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Survival Outcome of Anaplastic Astrocytoma patients post radiation- Retrospective Single InstitutionStudy

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Abstract:Aim:*To retrospectively assess the survival outcome of Anaplastic Astrocytoma patients with patientand treatment related factors among those who underwent post-operative radiation with or without chemotherapy in our hospital.*
Material and methods: *Medical records of Anaplastic Astrocytoma patients treated in our hospital during 2013-2017 were analyzed from our hospital records. Patient and treatment related factors were recorded and assigned according to RTOG RPA classification. Statistical analyses were performed using Kaplan Meier, Log rank test and Cox regression models.*
Results: *The analysis of 84 Anaplastic Astrocytoma patients showed median age of 45yrs, with male predominance; KPS≥70 in 80%, surgery biopsy(27%),near-total excision(15.5%),partial excision(10.5%),subtotal excision(47%). Post-surgery radiation dose was 60Gy in 76%patients.Cox regression models on comparison with other groups revealed an association of survival with RT alone (HR, 2.634; 95% CI, 1.476-4.699; p=0.001), with TMZ alone did not reveal any significant association (HR, 1255885.813; 95% CI, 0-41.365E94;p=0.892) and with RT+TMZ revealed a significant association (HR, 0.199; 95% CI, 0.111-0.357; p<0.001).Overall median survival was 17.493months and overall 2yr survival was 51.4%.*
Conclusions: *Though this retrospective study shows significant improvement in overall survival of Anaplastic Astrocytoma patients treated with Radiation and temozolomide further prospective trials are essential to prove this data.*
Key words:*Anaplastic Astrocytoma, radiation, chemo- temozolomide, survival.*

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I. Introduction

As per Global Cancer Statistics 2018, GLOBOCAN issued by International Association of Cancer Registries associated with WHO, 298,851 new brain and nervous system cases reported in India in 2018 with death about 241,037 cases[1]. Among the Malignant Neuroepithelial tumors, ANAPLASTIC ASTROCYTOMA (AA) and GLIOBLASTOMA MULTIFORME (GBM) are common. Glioblastoma Multiforme being the most aggressive tumor with poor survival rates[3,4]. According to the central brain tumor registry of United States Anaplastic Astrocytoma constitutes 1.7% of the central nervous system tumors.[2]

The treatment of choice for GBM includes maximum safe resection followed by radiation with concurrent temozolomide followed by adjuvant temozolomide[3,4]. The potential benefit of adding temozolomide with radiation in Anaplastic Astrocytoma patients is still not clear. In spite of this post-surgery radiation with concurrent temozolomide has showed increased survival rates in Anaplastic Astrocytoma patients in many trials[4,5,6.]

In this current study we retrospectively analyzed the survival outcomes and predictive factors of Anaplastic Astrocytoma patients treated in our hospital with radiation and temozolomide after surgery

II. Material And Methods

This retrospective clinical study conducted in our hospital with approval from our institutional ethical committee. The records of 84 Anaplastic Astrocytoma patients treated in our hospital between the years 2013 – 2017 was analyzed from our hospital data. Biopsy proven Anaplastic Astrocytoma patients age >18yrs, who underwent surgery followed by postoperative radiotherapy with or without chemotherapy are included. Data regarding age, gender, performance status, mental status and extent of surgery followed by postoperative radiation with or without temozolomide followed by adjuvant temozolomide details were collected. Tumor characteristics like location, size, extent and associated edema were identified with MRI/CT brain. Studies for molecular profiling were not routinely performed in our hospital during study period. Follow up details regarding survival and status of the patients was collected from the medical records and through telephonic

conversation whenever necessary. Patients are then assigned according to the RTOG RPA classification[7] mentioned in table no.1

Table no.1 Criteria for RTOG classification of AA patients

RTOG RPA Classification	Criteria for assignment to classification			
	Age	Mental status	KPS	Duration of symptoms prior to diagnosis
I	< 50 years	Normal		
II	≥ 50 years		≥ 70	> 3 months
III	< 50 years	Abnormal		
IV	≥ 50 years		≥ 70	≤ 3 months
V	≥ 50 years	Normal	< 70	
VI	≥ 50 years	Abnormal	< 70	

RTOG RPA=Radiation Therapy Oncology Group recursive partitioning analysis; KPS=Karnofsky performance status.

Radiotherapy and chemotherapy Treatment

After maximal safe surgery (biopsy/partial/subtotal/near total resection), postoperative radiotherapy was started within 3- 4weeks. A total dose of 60Gy in1.8/ 2Gy per fraction over a period of 6-7 weeks was delivered in 3DCRT/IMRT in Linear accelerator machine. Patients who received chemo were given concurrent temozolomide (TMZ - 75mg/m^2/day) 7 days per week one hour before radiation and 6 cycles of adjuvant TMZ(150- 200mg/m^2/day)day1 to day 5(every 28 days). Patients were monitored by complete haemogram, liver function test, and renal function test periodically. Only minor (grade 1&2) haematological toxicities were seen in patients who received TMZ. No treatment breaks required due to treatment toxicity. Patients'responses were assessed at 6 weeks after completion of treatment by MRI brain and monthly follow up was done.

Statistical analysis:

Data were entered in MS Excel and analysis was done using SPSS 16.0 version. Data were presented as percentages since the variables were categorical in nature. Kaplan Meier test was done to estimate the survival probability of patient undergone different treatment modalities. Log rank test was done to compare the survival probabilities of different treatment modalities. Cox regression was done to estimate the hazard ratio for each intervention.

Model 1 analyzed the association of survival in patients that received RT alone vs others (TMZ alone or RT+TMZ)

Model 2 analyzed the association of survival in patients that received TMZ alone vs others (RT alone or RT+TMZ)

Model 3 analyzed the association of survival in patients that received RT+TMZ vs others (RT alone or TMZ alone)

Hazards ratios and 95% confidence intervals were reported.

III. Result

The analysis of 84 patients in this study, the patient related and treatment related baseline characteristics are mentioned in table no.2and table no.3. Among the 84 patients, 14 patients where unfit for radiation due to poor performance status; 6 patients didn't receive any treatment and 8 patients received only TMZ chemotherapy. Also there was 7 patients with prior irradiation history for lesions like low grade glioma, diffuse astrocytoma. The dose of radiation given was 54Gy; there was no history of chemotherapy usage. Hence these patients represent secondary anaplastic astrocytoma.

Among the 70 patients in radiation, 6 patients didn't complete the full dose of radiation 60Gy and expired during treatment due to medical causes. Remaining 64 patients completed radiation dose 60Gy; 41 patients received RT with concurrent TMZ and 23 patients received RT alone. The 41 patients who received RT with concurrent TMZ where given post RT chemo with TMZ, only 13 patients completed entire 6 cycles remaining patients didn't complete because of progression of disease and other medical conditions.

The Log rank test shows significant difference in survival among three treatment groups ($p<0.001$). The median survival time for patients who treated with RT alone, TMZ alone and RT+TMZ were 10 months, 2 months and 28 months respectively.

Overall median survival was 17.493 months and overall 2 year survival was 51.4%.Cox regression model 1 revealed an association of survival with RT alone when compared to other groups (HR, 2.634; 95% CI, 1.476-4.699; p=0.001), model 2 with TMZ alone did not reveal any significant association when compared to

other groups (HR, 1255885.813; 95% CI, 0-41.365E94; p=0.892) and model 3 with RT+TMZ revealed a significant association when compared to others(HR, 0.199; 95% CI, 0.111-0.357; p<0.001). figure no.1

Cox regression analysis for RTOG RPA classification shows RPA I with HR0 .629(95% CI 0.366-1.081); RPA II HR0.349 (95% CI0.156 -0.780); RPA III HR 34.997 (95% CI 3.173-385.966); RPA IV HR 2.180 (95% CI1.118-4.249); RPAV HR 7.903 (95%CI 2.557-24.425); RPA VI HR 39.112(95% CI 9.206-166.167). figure no.2. The class RPA III and RPA VI has very high HR with minimal survival whereas RPA II has maximum survival outcome. Overall comparison proved significant p value(<.001).

The overall 2yr survival are represented in figure 3 and 4 are consistent with the results above.

Table no: 2 Patient Characteristics

	VARIABLES	NO(%)
AGE	20-29	5(6%)
	30-39	17(20%)
	40-49	18(21%)
	50-59	25(30%)
	60-69	19(23%)
SEX	MALE	45(53.5%)
	FEMALE	39(46.5%)
KPS	≥70	67(80%)
	<70	17(20%)
DURATION OF SYMPTOMS BEFORE SURGERY	<3MONTHS	31(37%)
	>3 MONTHS	53(63%)
MENTAL STATUS	NORMAL	72(86%)
	ABNORMAL	12(16%)

Table no: 3 Treatment characteristics

		NO (%)
SURGERY	EXCISION BIOPSY	23(27%)
	NEAR TOTAL EXCISION	13(15.5%)
	PARTIAL EXCISION	9(10.5%)
	SUB TOTAL EXCISION	39(47%)
RADIATION	NOT RT	14(17%)
	<30Gy	6(7%)
	60Gy	64(76%)
PRIOR RADIATION(54Gy)	YES	7(8%)
	NO	77(92%)
CHEMOTHERAPY	TMZ WITH RT	47
	ONLY TMZ	8
POST RT CHEMO	TMZ 6CYCLES	13
	<6CYCLES	28

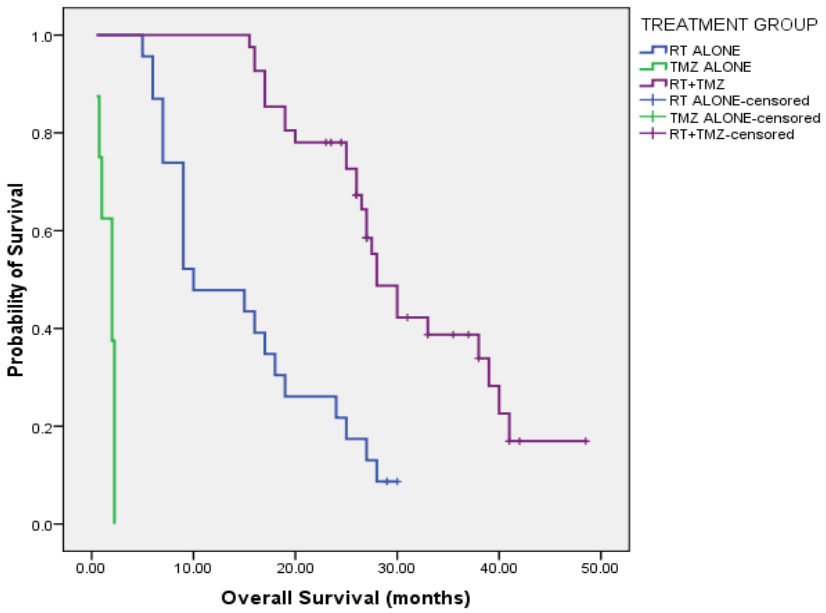

Figure 1– overall survival of anaplastic astrocytoma patients depending on treatment modalities

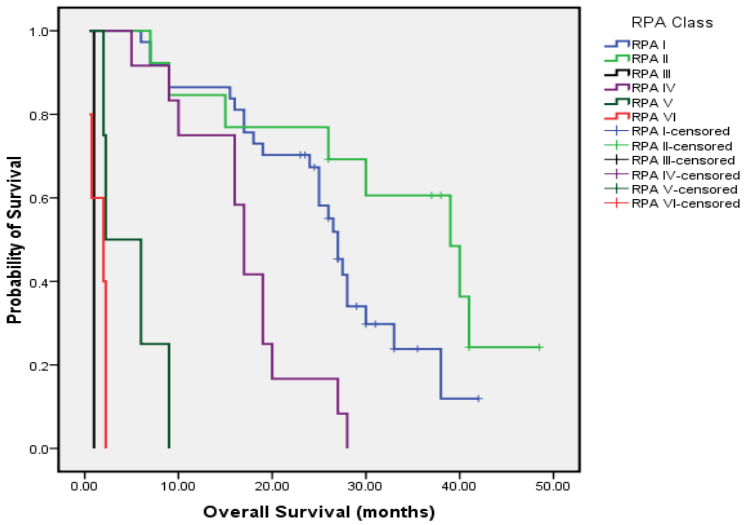

Figure 2 – overall survival of anaplastic astrocytoma patients depending on RTOG RPA classification.

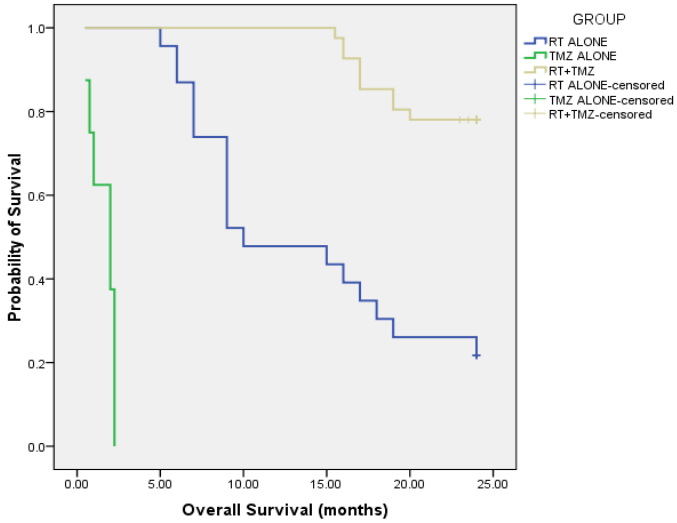

Figure 3 – 2yr overall survival dependingon treatment modalities.

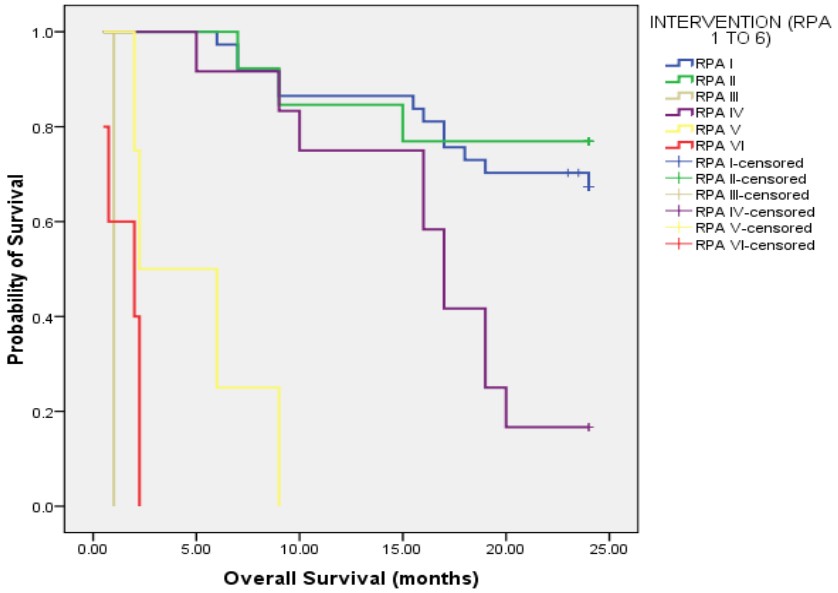

Figure 4 – 2yr overall survival depending on RTOG RPA classification.

IV. Discussion

The RTOG RPA classification of Curran et al[7] has been widely used in many clinical trials. In that trial several prognostic factors like age, performance status, duration of symptoms, mental status, surgery, extent of resection determines the outcome of patients. Also in this study 18% of the patients belonged to astrocytoma with anaplastic or atypical foci. The validation of RTOG RPA by Scott et al[8], a cohort study retrospectively proved the significance of RPA classification indicates poor prognosis in patients with RPA V and VI categories. Similar to this study, our study also proves poor prognosis in RPA category VI with survival less than two months.

Several studies have proved the effect of TMZ in GBM patients. EORTC 22981 Stupp et al[9], a randomized phase III trial in GBM patients showed median survival of 14.6 months for postoperative radiation with concurrent and adjuvant TMZ versus 12.1 months for postoperative radiation alone.

The comparative studies with postoperative radiation alone or with chemotherapy has clearly showed the prognostic factors like performance status, extent of surgery before radiation plays a major role in survival outcome[10,11]

Retrospective study of survival of AA patients by Christopher et al[12], at MSKCC 126 patients were assigned according to RTOG RPA classification. The results showed median survival was 31 months with 2yr OS was 58%. RTOG RPA class was associated with survival ($p<0.001$, but the use of TMZ during or after RT was not ($p>0.05$).

Retrospective study by Shonka et al[13], comparison of outcomes of 163 AA patients RT alone, RT with TMZ ,RT followed by TMZ showed Median overall survival (OS) was 5.7 years, and did not differ significantly by treatment group**.** The 3-year PFS rate was 0.37 (95 % CI: 0.24–0.50) among patients treated with CRT, compared to 0.55 (95 % CI: 0.42–0.66) among patients treated with RT-C, and 0.62 (95 % CI: 0.46–0.75) among patients treated with RT alone (log-rank $p = 0.010$). Pair wise comparison after adjustment for multiplicity revealed that the difference existed between CRT and RT groups (adjusted $p = 0.033$), and between CRT and RT-C groups (adjusted $p = 0.050$), but no difference existed between the RT and RT-C groups**.**

Another retrospective study by Roy et al[14], compared the prognostic factors and survival outcome in the era prior to TMZ (pre cohort) and after TMZ (post cohort).Survival was longer in the post cohort (37 mon, 24–64) than pre cohort (27 mon, 19–40; HR 0.75, 0.53–1.06, $p = 0.11$). Multivariate analysis controlling for age, Karnofsky performance status, and extent of resection revealed a 36 % reduced risk of death (HR 0.64, 0.44–0.91, $p = 0.015$) in patientstreated post cohort. This retrospective review found survival in newly diagnosed patients with AA improved with the addition of temozolomide to standard radiation.

The EORTC 26951 shows the effectiveness of adjuvant PCV in adjuvant oligodendrogliomaa and the CATNON trial interim results also shows effectiveness of adjuvant temozolomide in non 1p/19q deletion, these trials could not be compared with our study since molecular profiling are not done.[15,16,17]

The analyses of AA patients in our institution to determine the patient related prognostic factors and treatment factors, clearly shows the effectiveness of concurrent TMZ with radiation.

In our present study, we have assigned patients according to RTOG RPA classification, more than 50% of patients were >40yrs of age, with male predominance; Karnofsky performance status >70 in 80% of patients with normal mental status in 86% of patients. Extent of surgery prior to radiation plays a major role in outcome of patients has discussed in trials above, in our study subtotal excision in 47% of patients. Most of the patients completed 60Gy EBRT; very few patients had grade 2 toxicity with TMZ. Our study shows significant improvement in survival with RT + TMZ with survival of 28months. Overall median survival was 17.493 months and overall 2 year survival was 51.4%.

Major drawbacks of this study are small cohort of patients, retrospective study; also molecular profile analyses are not done during study period. The major studies with adjuvant TMZ in newly diagnosed AA patient require molecular profiling[14,15]; though present study clears shows significant improvement with survival on addition of TMZ with RT further prospective phase III trials are essential to prove its outcome.

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