Short-course palliative hypofractionated radiotherapy in patients with poor-prognosis high-grade glioma: quality-of-life outcomes from a prospective phase II study

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Abstract

Purpose: To report longitudinal quality-of-life (QoL) outcomes in patients with poor prognosis high-grade glioma (HGG) treated with palliative hypofractionated radiotherapy (RT).

Methods: Patients with poor-prognosis HGG based on age and performance status were accrued on a prospective study of short course palliative hypofractionated RT delivering 35Gy in 10 fractions over 2 weeks after written informed consent. European Organization for Research and Treatment of Cancer (EORTC) QoL core questionnaire (QLQ-C30) and brain cancer module (BN20) were used in English or validated Indian vernacular languages (Hindi and Marathi) for QoL assessment at baseline (pre-RT), conclusion of RT, 1-month post-RT and subsequently at 3-monthly intervals until disease progression/death. Summary QoL scores were compared longitudinally over time by related samples Friedman's two-way test.

Results: Forty-nine (89%) of 55 patients completed the planned course of hypofractionated RT. Longitudinal QoL data was available in 42 (86%) patients that constitutes the present study cohort. Median age of included patients comprising mainly of glioblastoma (81%) was 57 years with median baseline Karnofsky score of 60. Baseline QoL scores of included patients were significantly worse for several domains compared to historical institutional cohort of HGG patients treated previously with conventionally fractionated RT indicating negative selection bias. QoL scores remained stable for most domains after palliative hypofractionated RT with statistically significant improvements in fatigue (p=0.032), dyspnea (p=0.042) and motor dysfunction (p=0.036) over time.

Conclusion: Short-course palliative hypofractionated RT in patients with poor-prognosis HGG is associated with stable and/or improved QoL scores in several domains making it a viable resource-sparing regimen.

Introduction

Diffuse high-grade glioma (HGG) defined histologically as World Health Organization (WHO) grade III and IV gliomas [1] are the most frequent malignant primary brain tumors in adults [2] comprising 70% of all glial neoplasms. The contemporary standard of care for adult diffuse HGG is maximal safe resection followed by post-operative focal conformal radiotherapy (RT) plus chemotherapy [3,4]. However, despite aggressive multi-modality treatment, prognosis for most HGG patients particularly the elderly with glioblastoma (GBM) and/or those with suboptimal performance status remains dismal with median survival ranging between 6-9 months [5,6]. Age and performance status have consistently been demonstrated to impact upon outcomes in HGG/GBM and are included in all prognostic scoring systems [7-10]. A better understanding of molecular biology of adult diffuse glioma has led to refinements in classification and prognostication [11-13] in the modern era. In patients with brain tumors, functional neurological status can be more reliably assessed by combining a general performance score such as Karnofsky performance status (KPS) [14] with a neurological scale such as neurological performance

status (NPS) [15]. Performance status is closely related and reflective of health-related quality-of-life (QoL) in patients with HGG [16]. We have previously proposed a pragmatic system [9] for classifying adults with diffuse HGG into favourable versus poor prognostic categories based on a combination of age and performance status. All adults (≥18 years) with newly-diagnosed biopsy-proven HGG in poor performance status (KPS ≤40 and NPS ≥3) were deemed to have poor prognosis. Older adults (>50 years but ≤65 years) were considered as having poor prognosis, if their performance status was poor to suboptimal (KPS ≤60 and/or NPS ≥2). The elderly cohort (>65 years) was assigned poor prognosis even if they had up to fair performance status (KPS ≤80 and/or NPS ≥1), excluding only those with no deficits (KPS ≥90 and/or NPS=0) from this definition.

Adult patients with poor prognosis HGG have a unique clinical course which differs considerably from other advanced cancers in the form of early cognitive and functional decline, rapid neurologic deterioration posing end-of-life issues from the time of initial diagnosis, all of which can have disproportionately negative impact upon QoL [17]. Optimal management of this subset remains controversial and continues to evolve rapidly [9,18,19]. The goal of treatment is to prolong survival and preserve/improve QoL. There exists level 1 evidence [20] supporting the use of RT compared to best supportive care alone in newly-diagnosed elderly GBM. Oncological non-inferiority of hypofractionated RT (delivered over 1-3 weeks) compared to conventionally fractionated RT (treating over 5-7 weeks) in elderly GBM is also well established [21-23]. The addition of temozolomide (TMZ) chemotherapy to moderately hypofractionated RT further improves survival outcomes [24]. However, morbidity of aggressive multi-modality therapy and its potential detrimental impact upon QoL needs to be carefully considered in patients with limited life-expectancy. There had been a paucity of prospective QoL data in patients with HGG [25,26], possibly due to therapeutic nihilism further confounded by challenges associated with evaluating QoL in this subset due to the impact of tumor and treatment on patients' mental and neurological status. However, QoL reflecting the patients' own perspective - an important patient reported outcome measure (PROM) is now being increasingly considered for therapeutic decision-making in HGG [26,27]. We had previously reported a resource-sparing palliative hypofractionated RT regimen (35Gy in 7 fractions, 5Gy/fraction, delivered once weekly over 6 weeks) in adults with poor prognosis HGG [28]. Although, median survival of patients completing planned RT regimen was acceptable (7.4 months), the compliance to 6-weeks of therapy was poor (only 44%) with patients dropping out after every weekly fraction. Furthermore, longitudinal QoL data in patients with poor prognosis HGG is generally lacking. We therefore designed a prospective phase II study using continuous short-course hypofractionated RT (35Gy in 10 fractions over 2 weeks) to assess the compliance and efficacy of such regimen in patients with poor prognosis HGG and its longitudinal impact on health-related QoL. Herein, we report QoL outcomes from this single-institution cohort.

Materials And Methods

Patient selection: Patients with biopsy-proven poor prognosis HGG based on our previously proposed system [9] attending the outpatient clinic of an academic neuro-oncology unit of a tertiary-care comprehensive cancer center were screened for accrual on a prospective phase II study of short course

palliative hypofractionated RT (online supplementary file S1). Patients satisfying the eligibility criteria were treated with 35Gy in 10 fractions (3.5Gy/fraction, once daily, 5 fractions per week delivered in 2 weeks) on a 6MV linear accelerator using focal conformal techniques after written informed consent. Oral TMZ was not given concurrently during RT. However, patients with stable and/or improving performance status at first response assessment 1-month after palliative RT were started on oral adjuvant TMZ chemotherapy (150-200mg/m^2 for 5 days D1-D5) cycled at 4-weekly intervals for 6-12 cycles with dose modifications as appropriate.

QoL assessments: The European Organization for Research and Treatment of Cancer (EORTC) QoL core questionnaire (QLQ-C30 version 3) and brain cancer module (BN20) were used for QoL assessments [29,30] either in English or validated Indian vernacular languages (Hindi and Marathi) as appropriate. QoL was assessed longitudinally during, initially at baseline (pre-RT), at RT conclusion, at first response assessment (1-month post-RT) subsequently periodically on follow-up at 3-monthly intervals till clinico-radiological progression/death. Patients were encouraged to complete the questionnaires by themselves (self-administered) with occasional assistance from caregivers in case of neurological deficits or illiteracy. Scoring of QoL was done as per the standard recommendations outlined in EORTC scoring manual. Higher score in functional domains and lower scores in symptom domains suggest better QoL. For statistical analysis, all raw scores from single item and/or multi-item scales of the questionnaires were linearly transformed to a score ranging from 0 to 100. Change in scores of ≥10 points on any given scale are interpreted as being clinically meaningful, while ≥20 points change represents large effects.

Statistical analyses: Summary scores for QLQ-C30 and BN20 were calculated from raw scores as per EORTC scoring manual, ranging from 0 to 100 with 0 being the lowest score and 100 highest possible score. Shapiro-Wilks normality test was used to assess the normality of data, with data being considered skewed if $p<0.05$. For non-normally distributed data, related samples two-way Friedman test, the non-parametric equivalent of repeated measures analysis of variance was used to analyze differences in paired summary scores at any time-point compared to baseline. We first compared baseline QoL scores of the present study cohort for various domains with the baseline scores of corresponding domains from a historical institutional cohort [31] of 110 HGG patients treated previously with conventionally fractionated RT using the two-sample independent 't' test. We then analyzed summary QoL scores from the present study cohort longitudinally over time, at baseline (prior to RT), at conclusion of RT, at 1st response assessment (1-month post-RT) and periodically on follow-up using the Friedman's test. Any p-value <0.05 was considered as statistically significant. Survival outcomes included progression-free survival (PFS) and overall survival (OS). PFS was calculated from date of surgery till documented clinico-radiological progression while OS was calculated from diagnosis till death or last follow-up. All time-to-event analyses were done using the Kaplan-Meier method and reported as 1-year estimates with 95% confidence interval (CI). All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, Armonk, NY, USA) and R^{TM} Version 4.03 (R Corporation, Vienna). The study was reviewed and approved by our Institutional Ethics Committee (IEC) that functions in accordance with the Declaration of Helsinki and is registered with the Clinical Trials Registry of India

(CTRI/2012/11/003141). All participants provided written informed consent for participation in the study. No funding support was involved in the conduct, analysis, or reporting of the study.

Results

Between 2012 and 2016, we accrued 55 patients with newly-diagnosed biopsy-proven poor-prognosis HGG on our prospective phase II study of short course palliative hypofractionated RT after written informed consent. Forty nine of 55 (89%) patients completed the planned course of palliative hypofractionated RT as per protocol. Longitudinal QoL data was available in 42 of 49 (86%) patients that constitutes the present study cohort. Baseline patient and disease characteristics are summarized in Table 1. Median age of included patients comprising mainly of glioblastoma (81%) was 57 years with inter-quartile range (IQR) of 50-66 years and median baseline KPS of 60 (IQR=50-60). All patients were treated with anti-epileptic drugs for seizure prophylaxis as per our institutional policy. Dexamethasone was not used electively during RT, but, administered for clinico-radiological features of raised intracranial pressure, worsening neuro-deficits, and/or radiological evidence of moderate to severe edema (on recent post-operative/RT planning imaging). Following palliative hypofractionated RT, 28 (66.7%) patients were started on oral adjuvant TMZ, of which 13 (31%) patients completed 6 or more cycles.

QoL outcomes: A total of 146 completed QoL assessments were available from 42 patients in the present study cohort. QoL assessments at baseline and at conclusion of RT were available for all 42 included patients; 25 patients also completed third QoL assessment at first post-treatment evaluation (1-month) after RT. Subsequently however, significant attrition was noted over time with decreasing number of patients completing QoL assessments at 3-month (n=11) and 6-month (n=8) follow-up due to disease progression and/or death limiting the longitudinal QoL analysis to first 3 time-points (up to 1-month post RT) only. The mean baseline (pre-RT) QoL scores of the present study cohort (N=42) treated with palliative hypofractionated RT were significantly worse for global health status (p=0.029), physical functioning (p=0.025), communication deficit (p=0.007), dyspnea (p=0.004) and itchy skin (p<0.001) compared to corresponding baseline scores of our historical institutional HGG cohort (N=110) treated previously with conventionally fractionated RT (Figure 1) indicating negative selection bias in the present cohort. Domain-wise results of the QLQ-C30 functional scores over time are summarized graphically in Figure 2. Clinically meaningful improvements (≥10-point change) although not statistically significant were noted for most QLQ-C30 functional domains such as physical functioning, role functioning, emotional functioning, cognitive functioning, and global health status, excepting social functioning which remained stable at 1-month post-RT compared to baseline. The evolution of QLQ-C30 symptom scores over time is presented graphically in Figure 3. Both clinically and statistically significant improvement was noted at 1-month post-RT compared to baseline in fatigue (p=0.032) and dyspnoea (p=0.042). Clinically meaningful improvement, though not statistically significant was also seen for insomnia, while other QLQ-C30 symptoms such as nausea/vomiting, loss of appetite, constipation, diarrhea, and financial difficulty remained stable over time. Symptom scores from BN20 are illustrated graphically in Figure 4. Clinically and statistically significant improvement was seen in motor dysfunction (p=0.036), while other BN20 symptoms such as future uncertainty, visual disorder, communication deficit, headache, seizure,

drowsiness, hair loss, itchy skin, weakness of limbs, and bladder control remained largely stable over time. Global health status of the present study cohort is demonstrated by swimmers-lane plot (Figure 5), a graphical representation of the longitudinal trajectory of individual patient over respective follow-up time.

Survival outcomes: By the time of this analysis, all 42 patients had succumbed to disease progression. At a median follow-up of 8 months (IQR=3.5-11.5 months) for the present study cohort, Kaplan-Meier estimates of 1-year PFS and OS were 33.3% (95%CI: 21.7-51.1%) and 38.1% (95%CI: 25.9-56%) respectively yielding a median PFS of 8.4 months (95%CI: 6.5-13.2 months) and OS of 10.5 months (95%CI: 7.6-13.8 months) respectively (online supplementary file S2).

Discussion

Survival outcomes in patients with poor prognosis HGG (elderly and/or in suboptimal performance status) remains dismal with a median OS between 6-9 months despite aggressive multi-modality therapy [5,6]. Optimal management of this cohort lacks consensus and is dictated largely by personal/institutional biases and patient/care-giver preferences despite availability of evidence from various randomized controlled trials (RCTs) particularly in the elderly GBM population [20-24]. A systematic review and network meta-analysis demonstrated moderately hypofractionated RT (delivered over 3 weeks) with concurrent and adjuvant TMZ to be the most optimal and preferred regimen in elderly patients with newly-diagnosed GBM [32]. This was also corroborated by a recent Cochrane review [33] providing high-quality evidence that combined chemoradiotherapy prolongs survival in elderly people with GBM who are self-caring compared to RT or TMZ monotherapy.

Our prospective study assessing QoL outcomes in high-grade glioma patients treated with palliative hypofractionated RT demonstrates lower QoL scores at baseline (pre-RT) in several domains compared to a historical cohort of HGG patients treated previously with conventionally fractionated RT indicating negative selection bias. The lower baseline QoL scores in the present cohort possibly reflect more aggressive disease biology with resultant higher symptom burden and suboptimal performance status which dictated the choice of palliative fractionation. However, it was reassuring to note that such palliative hypofractionated RT was not associated with detrimental impact upon QoL in the short-term with most patients achieving stable/improved scores in most domains at 1-3 months after completion of planned RT.

Patients with HGG experience highly intrusive symptoms, cognitive and functional decline, and emotional and existential distress throughout their disease trajectory [34]. Caregiver burden is also substantial with limited evidence to guide palliative management. QoL in patients with HGG is already impaired at diagnosis when compared to the general population; however, both anti-glioma treatment and disease progression can cause further deterioration. Maintenance of QoL in HGG remains an important endpoint, particularly in patients with poor prognosis and limited life expectancy. However, reliable serial and longitudinal measurement of QoL in this subset is difficult and challenging due to various factors

including high dropout rates and/or inability to complete complex forms repeatedly. Palliative cranial irradiation can preserve and/or improve QoL by achieving tumor regression and providing growth arrest of rapidly growing brain tumor with resultant symptomatic relief; however, it might also lead to deterioration in QoL due to RT-induced acute toxicity such as nausea/vomiting, anorexia, fatigue, somnolence, dermatitis, and alopecia which are mostly self-limiting and reversible. Treatment-related changes (enhancement, necrosis, edema) in and around the tumor-bed occurring either during RT or more commonly 1-3 months later can cause significant neurologic worsening with profound negative impact upon QoL necessitating aggressive supportive therapy. Neurocognitive dysfunction following partial brain irradiation also leads to impairment in health-related QoL; however, it is generally a late effect of RT and manifests in a small subset of poor-prognosis HGG patients typically surviving beyond 9-12 months. The concepts of 'deterioration-free survival' and 'time-to-deterioration' are now being used as endpoints for measuring change in QoL as a time-to-event outcome [35]. Deterioration-free survival is defined as the time interval from diagnosis to deterioration in QoL either due to disease progression or death, whereas the time-to-deterioration excludes progressive disease as an event, better reflecting the possible impact of adverse effects of anti-glioma therapies on various domains of QoL [35]. The CODAGLIO (COmbining clinical trial DAtasets in GLIOma) project that captures QoL data of individual glioma patients assessed using QLQ-C30 and BN20 from previously published randomized controlled trials is the largest database interrogating the evolution of QoL throughout the disease trajectory. Recent analysis [35] from the CODAGLIO dataset involving 5539 patients (64% with GBM) reported 7.6 months as the median time from randomization to disease progression. Between 9-29% of patients deteriorated before disease progression on the evaluated QoL scales. When considering all scales simultaneously, 47% of patients deteriorated on 1 or more scale prior to progression. Median deterioration-free survival period ranged between 3.8-5.4 months while median time-to-deterioration varied from 8.2-11.9 months. Linear mixed model analysis demonstrated that poor performance status was the only factor independently associated with clinically relevant QoL deterioration while allocated treatment was not associated with QoL deterioration in the progression-free period [35]. Disease progression had the largest share as event in deterioration-free survival analysis (49-82%) compared with QoL deterioration in the absence of disease progression (9-25%) or death (8-35%) reaffirming the notion that recurrent/progressive disease remains the strongest driver of QoL decline in patients with HGG which accelerates substantially at relapse.

Strengths and limitations: The present analysis is one amongst the few prospective studies evaluating QoL longitudinally in poor-prognosis HGG patients treated with palliative hypofractionated RT. Patients were selected based on pre-specified eligibility criteria and treated uniformly with focal conformal RT techniques. Only patients with complete QoL data were analyzed without the need for missing data imputation. However, despite the above strengths, several limitations remain. There was significant patient attrition over time precluding assessment of the impact of palliative hypofractionated RT on QoL in the medium to long-term (3-6 months and beyond). None of the patients in our study received TMZ concurrently during short-course RT and only patients with stable/improved performance status after RT received adjuvant TMZ; this would be considered as sub-optimal therapy given that combined modality chemoradiotherapy (RT plus concurrent and adjuvant TMZ) is considered the current standard of care for

this subset. Our analysis of QoL was restricted to patients who completed their planned course of RT; it is possible that patients who were unable to comply with their planned treatment had worse QoL scores (both at baseline and during therapy) which is not reflecting in the present dataset. Although not used prophylactically, most patients received corticosteroids based on clinical/neurological status either during RT or subsequently on follow-up which might have contributed to symptomatic improvement reflecting in stable/improved QoL scores. The QoL forms were largely self-administered in our study; however, occasionally such forms might have been filled by care-givers raising some concerns regarding the veracity of assessment. We did not assess the QoL after documented clinico-radiological progression potentially introducing bias and confounding the interpretation of results. Finally, ours was a single-arm study with lack of appropriate controls for comparison.

Conclusion

Short-course palliative hypofractionated RT in patients with poor-prognosis HGG does not impair QoL in the short-term; but is rather associated with stable and/or improved QoL scores in several domains/symptom scales making it a viable resource-sparing alternative regimen.

Statements & Declarations

The study is registered with Clinical Trials Registry of India (CTRI/2012/11/003141) and was duly approved by the Institutional Ethics Committee (IEC) of Tata Memorial Centre, Mumbai, India that functions in accordance with the Declaration of Helsinki. No source of funding was involved in the conduct, analysis, or reporting of the study. None of the authors have any conflicts of interest to declare.

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References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol*. 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106.
2. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2021;23(12 Suppl 2):iii1-iii105. doi:10.1093/neuonc/noab200.
3. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G. High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25 (Suppl 3):iii93-101. doi:10.1093/annonc/mdu050.
4. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. 2021;18(3):170-186. doi:10.1038/s41571-020-00447-z.
5. Iwamoto FM, Reiner AS, Panageas KS, Elkin EB, Abrey LE. Patterns of care in elderly glioblastoma patients. *Ann Neurol*. 2008;64(6):628-634. doi:10.1002/ana.21521.
6. Saeed H, Tseng YD, Lo SS. Narrative review of palliative hypofractionated radiotherapy for high grade glioma. *Ann Palliat Med*. 2021;10(1):846-862. doi:10.21037/apm-20-1246.
7. MRC Brain Tumor Working Party. Prognostic factors for high-grade malignant glioma: Development of a prognostic index. A report of the Medical Research Council Brain Tumor Working Party *J Neurooncol*. 1990;9(1):47-55. doi: 10.1007/BF00167068.
8. Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three radiation therapy oncology group malignant glioma trials. *J Natl Cancer Inst*. 1993;85(9):704-710. doi:10.1093/jnci/85.9.704.
9. Gupta T, Sarin R. Poor-prognosis high-grade gliomas: Evolving an evidence-based standard of care. *Lancet Oncol*. 2002;3(9):557-564. doi:10.1016/S1470-2045(02)00853-7.
10. Li J, Wang M, Won M, et al. Validation and simplification of the radiation therapy oncology group recursive partitioning analysis classification for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2011;81(3):623-630. doi:10.1016/j.ijrobp.2010.06.012.
11. Bell EH, Pugh SL, McElroy JP, et al. Molecular-based recursive partitioning analysis model for glioblastoma in the temozolomide era a correlative analysis based on NRG Oncology RTOG 0525. *JAMA Oncol*. 2017;3(6):784-792. doi:10.1001/jamaoncol.2016.6020.

12. Yang Y, Yao M, Long S, et al. Prognostic Nomograms for Primary High-Grade Glioma Patients in Adult: A Retrospective Study Based on the SEER Database. *Biomed Res Int*. 2020:1346340. doi:10.1155/2020/1346340.
13. Sharma A, Graber JJ. Overview of prognostic factors in adult gliomas. *Ann Palliat Med*. 2021;10(1):863-874. doi:10.21037/apm-20-640.
14. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma: With particular reference to bronchogenic carcinoma. *Cancer*. 1948;1(4):634-656. doi:10.1002/1097-0142(194811)1:4<634.
15. MRC Working Party. A study of the effect of misonidazole in conjunction with radiotherapy for treatment of grades 3 and 4 astrocytoma. A report from the MRC Working Party on misonidazole in gliomas. *Br J Radiol*. 1983;56(669):73-82. doi: 10.1259/0007-1285-56-669-673.
16. Brown PD, Ballman KV, Rummans TA, et al. Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. *J Neurooncol*. 2006;76(3):283-291. doi:10.1007/s11060-005-7020-9.
17. Crooms RC, Goldstein NE, Diamond EL, Vickrey BG. Palliative care in high-grade glioma: A review. *Brain Sci*. 2020;10(10):1-24. doi:10.3390/brainsci10100723.
18. Farina P, Lombardi G, Bergo E, Roma A, Zagonel V. Treatment of malignant gliomas in elderly patients: A concise overview of the literature. *Biomed Res Int*. 2014;2014. doi:10.1155/2014/734281.
19. Pellerino A, Bruno F, Internò V, Rudà R, Soffietti R. Current clinical management of elderly patients with glioma. *Expert Rev Anticancer Ther*. 2020;20(12):1037-1048. doi:10.1080/14737140.2020.1828867.
20. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for Glioblastoma in the Elderly. *N Engl J Med*. 2007;356(15):1527-1535. doi:10.1056/nejmoa065901.
21. Roa W, Brasher PMA, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. *J Clin Oncol*. 2004;22(9):1583-1588. doi:10.1200/JCO.2004.06.082.
22. Malmström A, Grønberg BH, Marosi C et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol*. 2012;13(9)(Sep 1):916-926. doi: 10.1016/S1470-2045(12)70265-6.
23. Roa W, Kepka L, Kumar N, et al. International Atomic Energy Agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol*. 2015;33(35):4145-4150. doi:10.1200/JCO.2015.62.6606.
24. Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. *N Engl J Med*. 2017;376(11):1027-1037. doi:10.1056/nejmoa1611977.
25. Cheng JX, Zhang X, Liu BL. Health-related quality of life in patients with high-grade glioma. *Neuro Oncol*. 2009;11(1):41-50. doi:10.1215/15228517-2008-050.
26. Dirven L, Aaronson NK, Heimans JJ, Taphoorn MJB. Health-related quality of life in high-grade glioma patients. *Chin J Cancer*. 2014;33(1):40-45. doi:10.5732/cjc.013.10214.

27. Rosenlund L, Degsell E, Jakola AS. Moving from clinician-defined to patient-reported outcome measures for survivors of high-grade glioma. *Patient Relat Outcome Meas*. 2019;10:267-276. doi:10.2147/prom.s179313.
28. Gupta T, Dutta D, Trivedi S, Upasani M, Jalali R, Sarin R. Assessment of compliance to treatment and efficacy of a resource-sparing hypofractionated radiotherapy regimen in patients with poor-prognosis high-grade gliomas. *J Cancer Res Ther*. 2010;6(3):272-277. doi:10.4103/0973-1482.73353.
29. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
30. Osoba O, Aaronson N, Zee B, Sprangers M, Te Velde A. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committes of the NCI of Canada Clinical Trials Group. *Qual Life Res*. 1997;6(2):103-108. doi: 10.1023/a:1026429831234.
31. Budrukkar A, Jalali R, Dutta D, et al. Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. *J Neurooncol*. 2009;95(3):413-419. doi:10.1007/s11060-009-9939-8.
32. Kalra B, Kannan S, Gupta T. Optimal adjuvant therapy in elderly glioblastoma: results from a systematic review and network meta-analysis. *J Neurooncol*. 2020;146(2):311-320. doi:10.1007/s11060-019-03375-w.
33. Hanna C, Lawrie TA, Rogozińska E, et al. Treatment of newly diagnosed glioblastoma in the elderly: a network meta-analysis. *Cochrane Database Syst Rev.* 2020;3(3):CD013261. doi: 10.1002/14651858.CD013261.pub2.
34. Crooms RC, Johnson MO, Leeper H et al. Easing the Journey-an Updated Review of Palliative Care for the Patient with High-Grade Glioma. *Curr Oncol Rep*. 2022;24(4):501-515. doi: 10.1007/s11912-022-01210-6.
35. Coomans MB, Dirven L, Aaronson N, et al. Factors associated with health-related quality of life (HRQoL) deterioration in glioma patients during the progression-free survival period. *Neuro Oncol*. 2022;(April):1-11. doi:10.1093/neuonc/noac097.

Table

Table 1: Baseline patient and disease characteristics of the study cohort (N=42)

Characteristics		*Number of patients (%)*
Gender	Male	25 (59.5%)
	Female	17 (40.5%)
Age distribution (at diagnosis)	36-45 years	7 (16.7%)
	46-55 years	12 (28.6%)
	56-65 years	13 (31.0%)
	66-75 years	9 (21.3%)
	76-85 years	1 (2.4%)
Karnofsky Performance Status	40-50	20 (47.6%)
	60-70	18 (42.9%)
	80-90	4 (9.5%)
Histological grade	Grade III	8 (19.0%)
	Grade IV	34 (81.0%)
Anatomic location of tumor	Frontal	12 (28.6%)
	Parietal	12 (28.6%)
	Temporal	16 (38.0%)
	Occipital	1 (2.4%)
	Thalamic	1 (2.4%)
Recursive Partitioning Analysis (RPA) class	RPA class IV	12 (28.6%)
	RPA class V	20 (47.6%)
	RPA class VI	10 (23.8%)

Supplementary File S1

Supplementary File S1 is not available with this version.

File S1: Clinical study protocol

Figures

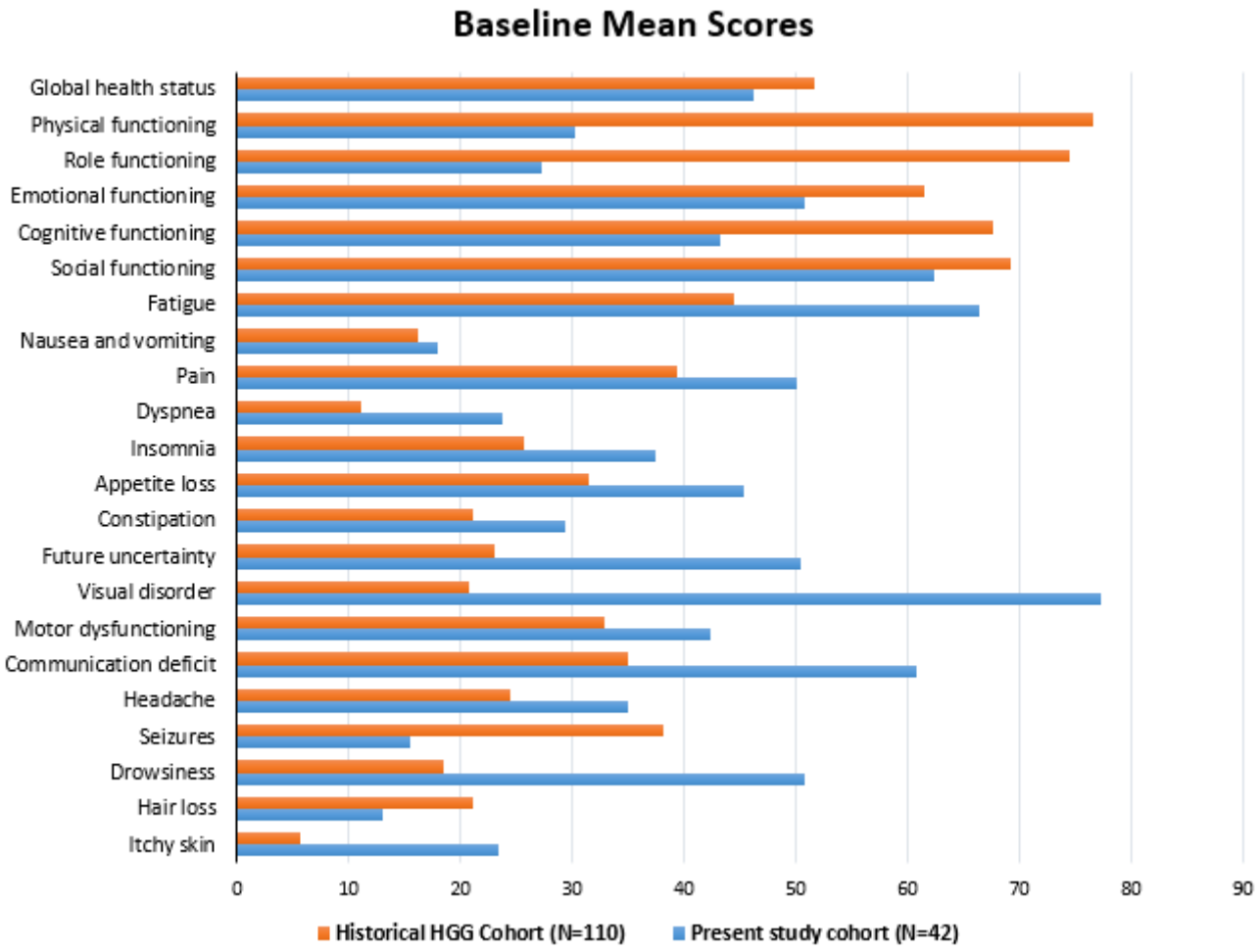
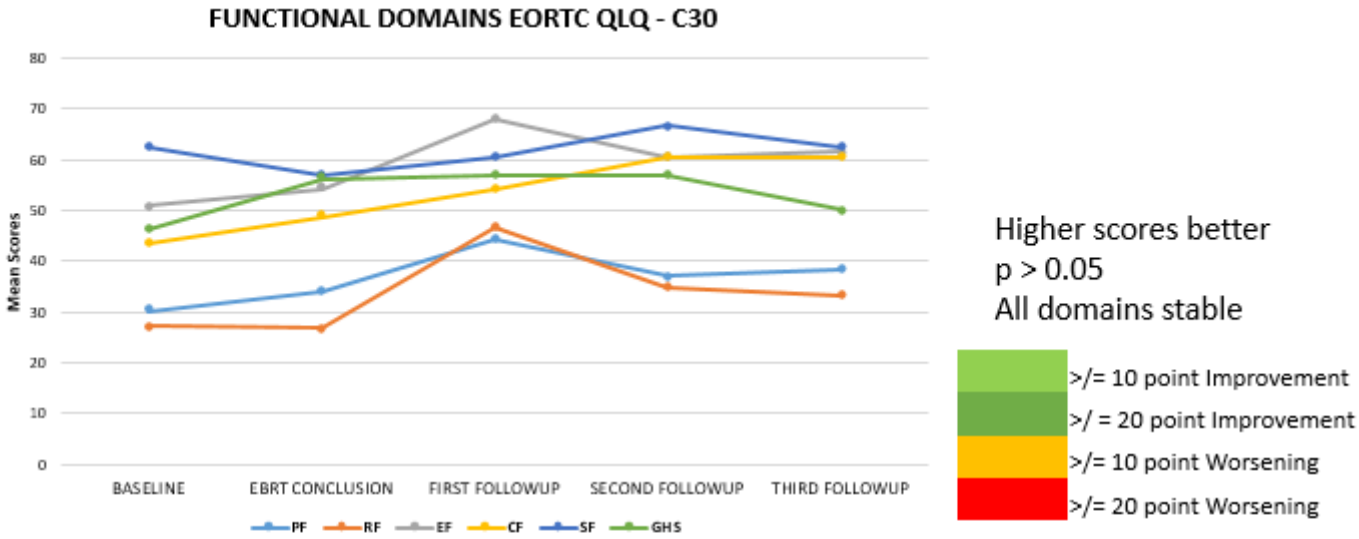


Figure 1

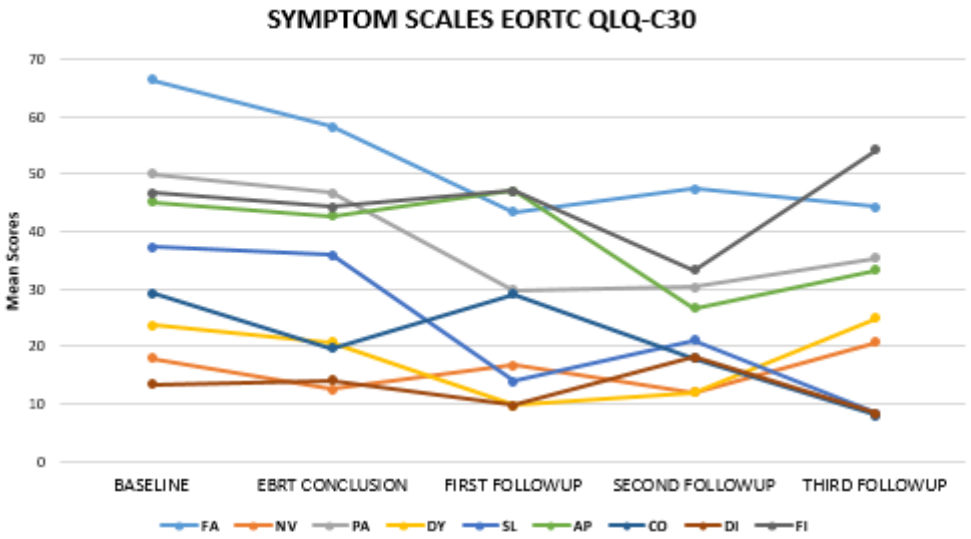
Mean baseline quality-of-life (QoL) scores of patients with poor prognosis high grade glioma (HGG) treated with palliative hypofractionated radiotherapy (present study cohort) compared to patients treated previously with normofractionated radiotherapy (historical HGG cohort). Higher scores in functional domains and lower scores in symptom scales denote better QoL. Note worse QoL at baseline in the present study cohort compared to historical HGG cohort reflecting higher symptom burden and suboptimal performance status dictating the choice of palliative fractionation



	PF	RF	EF	CF	SF	GHS
BASELINE	30	27	51	43	62	46
EBRT CONCLUSION	34	27	54	49	57	55
FIRST FOLLOWUP	44	47	68	54	60	57
SECOND FOLLOWUP	37	35	61	61	67	57
THIRD FOLLOWUP	38	33	62	60	63	50

Figure 2

Mean scores of various functional domains of quality-of life questionnaire (QLQ-C30) assessed at baseline, conclusion of palliative hypofractionated external beam radiotherapy (EBRT), and subsequently longitudinally on follow-up at 1, 3, and 6-months after EBRT. Note stable and/or clinically improved scores in physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF) and global health status (GHS) over time



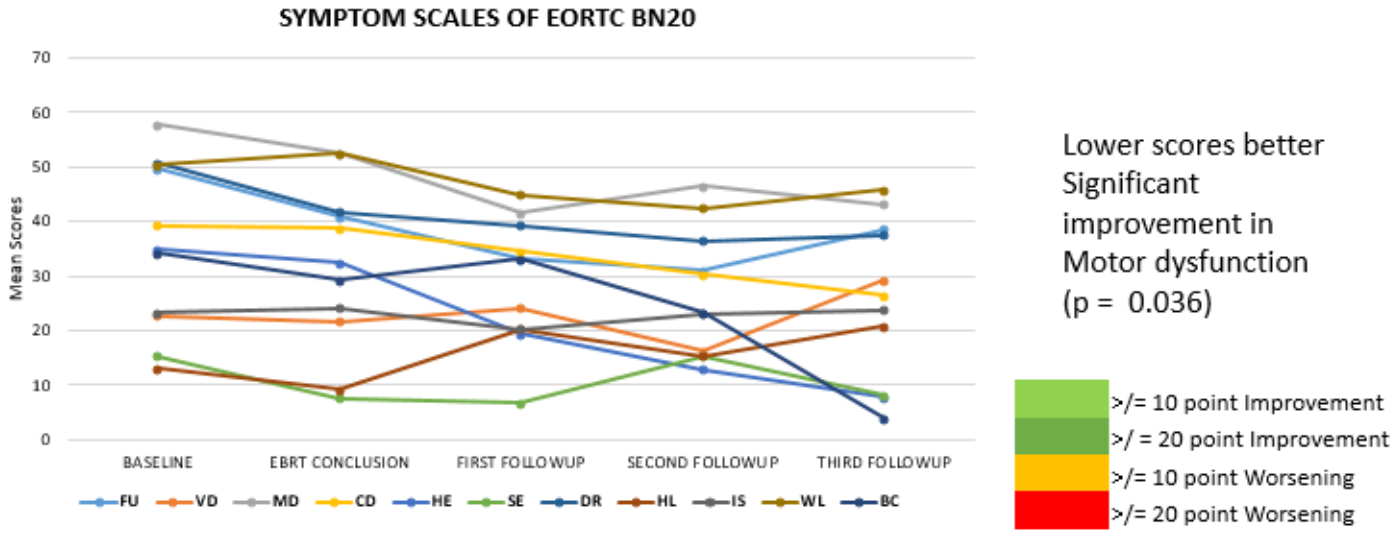
Lower scores better
Significant improvement in fatigue (p =0.032), dyspnea (p =0.042)

>/= 10 point Improvement
>/ = 20 point Improvement
>/= 10 point Worsening
>/= 20 point Worsening

	FA	NV	PA	DY	SL	AP	CO	DI	FI
BASELINE	66	18	50	24	37	45	29	13	47
EBRT CONCLUSION	58	13	47	21	36	43	20	14	44
FIRST FOLLOWUP	44	17	30	10	14	47	29	10	47
SECOND FOLLOWUP	48	12	30	12	21	27	18	18	33
THIRD FOLLOWUP	44	21	35	25	8	33	8	8	54

Figure 3

Mean symptom scores of quality-of life questionnaire (QLQ-C30) assessed at baseline, conclusion of palliative hypofractionated external beam radiotherapy (EBRT), and subsequently longitudinally on follow-up at 1, 3, and 6-months after EBRT. Note statistically significant improvement in scores for fatigue (FA) and dyspnoea (DY), while scores for nausea/vomiting (NV), pain (PA), insomnia (SL), appetite (AP), constipation (CO), diarrhoea (DI) and financial difficulty (FI) remained largely stable



	FU	VD	MD	CD	HE	SE	DR	HL	IS	WL	BC
BASELINE	50	77	58	61	35	15	51	13	23	50	34
EBRT CONCLUSION	59	78	52	61	33	8	42	9	24	53	29
FIRST FOLLOWUP	67	76	42	65	19	7	39	20	20	45	33
SECOND FOLLOWUP	31	16	47	30	13	15	36	15	23	42	23
THIRD FOLLOWUP	39	29	43	26	8	8	38	21	24	46	4

Figure 4

Mean symptom scores of brain cancer module (BN20) assessed at baseline, conclusion of palliative hypofractionated external beam radiotherapy (EBRT), and subsequently longitudinally on follow-up at 1, 3, and 6-months after EBRT. Note statistically significant improvement in scores for motor dysfunction (MD), while scores for future uncertainty (FU), visual disorder (VD), communication deficit (CD), headache (HE), seizure (SE), drowsiness (DR), hair loss (HL), itchy skin (IS), weakness of limbs (WL) and bladder control (BC) remained largely stable over time

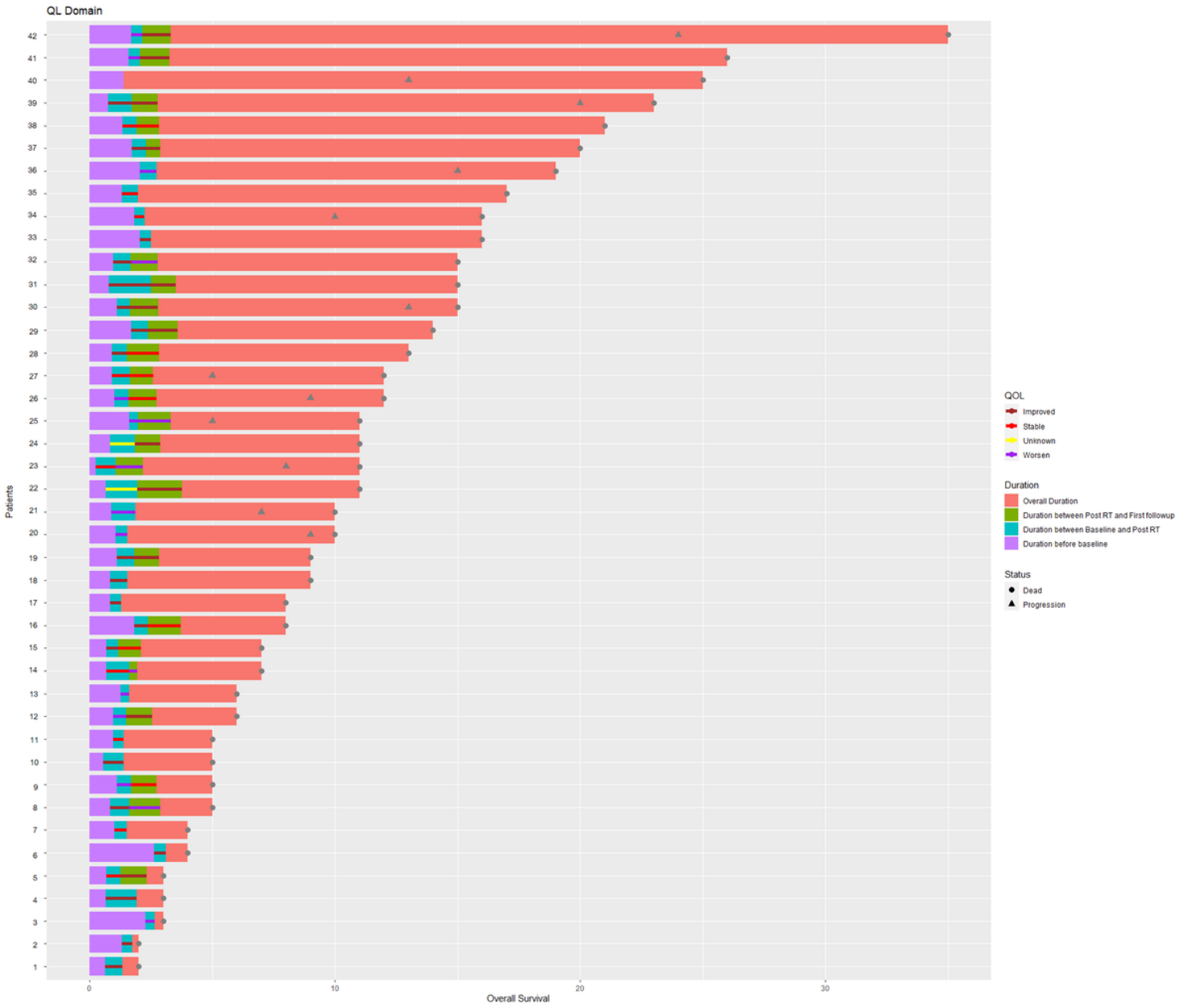


Figure 5

Swimmers-lane plot representing longitudinal quality-of life (QoL) trajectory of individual patients in the present study cohort for global health status. The graph is a bar diagram showing the length of follow-up for each patient with indicators of disease progression (triangle) and death (circle)

Supplementary Files

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- S2KMcurves.tiff