# Adjuvant whole brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase 3 trial

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Acknowledgements

We acknowledge and thank the Australia and New Zealand Melanoma Trials Group for co-ordination and support of this trial; Melanoma Institute Australia, the Trans-Tasman Radiation Oncology Group (TROG) and Melanoma and Skin Cancer Trials (MASC Trials) for their involvement; Cancer Australia for their funding support in Australia (PdCCRS Grants 512358, 1009485, 1084046) and Cancer Research UK (Grant C2195/A11885) for support of the trial in the United Kingdom. We thank the investigators and site staff at all participating centers, and the patients and their families, without whom these valuable data would not have been obtained.

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Running title: Randomized adjuvant whole brain radiotherapy in melanoma

Abstract

Purpose

The brain is a common site of metastasis for patients with high-risk melanoma. Although surgery or stereotactic radiosurgery are highly effective local treatments for small number of metastases, the risk of developing further brain metastases is high. The role of adjuvant whole brain radiotherapy (WBRT) in reducing new metastases is controversial, with a lack of high-level evidence specifically for melanoma.

Methods

In this randomized, phase 3 trial, patients who had local treatment of 1-3 melanoma brain metastases were randomized to WBRT or observation. The primary endpoint was distant intracranial failure within 12-months and secondary endpoints included time to intracranial failure, survival and time to deterioration in performance status.

Results

Between April 2009 and September 2017, 215 patients were randomized from 24 centers. Median follow-up was 48.1 months (range 39.6-68 months). 42.0% of patients in the WBRT group and 50.5% of patients in the observation developed distant intracranial failure within 12 months (OR 0.71, 95% CI, 0.41-1.23, p=0.22) and the rates over the entire follow-up period were 52.0% and 57.9% respectively (OR 0.79, 95% CI 0.45-1.36, p=0.39). The local failure rate was lower after WBRT (20.0% vs. 33.6% p=0.03). At 12 months, 41.5% of patients in the WBRT group and 51.4% of patients in the observation group had died (p=0.28), with no difference in the rate of neurological death. The median time to deterioration in performance status was 3.8 months after WBRT and 4.4 months with observation (p=0.32). WBRT was associated with more grade 1-2 acute toxicity.

Conclusion

After local treatment of 1-3 melanoma brain metastases, adjuvant WBRT does not provide clinical benefit in terms of distant intracranial control, survival, or preservation of performance status.

## Introduction

Brain metastases are the most common brain tumors and melanoma is one of the commonest primary sites from which they originate.[1,2] In patients with systemic spread of their melanoma, brain metastases are diagnosed in 20-30% of them by one year, in 30-40% by three years, and in up to 73% in autopsy series.[3,4] For patients with single or few melanoma brain metastases (MBM), a high rate of local control can be achieved with surgery and/or stereotactic radiosurgery (SRS).[5,6] However, the risk of intracranial progression within the first year is up to 70%, due to development of new metastatic lesions.[7,8] Effective adjuvant therapy is needed to prevent the development of further MBM.

One adjuvant therapy option is whole brain radiation therapy (WBRT) but there has been ongoing debate about its benefits after local treatment of MBM.[9,10] Most previous randomized trials (including mixed tumor types, with few patients with melanoma) have demonstrated an improvement in intracranial control with the addition of WBRT.[5,6,8,11] However, no survival advantage for WBRT has been demonstrated. Furthermore, WBRT can be associated with deterioration of neurocognitive function (NCF) and quality of life (QOL).[8] The recent demonstration of intracranial activity of immune checkpoint inhibitors and targeted therapies has added another adjuvant therapy option after local treatment of MBM.[12-16]

We conducted this international phase 3 randomized trial (ANZMTG 01.07) to determine the effect of adjuvant WBRT in patients with 1-3 MBM after definitive local treatment. The primary hypothesis was that WBRT would reduce the risk of

distant intracranial metastasis within the first 12 months, compared with observation.

## Methods

### Study population and design

This was a multicenter, prospective, open-label, phase 3 randomized trial. The study protocol was approved by the Cancer Institute New South Wales Ethics Committee (Reference 2007C/11/032) and the Sydney Local Health District Ethics Committee (Reference X13-0329 & HREC/13/RPAH/465), and by institutional review boards at each site. The trial was registered with the Australian Clinical Trials Registry (ACTRN12607000512426) and ClinicalTrials.gov (NCT01503827). One pre-planned interim analysis was performed when the first 100 patients reached 12 months of follow-up.[17] An independent data and safety monitoring committee reviewed the interim data and recommended continuation of the trial.

Patients ≥18 years of age with 1-3 MBM identified on gadolinium-enhanced magnetic resonance imaging (MRI), locally treated by either surgery and/or SRS, were eligible. Patients were randomized 1:1 within six-weeks of local treatment to observation or WBRT. Brain metastases were considered melanoma if the patient had histologically-confirmed extracranial metastatic melanoma. For first presentation of systemic metastasis, one MBM or extracranial site had to be histologically-proven to be melanoma. Other eligibility criteria included Eastern Cooperative Oncology Group performance status 0-2, life expectancy of at least six months, and serum lactate dehydrogenase ≤2 times the upper limit of normal. Any form of systemic therapy before, during and after treatment of the MBM was permitted.

Randomization was performed with an interactive voice-response system, stratified by the number of MBM (1 vs. 2-3), extracranial disease (presence vs. absence), sex, age (<65 or ≥65) and planned WBRT dose (30Gy vs. higher).

## Study Treatment

The minimum WBRT dose was 30Gy in 10 fractions. WBRT quality assurance was performed by the Trans-Tasman Radiation Oncology Group. Patients randomized to WBRT were required to start treatment within eight weeks of local treatment. During the study period, the hippocampal-avoidance WBRT technique became available and a protocol amendment was approved in March 2016 to allow for use of this technique at the discretion of the treating radiation oncologist. Subsequent treatment of intracranial failure was as per the standard of the treating center.

## Assessments

Each patient underwent baseline evaluation including history and physical examination. Patients treated at English-speaking centers had assessment of NCF (Hopkins Verbal Learning Test -Revised, Controlled Oral Word Association Test, Trail Making Test Parts A and B, Stroop–Colour and Word Test, Wechsler Memory Scale III Digit Span) and QOL (EORTC QLQ-C30 and QLQ-BN-20). Healthcare resource utilization data and preference-based QOL measures (EuroQoL EQ-5D-5L) were collected for cost-effectiveness evaluation. All baseline evaluations and adverse event assessments were repeated at two-monthly intervals. MRI was performed at baseline (after randomization), then three-monthly. Staging scans for extracranial disease were performed at the discretion of treating clinicians.

## Endpoints

The primary endpoint was the proportion of patients with distant intracranial failure (as determined by MRI) within 12-months of randomization. Distant intracranial failure was defined as new disease appearing 1cm or more from

baseline MBM. The study radiologist, blinded to the randomization, reviewed the MRI of the first five patients then every fifth patient from each centre. Secondary endpoints were time to intracranial failure (local or any), overall survival, time to deterioration in performance status, QOL, NCF and cost-effectiveness. The QOL, NCF, and cost-effectiveness results will be reported separately.

Sample Size

The original sample size of 200 patients had 80% power to detect an absolute risk reduction of 22.0% (from 55.0% to 33.0%) at the 5.0% significance level (two-tailed), assuming 10.0% non-adherence. The sample size in the amended protocol was 220 to allow for increased power for assessment of the NCF endpoint. This had >84.0% power to detect an absolute 12 month distant intracranial metastases reduction of 22.0%. However, the data safety monitoring committee recommended early stopping of the trial in September 2017 after recruitment of 215 patients due to a marked slowing of accrual in the preceding year.

Statistical Analysis

All analyses were performed according to the intention to treat principle excluding patients with missing outcome data, as per the statistical analysis plan completed prior to data lock on 8th October 2018.[18] The primary endpoint was assessed using the Pearson chi-squared test with no multiplicity adjustment. Overall treatment effect was summarised using the odds ratio and its 95% confidence intervals (CI). Other binary endpoints were analysed using the chi-square test or Fisher's exact test, as appropriate. The results were summarized using proportions and odds ratios. Time-to-event outcomes were reported graphically using either the Kaplan-Meier methods or cumulative incidence function in the presence of competing risk events. Differences between groups were tested with the log-rank test or Gray's test, as appropriate. Hazard ratios,

estimated from Cox models and sub-distribution hazard ratios, estimated from Fine and Gray models along with their 95% CIs, were displayed within corresponding figures.[19] Subgroup analyses were performed using an unadjusted test of interaction in a logistic model with results displayed using a forest plot. Analyses were performed using R version 3.4.1 (R Core Team 2017) and Statistical Analysis System version 9.4 (SAA Institute Inc.).

## Results

### Patient Characteristics

Between April 2009 and September 2017, 215 patients were enrolled from 24 centres (Supplementary Table 1); 107 patients were randomized to WBRT and 108 patients to observation (Figure 1). Seven patients (six in the WBRT group and one in the observation group) withdrew consent for further data collection and were excluded. One patient who died of thromboembolism before any baseline data collection was included in the overall survival analysis only. The WBRT completion rate was 97.0%. 95% of the patients received 30Gy in 10 fractions. Twenty-four patients received hippocampal-avoidance WBRT. Median follow-up was 48.1 months (range 39.6-68 months) and all surviving patients were followed for at least 12 months.

Baseline characteristics including the number and local treatment of the MBM were similar between groups (Table 1a and 1b). The median age was 64.0 years, 66.0% were males, over 90.0% had an ECOG performance status 0-1, 67.0% of patients had extracranial disease at the time of randomization, and 60.0% had a single MBM. The median diameter of the largest MBM was 24mm in the WBRT group and 19mm in the observation group. The majority had surgery to one or

more of the MBMs (64.0% of patients in the WBRT group and 59.8% of the patients in the observation group had surgery).

Intracranial Control

Within the first 12 months, 42.0% of patients in the WBRT group and 50.5% of patients in the observation group developed distant intracranial failure (OR 0.71, 95% CI, 0.41-1.23, p=0.22). The median time to development of distant intracranial failure was 26.4 months in the WBRT group and 11.5 months in the observation group (p=0.20). The distant intracranial failure rate over the entire follow-up period and at specific time points is shown in Table 2. The time to distant intracranial failure considering death as a competing risk also showed no significant difference between the two groups (Figure 2a). In patients with a single metastasis, 37.3% of patients in the WBRT group and 52.9% patients in the observation group developed distant intracranial failure within the first 12 months (OR 0.53, 95% CI 0.26-1.08, p=0.08) (Supplementary Table 2a). For patients with 2-3 metastases, the risk of distant intracranial failure within the first 12 months was 48.8% in the WBRT group and 46.2% in observation group (OR 1.11, 95% CI 0.46-2.67, p=0.81). Factors such as age, sex, extracranial disease status, and treatment with systemic therapy did not influence distant intracranial control. A subgroup analysis by treatment with potentially effective systemic therapy (immune checkpoint inhibitor and/or BRAF-targeted therapy) before reaching the primary endpoint revealed that the best distant intracranial control was seen in patients who received WBRT and systemic therapy, for whom the 12 months intracranial failure rate was 29.5% (Figure 2c). The distant intracranial failure rates were similar for those who had WBRT with no or non-effective

systemic therapy (chemotherapy), observation with effective systemic therapy, and observation alone (43.7%, 42.0%, and 48.0% respectively).

Patients in the WBRT group had a significantly lower failure rate at the site of the initial MBM (Figure 2b). Within 12-months of randomization, local failure was seen in 20.0% of patients in the WBRT group and 33.6% of patients in the observation group (OR 0.49, 95% CI 0.26-0.93, p=0.03). The median time to development of local failure was not reached in either group. In patients with a single metastasis, the intracranial failure rate was significantly lower in the WBRT group than in the observation group (18.6% vs. 41.2%, OR 0.33, 95% CI 0.15-0.74, p=0.007) (Supplementary Table 2b). This statistically significant local failure rate difference at 12 months was driven by patients who received surgery as local treatment; the local failure rate was 20.3% in the WBRT group and 42.2% in the observation group (OR 0.35, 95% CI 0.16-0.77). For those patients with a single metastasis treated by SRS, there was no significant improvement in local control with the addition of WBRT (20.0% vs. 22.6%, OR 0.86 95% CI 0.25-2.93). For patients with 2-3 metastases, WBRT did not reduce the local failure rate. The effect of WBRT on local failure was greater in patients who did not receive any systemic therapy; in these patients the local failure rate was 11.9% in the WBRT group and 42.6% in the observation group (OR 0.18, 95% CI 0.06-0.54, p=0.002). For those who had systemic therapy, local intracranial relapse rates were very similar, 25.9% after WBRT and 24.5% for observation (OR 1.07, 95% CI 0.45-2.53, p=0.87).

The cumulative incidence of any intracranial failure over the study period was similar in the two groups (61.0% in the WBRT group and 68.2% in the observation group, p=0.28) (Figure 2d). Most intracranial failure occurred in the first 12-

months; the rate was 50.0% in the WBRT group and 62.6% in the observation group (OR 0.60, 95% CI 0.34-1.04, p=0.067).

Survival Outcome

There was no significant difference in overall survival between the two groups (Figure 3a). The median overall survival was 16.5 months (95% CI 13-24) in the WBRT group and 13 months (95% CI 10-19) in the observation group (p=0.86). At 12 months, the overall survival was 58.4% (95% CI 49.6-68.9%) in the WBRT group and 54.0% (95% CI 45.3-64.3%, p=0.89) in the observation group. There was no significant difference in neurological death incidence between the two groups (43.6% and 45.8%, p=0.38, Figure 3b). Factors such as number of MBM, age, sex, presence of extracranial disease, systemic therapy and steroid use did not influence the overall survival (Supplementary Table 2c).

Time to deterioration in performance status was similar between groups, with most deterioration occurring within the first 12 months (Figure 3c). The median time to deterioration was 5.3 months in the WBRT group and 6.0 months in the observation group (p=0.32).

Safety

Patients in the WBRT group had more grade 1-2 toxicity in the first 2-4 months (Supplementary Table 3) with more fatigue (68.2% vs. 28.1%, p<0.001), anorexia (45.2% vs. 8.3%, p=<0.001), nausea (33.0% vs. 15.7%, p<0.001), dermatitis (11.8% vs. 0%, p<0.001) and alopecia (62.4% vs. 4.4%, p=<0.001). However, there was no difference in these types of toxicity up to 24 months after randomization.

There were no severe adverse events related to WBRT within 90 days of randomization.

## Discussion

In this phase 3 randomized trial, adjuvant WBRT did not significantly reduce the risk of distant intracranial relapse after local treatment of 1-3 MBM. Nor did it improve overall survival, performance status or reduce neurological death. The trial provides additional data to resolve the long-running clinical dilemma of whether to recommend adjuvant WBRT after local treatment of single or a small number of MBM.

The trial demonstrates the importance of tumor-specific studies when evaluating therapeutic interventions, as our findings differed from those of previous randomized adjuvant WBRT trials involving patients with mixed tumor histologies. All these previous randomized trials demonstrating significantly improved intracranial control with adjuvant WBRT included mainly lung and breast cancer patients, and only about 5-6% were patients with melanoma.[5,6,8,11] Additionally, adjuvant WBRT did not improve overall survival and was associated with NCF decline in these studies.[5,6,8] In this era of personalized medicine, it is difficult to extrapolate findings from such studies specifically to patients with melanoma. With the high incidence and serious consequences of MBM in patients with disseminated melanoma, we sought to generate high-level evidence by conducting this first randomized trial of adjuvant WBRT for a single histology.[20]

Despite multiple previous trials reporting improved intracranial control with adjuvant WBRT,[5,6,8,11] this trial did not demonstrate a statistically significant reduction in distant intracranial failure. The 12-month distant intracranial failure rate of 50.5% in the observation group was close to the hypothesized rate of 55.0% used in the power calculation. We observed an absolute reduction of 8.5%

in distant intracranial failure at 12 months in the WBRT group, a smaller reduction than that observed in previous mixed-histology randomized trials using similar adjuvant WBRT doses. The cumulative incidence of any intracranial failure over the study period was also not significantly reduced by WBRT. The lack of a significant reduction in intracranial failure in our study may be a reflection of melanoma being a more radioresistant tumor.[21] Therefore 30Gy in 10 fractions of WBRT may not be sufficient to eradicate microscopic disease. In some patients, the use of targeted therapy and immunotherapy may have modified the intracranial relapse rates.[14,15,22] To examine this, an exploratory subgroup analysis by systemic therapy use prior to reaching the primary endpoint was performed. Although numbers were small, treatment with WBRT and targeted therapy and/or immunotherapy prior to reaching the primary endpoint appeared to give the lowest intracranial failure rate (30.1% at 12 months). However the intracranial failure rate for those who had systemic therapy in the observation group was similar to that in the observation group without systemic therapy. Consistent with previous randomized trials, our study did not show an improvement in survival with adjuvant WBRT. The survival of our study cohort was poor, with almost half dying within the first 12-months. This lack of a survival benefit adds further weight to argument against its routine use after definitive local treatment of MBM.

For patients with a single MBM, the majority had surgery as the local treatment and control at the site of the initial MBM was significantly better with the addition of WBRT. Within the first 12 months, the risk of relapse at the site of initial metastasis was halved with adjuvant WBRT. However, this alone would not justify the routine use of WBRT, as a similar improvement in local control can also be achieved with postoperative SRS to the surgical cavity without the neurocognitive

decline associated with WBRT.[23] A recent randomized, phase 3 study of mixed histology showed that adding a SRS boost to the surgical cavity significantly improved the 12-month freedom from local recurrence rate compared with observation in patients with 1-3 resected brain metastases (72.0% vs. 43.0%, HR=0.46, p<0.02). In another randomized trial of SRS vs. WBRT after resection of a single brain metastasis, SRS to the cavity was associated with a longer cognitive-deterioration free survival (3.7 months vs. 3.0 months, HR=0.47, p <0.0001).[7]

An important limitation of this trial is that the recruitment over 8.5 years coincided with the revolution in systemic therapy for metastatic melanoma. At the time the trial commenced, systemic therapy was limited to minimally-effective chemotherapy.[24] Since early 2010, BRAF-directed targeted therapy and immune checkpoint inhibitors became available via clinical trials, and after 2013-2015, generally available in the countries in which this study was conducted. Importantly, these therapies have now been shown to have activity against intracranial metastases.[12-16] Our trial did not prospectively stratify for use of systemic therapy, nor were detailed data available to examine the timing and response to systemic therapy as part of this study. Therefore, the true effect on intracranial control of combination WBRT with these drugs could not be assessed. Although the trial recruitment (215 patients) did not reach the target of 220 patients, it exceeded the originally planned sample size of 200 patients and there was thus no negative impact on the statistical power of the study.

The role of radiation therapy for MBM in combination with other treatments has become more complex with recent advances in SRS technology and intracranially-effective systemic therapies. There are ongoing randomized trials defining the role of combining radiation therapy with BRAF-directed targeted therapy or immune

checkpoint inhibitors in MBM (ClinicalTrials.gov identifier: NCT03340129, NCT02974803). Multidisciplinary team input considering all available treatment modalities has become essential in determining the most appropriate management of patients with MBM.[25]

In conclusion, for patients who have had definitive local treatment of 1-3 MBM using either surgery or SRS, adjuvant WBRT does not provide any significant clinical benefit and should not be recommended.

Legends

Table 1a. Characteristics of patients at baseline

Table 1b: Characteristics of the baseline lesion(s) and local treatment details

Table 2. Distant intracranial failure over the entire follow-up period and at specific time points

Figure 1. Trial Profile.

Figure 2a. Cumulative incidence of distant intracranial failure during follow-up

Figure 2b. Cumulative incidence of local intracranial failure during follow-up

Figure 2c. Cumulative incidence of distant intracranial failure during follow-up stratified by whether or not patients received systemic therapy before reaching primary endpoint

Figure 2d. Cumulative incidence of intracranial failure (distant and local) during follow-up

Figure 3a. Kaplan-Meier estimates of overall survival according to treatment group

Figure 3b. Cumulative incidence of death due to intracranial disease during follow-up

Figure 3c: Time-to-deterioration in ECOG performance status during follow-up

**Figure 1. Trial Profile.**

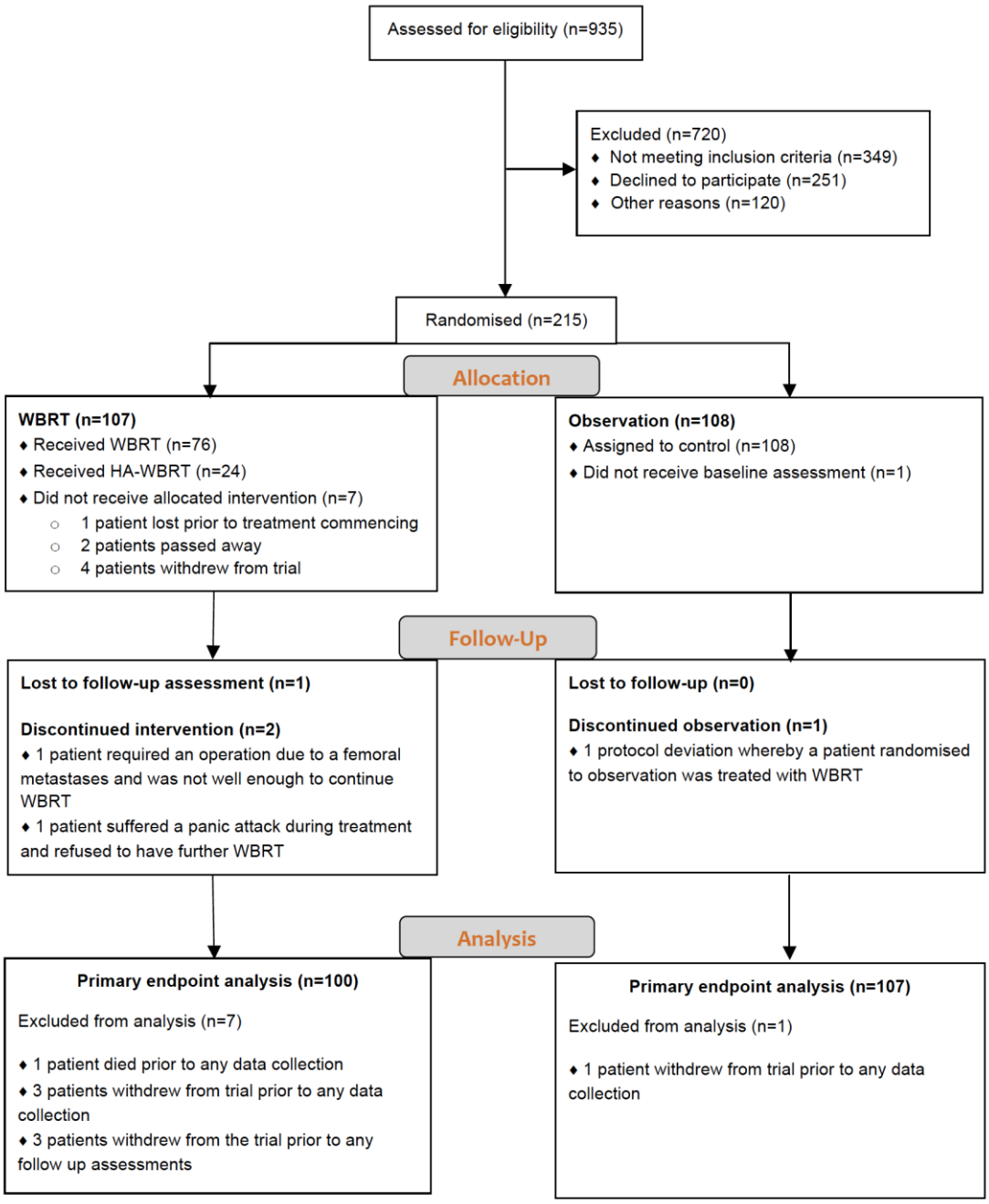


**Table 1a. Characteristics of patients at baseline**

| | Observation (n=107) | WBRT (n=100) |
|---|---|---|
| **Sex** | | |
| Male | 72 (67.3%) | 66 (66.0%) |
| Female | 35 (32.7%) | 34 (34.0%) |
| **Age** | | |
| Median (range) | 64 (27-83) | 63 (27- 88) |
| < 65 | 58 (54.2%) | 57 (57.0%) |
| ≥ 65 | 49 (45.8%) | 43 (43.0%) |
| **ECOG Performance Status** | | |
| 0 | 62 (57.9%) | 53 (53.0%) |
| 1 | 42 (39.3%) | 41(41.0%) |
| 2 | 3 (2.8%) | 6 (6.0%) |
| **Breslow thickness of the primary lesion (mm)** | | |
| <1 | 15 (14.0%) | 15 (15%) |
| 1.01-2 | 26 (24.3%) | 18 (18%) |
| 2.01-4 | 21 (29.6%) | 16 (16%) |
| >4 | 18 (16.8%) | 15 (15%) |
| Unknown primary | 24 (22.4%) | 32 (32%) |
| Missing | 3 | 4 |
| **Number of metastases** | | |
| 1 | 66 (61.7%) | 59 (59%) |
| 2-3 | 41 (38.3%) | 41 (41%) |
| **Presence of extracranial disease at baseline** | 72 (67.3%) | 67 (67%) |
| **Systemic therapy use at Baseline** | | |
| None | 82 (77.6%) | 77 (77.0%) |
| Chemotherapy | 11 (10.3%) | 12 (12.0%) |
| BRAF/Mek inhibitor | 3 (2.8%) | 6 (6%) |
| Immune checkpoint inhibitor | 10 (9.3%) | 5 (5.0%) |
| Topical/intralesional therapy | 1 (0.9%) | 0 (0.0%) |

**Table 1b: Characteristics of the baseline lesion(s) and local treatment details**

| Characteristics | Observation (N = 107) | WBRT (N = 100) |
|---|---|---|
| **Lesion 1** | N=107 | N=100 |
| Median of the maximal diameter (mm, range) | 19.0 (1, 68.0) | 24.0 (2, 70.0) |
| Surgery alone | 64 (59.8%) | 64 (64.0%) |
| SRS alone | 31 (29.0%) | 30 (30.0%) |
| Median diameter of stereotactic volume (mm, range) | 17 (5, 47) | 18 (2, 46) |
| Surgery and SRS | 11 (10.3%) | 6 (6.0%) |
| Missing | 1 | 0 |
| **Lesion 2** | N=41 | N=40 |
| Median of the maximal diameter (mm, range)) | 9.0 (1, 42.0) | 13.0 (3, 70.0) |
| Surgery alone | 9 (22.0%) | 13 (32.5%) |
| SRS alone | 30 (73.2%) | 24 (60.0%) |
| Median diameter of stereotactic volume (mm, range) | 13 (8.0, 25.0) | 13 (2.0, 65.0) |
| Surgery and SRS | 0 (0%) | 1 (2.5%) |
| Missing | 2 | 2 |
| **Lesion 3** | N=15 | N=14 |
| Median of the maximal diameter (mm, range) | 5 (1.0, 21.0) | 5 (3.0, 20.0) |
| Surgery alone | 0 | 0 |
| SRS alone | 14 (93.3%) | 14 (100%) |
| Surgery and SRS | 0 | 0 |
| Missing details | 1 | 0 |

**Table 2. Distant intracranial failure over the entire follow-up period and at specific time points**

| Follow up time points | WBRT (N = 100) | Observation (N = 107) | Odds ratio (95% CI) | P value |
|---|---|---|---|---|
| Within 3 months | 16/100 (16.0%) | 24/107 (22.4%) | 0.66 (0.33, 1.33) | 0.242 |
| Within 6 months | 29/100 (29.0%) | 44/107 (41.1%) | 0.58 (0.33, 1.04) | 0.068 |
| Within 9 months | 37/100 (37.0%) | 49/107 (45.8%) | 0.70 (0.40, 1.21) | 0.199 |
| Within 12 months | 42/100 (42.0%) | 54/107 (50.5%) | 0.71 (0.41, 1.23) | 0.222 |
| Over study period | 52/100 (52.0%) | 62/107 (57.9%) | 0.79 (0.45, 1.36) | 0.390 |

**Figure 2a. Cumulative incidence of distant intracranial failure during follow-up**

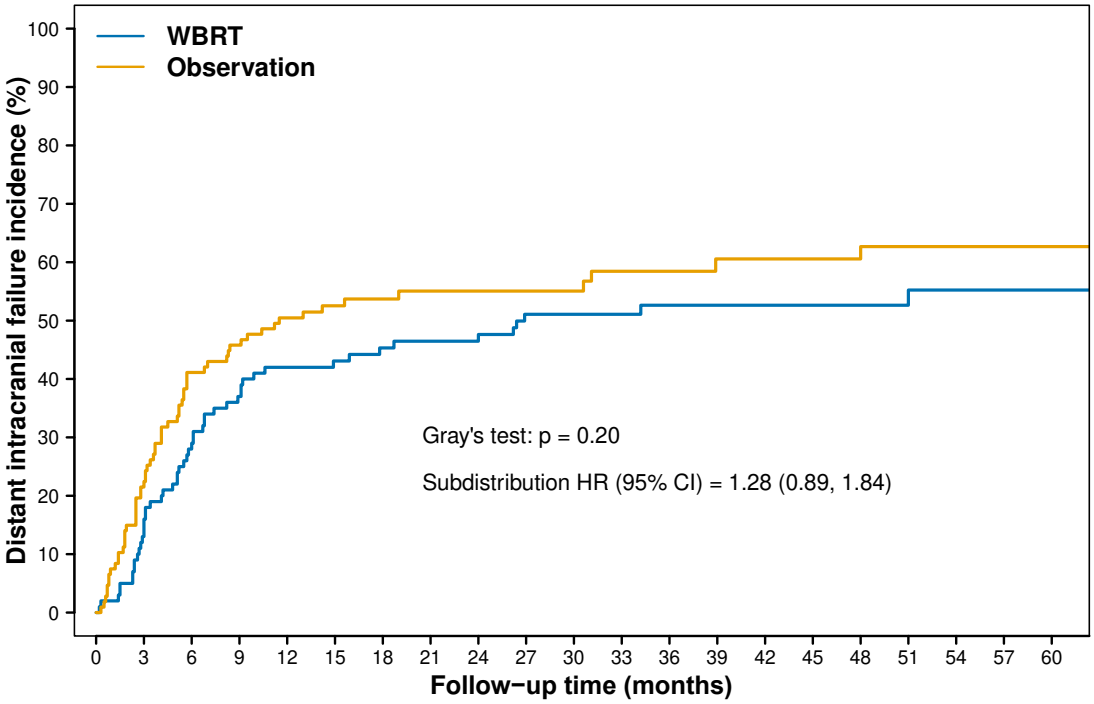


**Figure 2b. Cumulative incidence of local intracranial failure during follow-up**

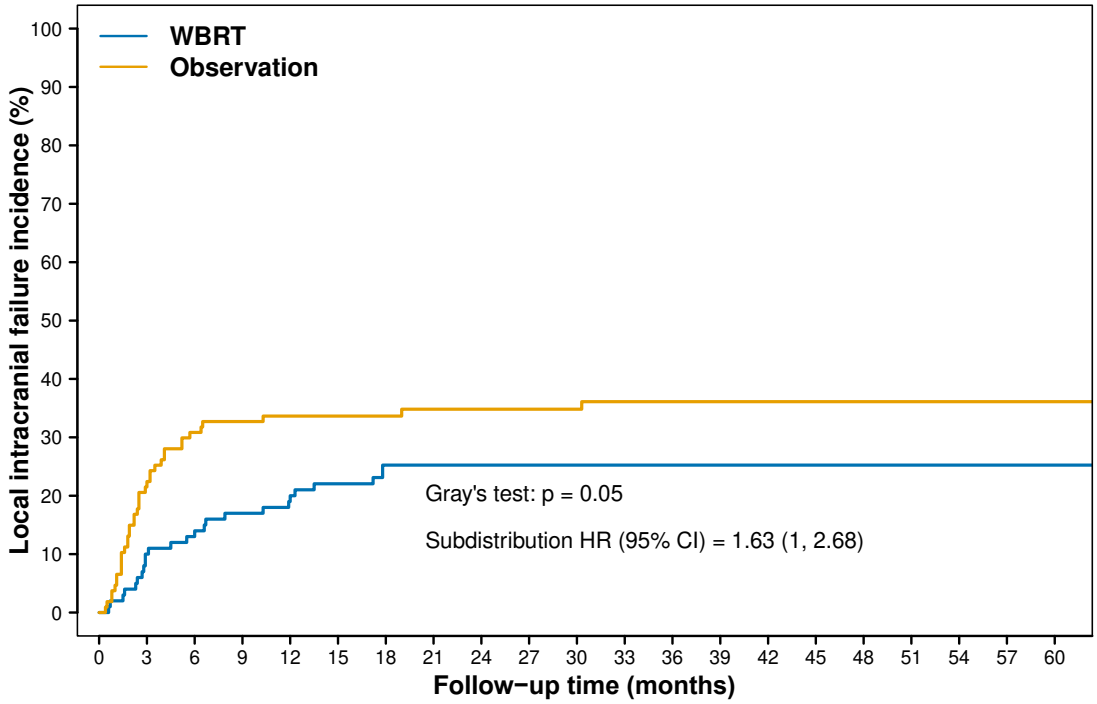
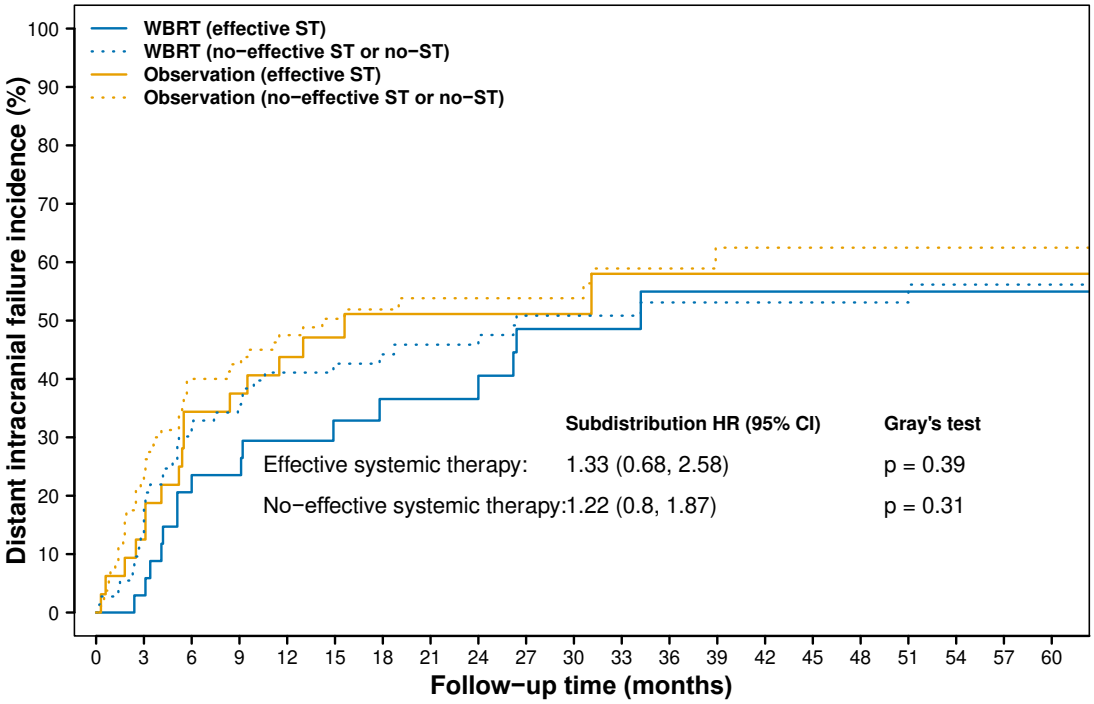


**Figure 2c. Cumulative incidence of distant intracranial failure during follow-up stratified by whether or not patients received systemic therapy before reaching primary endpoint**




*ST=systemic therapy. Effective systemic therapy was BRAF targeted therapy and/or immune checkpoint inhibitor. No-effective therapy was cytotoxic chemotherapy or intralesional therapy.

**Figure 2d. Cumulative incidence of intracranial failure (distant and local) during follow-up**

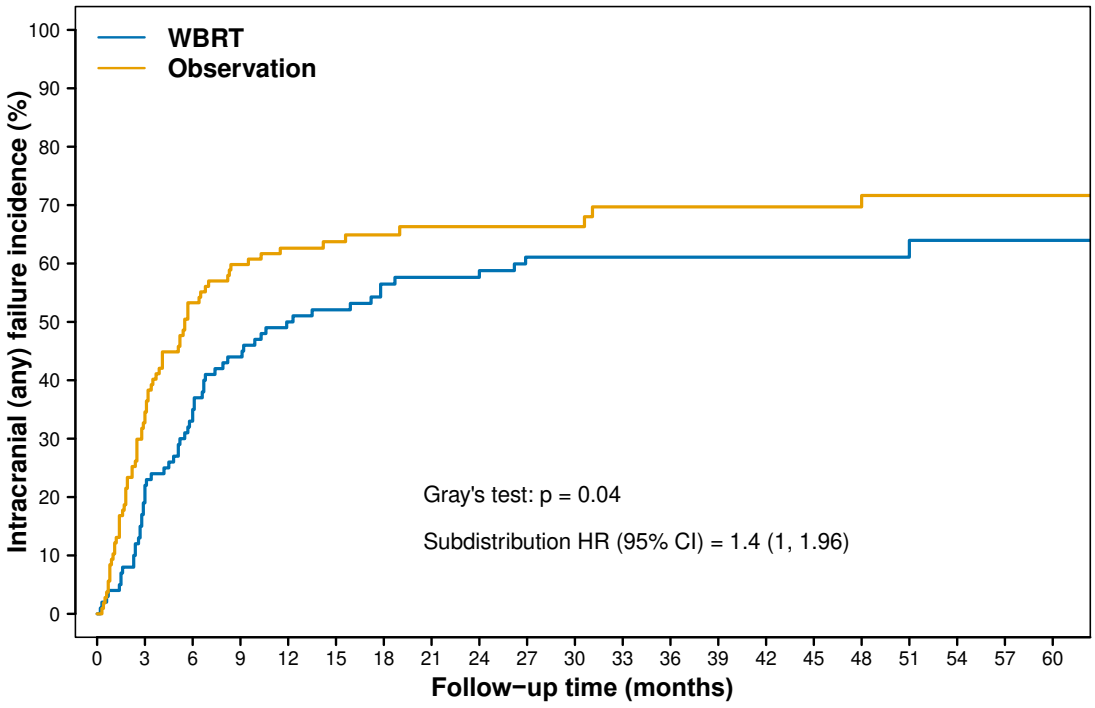
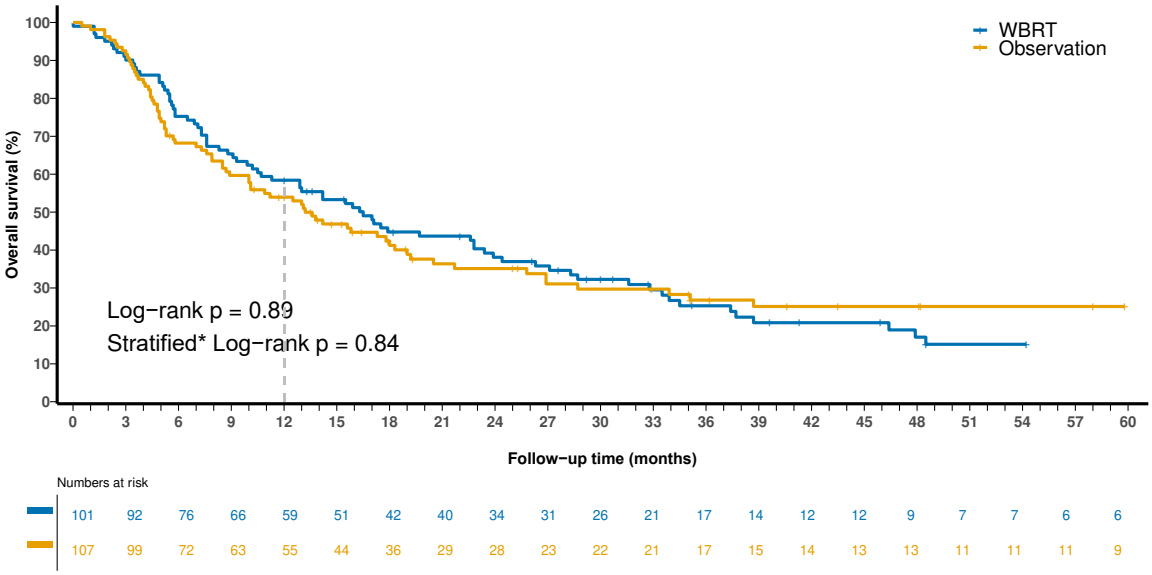


**Figure 3a. Kaplan-Meier estimates of overall survival according to treatment group**




*One WBRT patient was included in the overall survival analysis only as no baseline or intracranial follow up data were collected.

**Figure 3b. Cumulative incidence of death due to intracranial disease during follow-up**

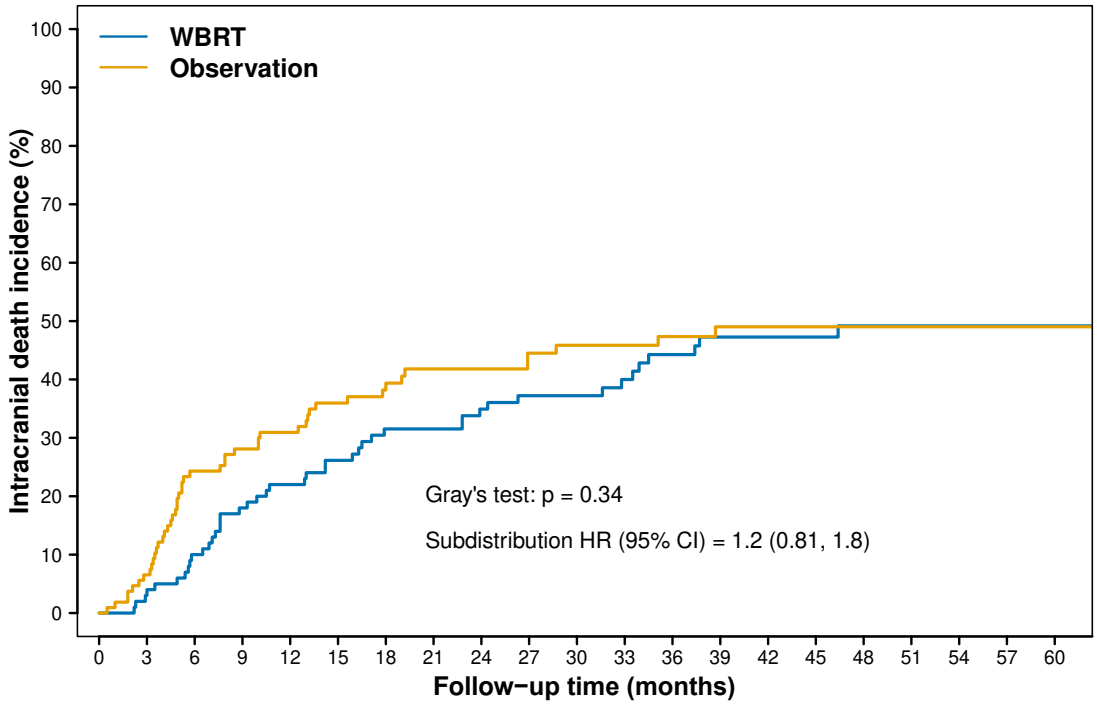
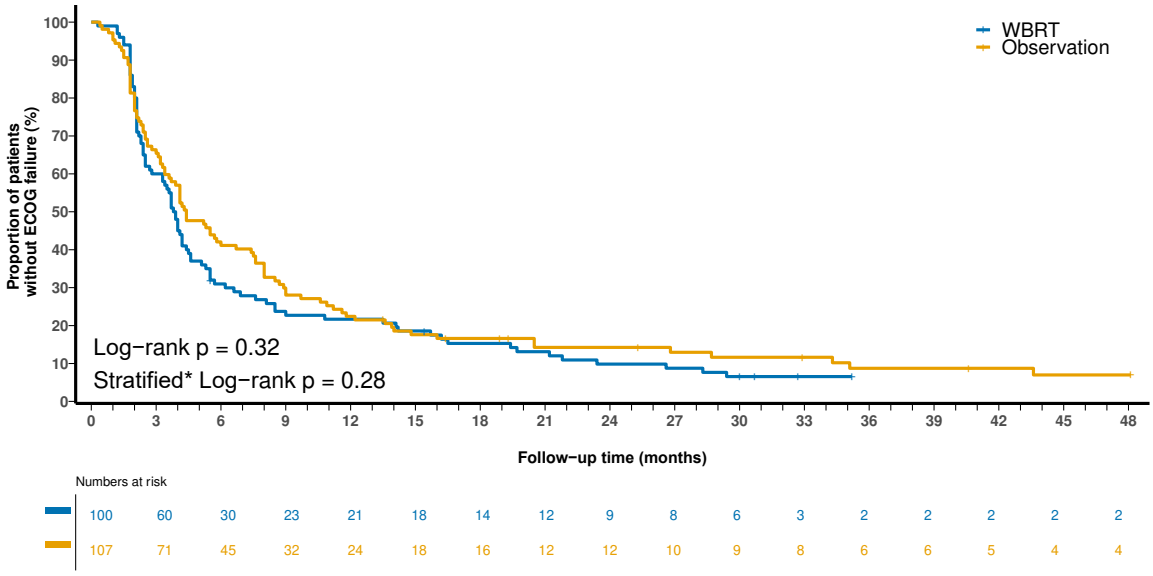



**Figure 3c: Time-to-deterioration in ECOG performance status during follow-up**




*ECOG failure is defined as the time that elapsed between randomization and the first recorded worsening in ECOG performance status.

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