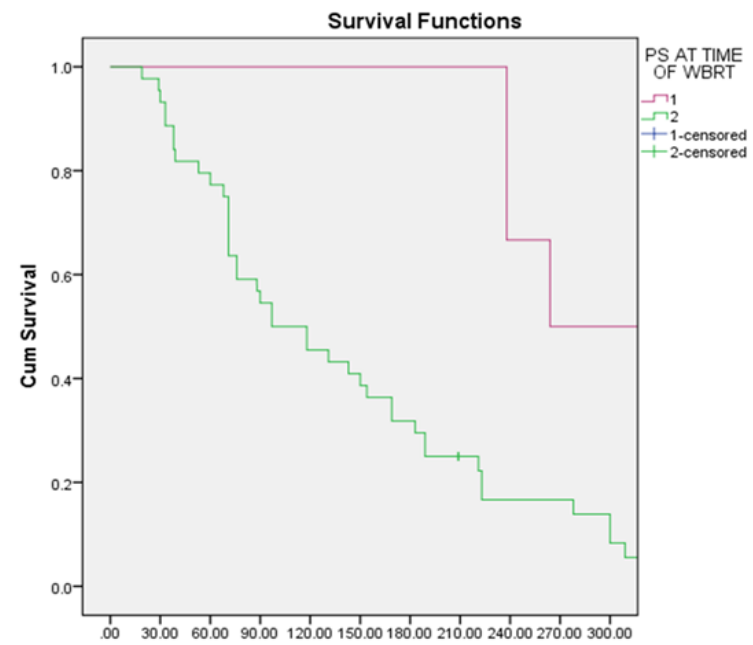
Median survival time is 146 days (IQR 73 -251 days) in 30Gy arm whereas in 40 Gy arm, median survival time is 169 days (71-223 days). There is no difference in overall survival between two arms. (p=0.837). There is no statistically significant difference among male and females (p=0.85). 6 months survival rate is 50% with 1-2 brain metastases and 40 % for 3 or more than 3 brain metastases which remained statistically insignificant (p=0.465). Extra-cerebral mets did not change the outcome despite a different radiation schedule. Though only 6 patients showed PS 1 presentation at the time of WBRT however they showed significantly better outcomes (p=0.001) (Graph 1). Similarly all those patients having some response post radiation showed significant survival patterns in both arms (p=0.05) (Graph 2). In terms of 6 months follow up there was no incidence in PS1 whereas only 31 % patients with PS 2 survived at the end of 6 months. Similarly 70% patients with "some response" in MRI survived compared to only 14.5% with "stable intracranial disease" (p=0.002)

**Table 2: Histopathology and Driver Mutations of Lung Carcinoma**

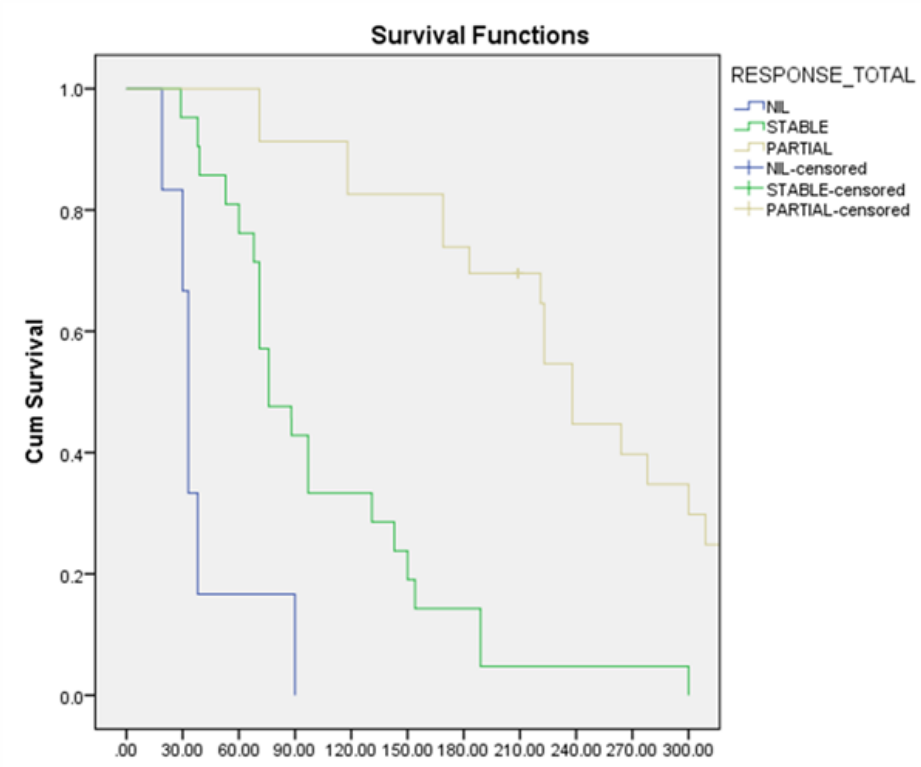
| Primary Lung Carcinoma | | | |
|---|---|---|---|
| Histopathology | | Immunohistochemistry | |
| NSCLC | SCLC | EGFR Positive | Driver Mutation Negative |
| 26 (89.7%) | 03 (10.3%) | 06 (20.7%) | 23 (79.3%) |

**Table 3: Histopathology and IHC details of Carcinoma Breast**

| Primary Breast Carcinoma | | | |
|---|---|---|---|
| TNBC | Luminal A | Luminal B | HER 2 Enriched |
| 06 (28.6%) | 06 (28.6%) | 05 (23.8%) | 04 (19%) |




**Graph 1**




**Graph 2**

## Discussion

WBRT remains a long standing treatment option for brain metastasis. Randomized Quartz study from the UK[10] suggests that WBRT for brain metastasis has marginal benefit over best supportive care. However optimal dose is yet to be established as data are quite heterogeneous in choosing dose regimes in different tumor sites. In a large Meta analysis by Gasper et al,[11] most trials used standard dose of 30 Gy in 10 fractions over two weeks but dose ranges from 10 GY in 1 fraction to 50.4 Gy in 28 fractions. Individual Alpha by beta ratio for separate tumor sites also plays a role for tumor response to radiation doses. Unfortunately it has not transformed into a survival benefit. Same result has been reported from the Cochrane database by Tsao et al.[12] Multiple recent trials have unequivocally voted for neurosurgery and a combination of stereotactic or fractionated focused Radiation along with WBRT.[13,14,15]. 2022 ASTRO guideline[16] categorically highlighted the role of various systemic therapy e.g. Tucatinib, Osimertinib, immunotherapy, stereotactic radiation and aggressive resection. Despite recommendations, large retrospective cohort and real world data suggested WBRT being the most practiced treatment for brain metastasis.[5] In Australia based TABITHA registry, WBRT remains the most common local therapy for brain mets. In this study patients not eligible for intensive therapy are included.[17] Reason behind this remains the sustained importance of poor performance status and uncontrolled extra-cranial metastasis as proven in Recursive partitioning analysis.[3] Recent trials also upholds the importance of cumulative volume of lesions to consider prior to SRS.[18]

Irrespective of radiation dose used, our study revealed no improvement of median survival which was similar in older studies.[19] Kyrhatii et al in an attempt to make a predictive model for WBRT in brain mets of lung carcinoma revealed median survival of 5.1 months.[20] Cochrane database update 2017 reported median survival of patients undergoing WBRT having 5.5 months.[21] SRS plus WBRT or Surgery followed by cavity SRS always have a better outcome in terms of survival however it only applies for better PS patients.[13] In a similar study by Chatani et al WBRT with 30 Gy in 10 Fractions vs 50 Gy in 20 fractions reported no difference of survival ( 5.4 months vs 4.8 months , P<0.084).[22] However In 2010 Graham et al reported 6.6 months in 40 Gy in 20 fractions (twice daily) citing improvement in intracranial disease control.[23] In 2011, Dirk Rades et al[6] in a retrospective study compared same dose fractionation in favorable group where escalated dose gained significant better survival. Survival rate at 1 year favored significant survival for 40 Gy and this is more pronounced in less radiosensitive tumors. Our study did not find any benefit of using higher doses and that may be attributable to multiple poor prognostic factors. Majority (88%) of patients being PS 2, absence of targetable driver mutation in carcinoma lungs, a significant number of TNBC and her 2 neu rich carcinoma breast patients.

In a large retrospective analysis of 595 patients of NSCLC with brain metastasis, using higher dose (> 30Gy) derived improved intracranial control and survival which is again augmented by use of subsequent cytotoxic and targeted therapy.[24] Mahalaxmi et al. reported better intracranial response by using WBRT with Temozolomide with an increased partial response >80% at the end of 3 months.[25] Similar high response rate (77.78%) has been reported in a study by Kouvaris et al.[26] In another Meta analysis by Yong Xin et al overall Response rate favored WBRT plus TMZ. (RR = 1.40, 95% CI 1.24–1.57; $Z = 5.51$; $P < 0.00001$).[25] In our study Higher dose produced partial response in 54.6 % patients in arm B compared to 38.5% in arm A ($p<0.471$).[27] No added benefit is found by using Temozolomide. This difference may be explained by multiple poor prognostic factors mentioned earlier. However, the response rate remained higher in the high dose arm.

This study has several limitations. Small sample size, Heterogeneous populations, lack of linear accelerator based conformal planning is some of its shortcomings. Presence of necrosis and volume are also not noted. This oncology center also primarily acts as a referral center for multiple rural outreach clinics. Most of the patients are from poor socio economic background often presenting late even after developing symptoms. They have often less access to modern systemic treatment like immunotherapy or targeted therapy. This may be reflected in their survival pattern.

## Conclusion

Higher dose WBRT along with TMZ is a feasible option in terms of safety and efficacy as it has produced higher numerical response rate. Though this response rate has not transformed into better survival. PS 1 remains a crucial factor for deciding on management for brain mets. Larger multi-institutional study with more homogenous populations and molecular data and conformal boost to brain lesion only can be planned to further investigate the improvement over WBRT.

## References


1. Amsbaugh MJ, Kim CS. Brain Metastasis. Stat Pearls Publishing; 2023.
2. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. Nat Rev Dis Primers. 2019;5(1).
3. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys [Internet]. 1997;37(4):745–51.
4. Stelzer KJ. Epidemiology and prognosis of brain metastases. Surg Neurol Int. 2013;4(Suppl 4):S192-202.
5. Barbour AB, Jacobs CD, Williamson H, Floyd SR, Suneja G, Torok JA, et al. Radiation therapy practice patterns for brain metastases in the United States in the stereotactic radiosurgery era. Adv Radiat Oncol. 2020;5(1):43–52.
6. Rades D, Panzner A, Dziggel L, Haatanen T, Lohynska R, Schild SE. Dose-escalation of whole-brain radiotherapy for brain metastasis in patients with a favorable survival prognosis: Dose-Escalation for Brain Metastasis. Cancer. 2012;118(15):3852–9.
7. Han J, Qiu M, Su L, Wu C, Cheng S, Zhao Z, et al. Response and safety of whole-brain radiotherapy plus temozolomide for patients with brain metastases of non-small-cell lung cancer: A meta-analysis. Thorac Cancer. 2021;12(23):3177–83.
8. Verger E, Gil M, Yaya R, Viñolas N, Villà S, Pujol T, et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. Int J Radiat Oncol Biol Phys. 2005;61(1):185–91.
9. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015; 16(6):e270-8.
10. 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; 388(10055):2004–14.
11. Gaspar LE, Mehta MP, Patchell RA, Burri SH, Robinson PD, Morris RE, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96 (1):17–32.
12. Tsao MN, Xu W, Wong RK, Lloyd N, Laperriere N, Sahgal A, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2018; 1:CD003869.
13. Khan M, Lin J, Liao G, Tian Y, Liang Y, Li R, et al. Whole brain radiation therapy plus stereotactic radiosurgery in the treatment of brain metastases leading to improved survival in patients with favorable prognostic factors. Front Oncol. 2019; 9:205.
14. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol. 2014;9(1).
15. Rostampour N, Badrigilan S, Rezaeian S, Sarbakhsh P, Meola A, Choupani J, et al. Efficacy of stereotactic radiosurgery as single or combined therapy for brain metastasis: A systematic

review and meta-analysis. Crit Rev Oncol Hematol. 2023;186(104015):104015.
16. Schiff D, Messersmith H, Brastianos PK, Brown PD, Burri S, Dunn IF, et al. Radiation Therapy for Brain Metastases: ASCO guideline endorsement of ASTRO guideline. J Clin Oncol. 2022;40(20):2271–6.
17. Tung I, Moldovan C, Wong V, De Boer R, Yeo B, Malik L, et al. Real-world outcomes in patients with brain metastases secondary to HER2-positive breast cancer: An Australian multicentre registry-based study. Clin Breast Cancer. 2022; 22(7):e764–72.
18. Routman DM, Bian SX, Diao K, Liu JL, Yu C, Ye J, et al. The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic radiosurgery. Cancer Med. 2018;7(3):757–64.
19. Suteu, P., Fekete, Z., Todor, N., & Nagy, V. Survival and quality of life after whole brain radiotherapy with 3D conformal boost in the treatment of brain metastases. Medicine and Pharmacy Reports, 2019;92(1): 43–51.
20. Trikhirhisthit K., Setakornnukul J., & Thephamongkhol K. Added survival benefit of whole brain radiotherapy in brain metastatic non-small cell lung cancer: Development and external validation of an individual prediction model. Frontiers in Oncology, 2022;12.
21. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev. 2017; 9:CD006121.
22. Chatani M, Teshima T, Hata K, Inoue T, Suzuki T. Whole brain irradiation for metastases from lung carcinoma. A clinical investigation. Acta Radiological Oncology. 1985; 24:311-4.
23. Graham PH, Bucci J, Browne L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. Int J Radiat Oncol Biol Phys. 2010;77(3):648–54.
24. Xin Y, Guo W, Yang CS, Huang Q, Zhang P, Zhang LZ, et al. Meta-analysis of whole-brain radiotherapy plus temozolomide compared with whole-brain radiotherapy for the treatment of brain metastases from non-small-cell lung cancer. Cancer Med. 2018;7(4):981–90.
25. M. Aal, V.B. Lakshman, N. Hanumanthappa, Y. Shivashankara, P. Venkatram Kumar, S. Prabaharan, R. Kumar, Temozolomide for concurrent therapy in brain metastases: Is it feasible in a developing country? Annals of Oncology.2016; 27 (suppl_9): ix184-ix189.
26. Kouvaris, John & Miliadou, Anthi & Koulouliaas, Vassilis & Kolokouris, Dimitrios & Balafouta, Myrsini & Papacharalampous, Xenofon & Vlahos, Lambros. Phase II Study of Temozolomide and Concomitant Whole-Brain Radiotherapy in Patients with Brain Metastases from Solid Tumors. Onkologie. 2007;30: 361-6.
27. Xin Y, Guo W, Yang CS, Huang Q, Zhang P, Zhang LZ, et al. Meta-analysis of whole-brain radiotherapy plus Temozolomide compared with whole-brain radiotherapy for the treatment of brain metastases from non-small-cell lung cancer. Cancer Med [Internet]. 2018;7(4):981–90.