**CLINICO-PATHOLOGIC PROFILE AND TREATMENT OUTCOMES OF BRAIN METASTASES FROM BREAST CANCER IN IBADAN, NIGERIA**

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**Source of grant:** None

**Conflict of Interest:** None

**Abstract**

**Background**: The development of brain metastases (BM) in breast cancer portends a significant systemic disease-progression for the patients. In sub-Saharan Africa, BM is wont to be seen as a terminal stage event in breast cancer. This study profiles BM among patients with breast cancer in an African oncological surgery practice.

**Aims and Objectives**: To study the clinico-pathologic profile and treatment outcomes of BM from breast cancer.

**Methods**: Over a 10-year period ending in December 2017, patients treated for breast cancer were followed up prospectively till development of BM. Each patient was enlisted at presentation into the Oncology database and followed up till development of BM if any. Clinical, histopathologic, radiologic and treatment details were extracted from the source data. Statistical analysis was done using SPSS Version 20.0. Univariate analysis was performed using the log rank test to compare overall survival between groups. Cox regression analysis was done to determine factors associated with the median survival time. This study is a descriptive observation for the occurrence of BM among these subjects. Statistically significance was set at a p value < 0.05.

**Results**: Of the 1971 histologically diagnosed breast cancer patients who underwent treatment over the study period, 266 (13.5%), females developed BM, although analysis was for 219 who had complete details. The median age was 46 (range 32-67 years). Synchronous disease was in 44 (20.1%) patients while 175 (79.9%) had metachronous disease. Invasive ductal carcinoma constituted 157 (71.7%) patients; 200 (91.3%) patients had either intermediate or high-grade lesions. One hundred and forty-eight (67.6%) had stage III or IV disease at time of primary diagnosis. Luminal A, Her2 and Basal-like were present in 97 (57.5%), 38 (23.1%) and 33 (19.4%) respectively out of 168. For the primary treatment of the breast cancer 162 (74.0%) had radical mastectomy and 210 (95.9%) had chemotherapy. Seventy- three (33.3%) had adjuvant external beam radiotherapy; 27 (12.3%) had been treated with Transtuzumab-Herceptin and 78 (35.6%) with hormone therapy. Ninety-eight (44.7%) had controlled locoregional disease while 121 (55.3%) had uncontrolled locoregional disease at the time of BM. The main neurological symptoms patients presented with were headaches in 192 (87.8%), paresis in 184 (84.0%), seizures in 114 (52.1%), altered mental state in 109 (49.8%) and visual complaints in 96 (43.8%). The cerebrum and cerebellum were involved in metastases in 106 (57.9%) and 57 (31.1%) respectively. The BM were multiple in 54.6% and solitary in 46.4% of patients. GPA-B was ≤ 2.0 in a total of 153 (69.9%) patients. All had steroid therapy; 96 (43.8%) had in addition whole brain radiotherapy (WBRTH) and 32 (14.6%) had in addition both metastasectomy and WBRTH. Two hundred and eight (95%) had died of disease at the end of the study period. Controlled locoregional disease, GPA ≥2.5 and Karnofsky score ≥70 were associated with longer survival.

**Conclusion:** Brain metastases occurred in 13.5% of our patients, with the patients having a median age of 46 years. Most of them had metachronous disease with predominance of invasive ductal carcinoma of intermediate/high grade histopathologic type, nodal involvement and stage III or IV disease at breast cancer diagnosis. Most cancers were Luminal A. The main treatment for the primary cancer had been surgery and chemotherapy. Neurological symptoms were mainly headaches, limb paresis, seizures and altered mental state. The cerebrum and cerebellum were the commonest sites of metastases, and multiple lesions were more common than solitary ones. Treatment with WBRTH and steroids, or steroids alone was the most commonly used, with metastasectomy in a few patients. The median survival after BM diagnosis was 4.6 months. Controlled locoregional disease, GPA≥2.5, and Karnofsky score ≥70 were associated with longer survival. Brain metastases are not uncommon, and appear to portend end-stage disease for a significant proportion of patients with breast cancer in our setting.

**Key words:** Breast cancer, Brain metastases, GPA-B, Karnofsky score, Management, Outcome, Ibadan

**Introduction**

Parenchymal brain metastasis (BM) is demonstrated in approximately 10-15% of breast cancer patients.1,2 Brain metastasis from breast cancer portends a poor prognosis 3, and is being seen more frequently in our clinical practice in Ibadan, Nigeria. This is probably a reflection of the improved overall survival of breast cancer patients with good loco-regional control after treatment of primary breast cancer3,4 The improved outcome is also likely attributable to the widespread availability of modern systemic therapy2,5,6,7; a multimodal approach to cancer care which consists of surgery, radiotherapy as well as chemotherapy, hormonal or immunotherapy deployed in a neoadjuvant or adjuvant chemotherapeutic setting. In addition, increasing availability of and accessibility to modern diagnostic tools like brain computed tomography (CT) scanning in our practice8 allows the detection of these metachronous or synchronous secondary brain lesions9,10 which represent the most frequent intracranial tumours in some clinical series.11

Existing treatment modalities for brain metastases include whole brain radiotherapy (WBRTH), surgical resection (metastasectomy), stereotactic radiosurgery (SRS) and palliative use of steroids 12. When deployed in the BM setting, the treatment modalities extend survival by between 2-37 months, with selected patients who have access to all modalities having a further extension of survival; while no intervention usually results in mortality within a limited time interval.2, 13-17

Surgical resection of BM from breast cancer is traditionally reserved for patients with controlled/stable locoregional disease; optimal clinical performance index as well as good neurologic functional state, and a favourable (especially surface) location in the CNS either as a solitary lesion or clustered configuration in multiple deposits.6,12,13 Ultimately the appropriate treatment option will be dependent on the patients’ graded prognostic assessment (GPA) score18 and available treatment modality.

There are many publications on the profile and outcome of management of cerebral metastases from breast cancer from developed countries1,2,3,7,9,12, but few from the developing countries.19 Our stated aim was to review our findings on the clinical and pathologic characteristics of brain metastases; from breast cancer along with outcomes of treatment in an oncological surgery practice of a developing country in sub-Saharan Africa. Specific objectives included; a review of the clinical course of breast cancer patients who develop brain metastases.

**Methods**

Over a 10-year period from December 2007 till December 2017, all patients treated for breast cancer in our clinical practice, who developed brain metastases during treatment or follow up (3-monthly in the first year, 6-monthly in the second year and yearly from the third year) were recruited.

All information was recorded in Microsoft Excel spreadsheet. Each patient’s demographic characteristics, clinical and pathologic details, immunohistochemistry, treatment and clinical follow-up details were recorded and updated at each clinical consultation into the Oncology database of the division till end of study or patient demise. Prior consent had been obtained from the patients. Statistical analysis was done using SPSS Version 20.0. Data were summarized as percentages, proportions, or means and standard deviations. Univariate analysis was performed using the log rank test to compare overall survival between groups within a factor. Relationships and differences were considered statistically significant when p was < 0.05.

Ethical approval was obtained from the state institutional review board under the Ministry of Health (MOH)

***Clinical management of BM from breast cancer in our unit***

 A clinical review (medical history and physical examination) that elicited neurological symptoms and signs suggestive of metastatic disease from a histologically confirmed primary breast cancer resulted in a cranial imaging, CT scan or magnetic resonance imaging (MRI). Upon confirmation of BM, stratification was made into synchronous or metachronous lesion, and as controlled or uncontrolled locoregional disease. The cohort with controlled locoregional disease had further CNS intervention viz WBRTH, surgery (metastasectomy) and/or steroids, whilst those with uncontrolled locoregional disease (with or without other systemic metastases) had palliative treatment (steroids) along with symptomatic care. Figure 1 shows this treatment algorithm. Using the Breast-Graded Prognostic Assessment (GPA-B)20 which is a more recent version of the original GPA21, we established scores using the Karnofsky performance status (KPS), immunohistochemistry and age. Those with scores greater than 2.0 with controlled/stable locoregional disease were reviewed by the neuro-surgical team to determine resectability of the BM; while those with unfavourable CNS disease-configuration had WBRTH and steroids. Select cases with multiple BM had surgery of the dominant lesion, the one producing significant neurologic compromise; adjacent lesions were sometimes resected via a common surgical approach.

**Results**

Out of a total of one thousand, nine hundred and seventy-one (1971) histopathologically confirmed cases of breast cancer over the study period, 266 patients (13.5%) had brain metastases. These were cases of breast cancer specifically managed in our surgical oncology unit. Cases lost to follow up were 47 (17.7%) and were excluded from the study. The results of 219 patients who had full clinical details were included in the analysis.

**Clinicopathologic Profile (Table 1)**

 The median age was 46 (range 32-67) years and the predominant histopathologic type was invasive ductal carcinoma in 157 (71.7%) patients. Synchronous BM was diagnosed in 44 (20.1%) patients while metachronous BM occurred in 175 (79.9%) patients. Intermediate/ high-grade histopathologic type predominated in 200 (91.3%), and a histopathologically positive nodal status was noted in 185 (84.5%) of the patients with brain metastases. One hundred and forty-eight (67.6%) had stage III or IV disease at the time of breast cancer diagnosis.

The ER, PR and Her2neu receptor status, available for 168 patients, showed that Luminal A was present in 97 (57.5%) patients, Her2 enriched in 38 (23.1%), and Basal like in 33 (19.4%). Ki-67 test was not routinely done- hence Luminal B cases could not be ascertained. Table 1 shows these clinicopathologic profiles.

The treatment of the primary breast carcinoma consisted primarily of surgery and chemotherapy. Surgical management for the primary breast lesions involved modified radical mastectomy in 162 (74.0%) patients. Chemotherapy was administered in 210 patients (95.9%); this was both neo-adjuvant and adjuvant in 99 patients (47.2%), neoadjuvant alone in 72 (34.3%) and adjuvant only in 39 (18.5%). A total of 27 (12.3%) patients had Transtuzumab-Herceptin based on the immunohistochemistry report. Adjuvant external beam radiotherapy was administered to 73 (33.3%) patients. Tamoxifen and Arimidex were the hormonal therapy drug therapies used.

At enrolment 98 (44.7%) patients had controlled locoregional disease whilst more than half, 121 (55.3%), had either loco-regional recurrence or systemic metastases, especially pulmonary in 83/121 (68.6%).

**Pattern of Brain Metastases in patients, and treatment (Table 2)**

The commonest neurologic symptomatology included headaches in 192 (87.7%), limb paresis in184 (84.0%), seizures in 114 (52.1%) and an altered mental state in 109 (49.8%). Others were visual complaints, nausea/vomiting, gait abnormalities, memory loss and dysphasia.

Radiologic information was available for 183 (83.6%) patients regarding the pattern of BM. Of these 183 patients, multiple metastases occurred in 101 (55.2%), while solitary lesions were seen in 82 (44.8%). The commonest sites of BM were the cerebrum and cerebellum; the brainstem was less often involved. Leptomeningeal Carcinomatosis (LMC) was diagnosed radiologically in 7 (3.8%). The GPA-B showed that 153 (69.9%) patients had a score ≤ 2.0 whilst 66 (30.1%) patients had scores ≥ 2.5. This resulted in the clinical decision to have most patients receive either WBRTH with steroids, or steroids alone. Of the 66 patients that merited local therapy (neurosurgery) along with WBRTH and steroids, only 32 (48.5%) patients had neurosurgery for various logistic reasons. We noted symptomatic relief within 48-96 hours of commencing treatment in up to 96% of patients administered steroids for the symptom of headaches. This steroid regimen involved intravenous dexamethasone 8mg stat or 10mg by mouth, followed by 4mg tablets 8-hourly.

The median duration from breast cancer diagnosis to development of symptoms and signs of BM was 17.2 (range 3.0-21.9) months, while from diagnosing BM to demise was 4.6 (range 0.2-37.8) months. Table 3 shows the univariate analysis of median survival following treatment of brain metastases by clinical characteristics. Eleven patients (5%) were alive with disease and 208 (95%) had died of disease at the end of the study period. Table 4 is a summary of the cox regression analysis. Notably patients who had controlled locoregional BM had 27% lower risk of mortality compared to those with uncontrolled locoregional BM and this was found to be statistically significant. Patients who had neurosurgery, WBRTH and steroid treatment did not differ significantly in the risk of mortality compared to women who had only steroid treatment. However, women who had WBRTH and steroid treatment had 18% lower risk of mortality when compared to those who had only steroid therapy.

However patients with a GPA score of ≤2 were significantly more likely to die earlier than those with GPA ≥2.5. Furthermore those with Karnofsky performance score <70 were 1.6 times at risk of mortality compared to those ≥70 and it was a statistically significant higher risk. The association between the pattern of BM metastatis and mortality was not statistically significant. Immunohistochemistry type had no statistically significant association with mortality.

**Discussion**

Brain metastases (BM) from breast cancer is an ominous prognostic sign3 as it many times heralds the last lap in the intricate interplay of the pathophysiology/biology of the disease, the patient and available treatment options. The CNS serves as a sanctuary for malignant cells and shields them from the effects of potent multiagent chemotherapeutic regimens that promote increased disease-free survival (DFS) time for patients with breast cancer.22-24 This has been attributed to the walling-off effects of the blood brain barrier which impairs the efficacy of the chemotherapeutic agents in the brain, in contrast to the situation with the malignant cells in other parts of the body.24-26 Standard treatment options for BM asides steroids for palliative treatment include whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and neurosurgical operative resection (metastasectomy).12

This study represents a large homogenous cohort of patients with breast cancer managed and followed over time with BM in an academic oncological surgery unit in sub-Saharan Africa. The patients had a median age of 46 years, predominantly invasive ductal carcinoma and had undergone treatment (Surgery, Chemotherapy, Radiotherapy, Hormonal and Immunotherapy) for mostly locally advanced breast cancer in the preceding years. This differed markedly from the pattern of presentation in the western world where most patients are post-menopausal, are screen-detected, and have small-sized and less aggressive tumours.27 The median age in our series for BM was reported as the average age for the diagnosis of primary breast cancer in the report by Wronski et al28; and their patient cohort developed BM approximately 5 years after index presentation with breast cancer. In comparing synchronous BM, only 2 patients had synchronous BM in their study compared to our data wherein 44 patients seen with breast cancer already had BM at presentation.28 This disparity may however be due to the differences in the study subjects of the two studies; our data representing those who developed BM from breast cancer whilst theirs involved only those who had surgical management of BM due to breast cancer.

A meta-analysis of 17 clinical articles regarding the site of distant metastases from breast cancer showed BM to be between 0-8%29, while our study had a 13.9% rate, closely approximating the reported rate from France of between 7.5- 12% 30. Indeed, autopsy studies showed rates between 30-42% of patients have cranial metastases at demise.31 The prevalence of BM across board may be influenced in part by the stage at presentation, duration of survival and its relationship to the clinicopathological characteristics of the primary tumour as well as immunohistochemistry29 and ultimately to the standard of care available. In this regard, we suspect that limited access to brain imaging, and less than optimal post-mortem practices are inherent problems contributing to under-reporting of this lesion, not only in our sub-Sahara African region but also from North Africa where the same challenges, albeit on a smaller scale, have been reported.19

Overall, seven in ten patients in our series had either multiple BM, uncontrolled locoregional disease, other systemic metastases or unfavourable CNS location of the BM which all somewhat precluded local treatment of the BM. Our approach to these groups with progressive disease and BM was to palliate symptoms and improve survival without compromising on their quality of life. Steroids and WBRTH (when available) formed the fulcrum of care in them as reported by others.3, 32, 33 Corticosteroids (dexamethasone) was the pivot of treatment for all patients for the following reasons: BM has been found to have a relatively large amount of vasogenic oedema relative to the size of the metastasis34,35, our patients’ average GPA-B score precluded active local treatment of the BM, and in cases adjudged able to benefit from surgery or WBRTH availability, waiting time, cost of treatment and lastly absence of stereotactic radiosurgery (SRS) all served to delay treatment. In this light palliative intent was the norm for about 2 in every 3 patients with BM in our centre.

Node-positive disease, high grade histology, ER-negative receptor status, and younger age at diagnosis predominated in the patients, thus leading to more cases of either locoregional disease and (or) systemic metastases to support the findings by others that these notable prognostic factors have clinical implications for any type of breast cancer recurrence or metastases, and not necessarily specific only for occurrence of BM.27, 36 The median survival was 6.8 months for the group who had steroids and WBRTH and this tallied with several other investigators’ findings 32, 33, 37. Suffice it to say that the ability to ensure strict and regular adherence to radiation treatment protocol in our setting is difficult with the considerable shortfall in the required number of megavoltage radiotherapy machines by WHO standards.38 The ER/PR-positive status showed statistically significant survival advantage on univariate analysis (p=0.001) as reported by others27, 39, however the Cox regression analysis did not show any survival advantage for Luminal A over the Basal-like groups. The major symptoms and signs of BM in our series reflected published works in which headaches, altered mental status, paresis and seizures occurred as the signs of note.12,30

The use of local therapies (WBRTH, Surgery and SRS) with varied outcomes necessitated the formulation of prognostic indices to assist with selecting potentially curable patients with BM from breast cancer. The GPA-B 19, which is a modification of the GPA developed in 2008 20, identifies patients who will benefit from local treatment of BM.31 The components are the Karnofsky performance score (KFS), ER/PR/HER2 status and age. A GPA-B score ≤ 2.0 suggests poor prognosis with little or no benefit accruable from local treatment while scores ≥ 2.5 suggest potential benefit from available local treatment.12,18 Our GPA-B score findings contrast with the report from Tunisia31: we had approximately 70% with poor prognostic score while they had mostly good prognostic scores. The North African cohort’s epidemiology also appears to mirror the European findings with most cases being diagnosed in the fifth decade 40,41.

Other notable prognostic indices in BM include the score index for radiosurgery, basic score for brain metastases, the Golden grading system and the Rades prognostic scoring systems.12 The occurrence of leptomeningeal carcinomatosis (LMC) in breast cancer42 is acknowledged as a surrogate marker of bad prognosis31; nonetheless, its diagnosis was made radiologically in only 7 patients in this cohort, despite the preponderance of headaches, altered mental state and seizures in the patients: which are the common manifestations of LMC. The sensitivity of brain CT scan (which was the main radiological investigation in the study) compared to a Gadolinium enhanced MRI for LMC is low43 and this may be the reason for the low pick-up rate for LMC in our series, due to the use of mainly CT scan in our patients. Nevertheless, the diagnostic modality of choice for LMC is multiple cerebrospinal fluid (CSF) taps with sensitivity approaching 100% when there is cytologic detection of malignant cells in the CSF.44 Adding an invasive lumbar tap with the risk of coning from an increased intracranial pressure for CSF cytology and biochemical assay to diagnose LMC in these patients will negate the principle of symptoms palliation and non-compromise of quality of life; without any potential improvement in outcome.

Apart from the use of steroids in palliation as explained above, the only available treatment options for BM in our centre are WBRTH and neurosurgical resection. WBRTH improves both survival and quality of life compared with corticosteroids alone, and produces a median survival of 4 to 5 months with two-thirds of patients having symptoms improvement, with seizures and headache most effectively palliated after WBRTH.36 Even so, WBRTH is not always readily available, due to various logistic constraints. This limits our ability to palliate neurological symptoms, maintain the performance status and achieve local control of metastatic disease. Stereo-tactic radiosurgery (SRS) with benefits of reduced radiation to contiguous brain parenchyma, and capability to treat single or multiple lesions or be used as salvage therapy following neurosurgery and/or WBRTH recurrence36,45 is not available.

One main limitation of this work is that it emanates from a single-institution, academic oncological practice. There may thus have been some patient accrual bias in the cohort studied hence, probably not representing the clinical experience in some other health facilities in our vast country.

**Conclusion:** Brain metastases occurred in 13.5% of our patients, with the patients having a median age of 46 years. Most of them had metachronous disease with predominance of invasive ductal carcinoma of intermediate/high grade histopathologic type, nodal involvement and stage III or IV disease at breast cancer diagnosis. Most cancers were Luminal A. The main treatment for the primary cancer had been surgery and chemotherapy. Neurological symptoms were mainly headaches, limb paresis, seizures and altered mental state. The cerebrum and cerebellum were the commonest sites of metastases, and multiple lesions were more common than solitary ones. Treatment with WBRTH and steroids, or steroids alone was the most commonly used, with neurosurgery in a few patients. The median survival after BM diagnosis was 4.6 months. Controlled locoregional disease, GPA≥2.5, and Karnofsky score ≥70 were associated with longer survival. Brain metastases are not uncommon, and appear to portend end-stage disease for a significant proportion of patients with breast cancer in our setting.

**Figure 1:** Treatment Protocol

Brain Metastases

* GPA – Breast ≤2.0
* Uncontrolled locoregional
* Systemic metastasis
* GPA – Breast ≥2.5
* Controlled locoregional
* No systemic metastasis

Breast Cancer

Index Presentation or Follow up

Cranial Imaging

CT Scan / MRI

* WBRTH
* Metastasectomy
* Steroids
* Steroids
* Palliative/ Symptomatic care
* CHEMOTHERAPY
* HORMONAL THERAPY
* IMMUNOTHERAPY

Used as necessary

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| --- |
| **Table 1:** Clinicopathologic profile of 219 patients |
| **Characteristic** | **Median (Range)** | **No.** | **Percentage** |
| **Age****Gender (Female)****Histology** Invasive ductal Others (lobular, medullary, mucinous, tubular, papillary)**Time lag** Synchronous Metachronous**Nodal status** Negative Positive**Immunohistochemistry (N=168)** Luminal A Her2enriched Basal like**Locoregional disease** Controlled Uncontrolled**Histopathology grade** High Intermediate Low**Clinical Stage** IA/B IIA/B IIIA/B/C IV**Karnofsky score**<70≥70**Primary** **Treatment of Breast cancer** Chemotherapy Neoadjuvant  Adjuvant  Both  External beam RTH Hormonal therapy Immunotherapy Surgery  |  | 46 (32 – 67)  | 21915168441753418597383398121137631927441183066 153210723999737827162 | 100%69%31.0%20.1%79.9%15.5%84.5%57.5%23.1%19.4%44.7%55.3%62.5%28.8%8.7%12.3%20.1%53.9%13.7%30.1%69.9%95.9%32.9%17.8%45.2%33.3%35.6%12.3%74.0% |
|   |
| **Table 2:** Pattern of Brain metastasis in patients |
|  **Neurologic symptoms(N=219)** |
|  Headache Paresis Seizures Altered mental state Visual Complaints Nausea/Vomiting Memory Loss Gait Abnormalities  Dysphasia Others (sensory loss, aphasia) | 192 184 114 109 96 85 78 73 47 23 | 87.7%84.0%52.1%49.8%43.8%38.8%35.6%33.8%21.5 %10.5% |
| **Number of Metastasis (n=183)** |
| SolitaryMultiple |  85 98  | 46.4%53.6% |
| **Location of Metastases** |
| CerebrumCerebellumBrain stem |  106 57 20 | 57.9% 31.1% 10.9% |
| **GPA-Breast** |
| 0 – 2.02.5 -3.03.5 – 4.0 |  153 32 34 |  69.9%  14.6%  15.5% |
| **Treatment of BM** |
| Surgery+ Steroids+ WBRTHWBRTH+ SteroidsSteroids |  32 96 91 |  14.6%  43.8%  41.6% |
| **Median Survival (Range)****Months** |  4.6 (0.2-37.8) |

|  |
| --- |
| **Table 3:** Univariate analysis of median survival following treatment of brain metastases by clinical characteristics |
| **Clinical characteristic** | **Median survival (months)** | **p value** |
| **Karnofsky performance score** <70 vs ≥70**GPA-Breast** 0 – 2.0 vs 2.5 – 4.0**Locoregional disease** Controlled vs Uncontrolled**Metastasis** Solitary vs Multiple**Immunohistochemistry**Lumina A vs Basal like**Treatment**Surgery/ WBRTH / Steroids WBRTH / Steroids Steroids | 2.1 vs 4.3 1.8 vs 8.2 9.8 vs 1.9 10 vs 6.2  6 vs 3.4186.81.7 | 0.0010.0010.0010.0010.0010.037 |

**Table 4:** Cox regression model

|  |  |
| --- | --- |
| Variable  | Hazard ratio (Confidence interval) |
| **Locoregional disease**Controlled vs Uncontrolled | 0.73 (0.45,0.92) |
| **Metastasis** Solitary vs Multiple | 0.77 (0.58, 1.01)  |
| **Immunohistochemistry**Lumina A vs Basal like | 0.81 ( 0.31,1.12) |
| **GPA-Breast** 0 – 2.0 vs 2.5 – 4.0 | 2.65 (2.16, 3.25) |
| **Treatment options** Surgery/ WBRTH / Steroids vs Steroids WBRTH / Steroids vs Steroids  | 0.75 (0.32, 1.14)0.82 ( 0.38, 0.94) |
| **Karnofsky performance score** <70 vs ≥70 | 1.60 (1.21, 2.10) |

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