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ARTICLE

A Comparative Survival Evaluation and Assessment of Interclassification Concordance in Adult Supratentorial Astrocytic Tumors

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Classification and grading of astrocytic tumors has been the subject of several controversies and no universally accepted classification system is yet available. Nevertheless, acceptance of a common system is important for assessing prognosis as well as easy comparative evaluation and interpretation of the results of multi-center therapeutic trials. We report the results of a single center study on comparative survival evaluation along with assessment of interclassification concordance in 102 cases of supratentorial astrocytic tumors in adults (≥16 years of age). Hematoxylin and eosin (H&E) stained slides of these 102 cases were reviewed independently by two pathologists and each case classified or graded according to four different classification systems viz. Kernohan, Daumas-Duport (SAM-A), TESTAST-268 and WHO. The histological grading was then correlated with the survival curves as estimated by the Kaplan-Meier method. The most important observation was that similar survival curves were obtained for any one grade of tumor by all the four classification systems. Fifty three of the 102 cases (51.9%) showed absolute grading concordance using all 4 classifications with maximum concordant cases belonging to grades 2 and 4. Intra-classification grade-wise survival analysis revealed a statistically significant difference between grade 2 and grades 3 or 4, but no difference between grades 3 and 4 in any of the classification systems. It is apparent from the results of this study that if specified criteria related to any of the classification systems is rigorously adhered to, it will produce comparable results. Hence, preferential adoption of any one classification system in practice will be guided by the relative ease of histologic feature value evaluation with maximum possible objectivity and reproducibility. We recommend the Daumas-Duport (SAM-A) system since it appears to be the simplest, most objectivized for practical application and highly reproducible with relative ease. (Pathology Oncology Research Vol 6, No 1, 46–52, 2000)

Keywords: Brain tumors, astrocytic tumors, classification, grading, survival

Introduction

The classification of astrocytic tumors by histological typing and grading has been one of most common important parameters used for prognostic assessment. However, several existing systems with relative merits and demerits are in use and a single consensus system is yet to emerge. Kernohan first introduced a 4 tier grading system[6] which was claimed to have a good survival correlation.[7,21] while others observed the contrary.[2,3,5,12,15,20] Ringertz[13] considered Kernohan's 4-tier grading system exaggerated and recommended a 3-tier grading system. The World Health Organization (WHO) classification of gliomas, first introduced in 1979[21] and subsequently modified in 1993[9] included histological typing with assignment of grade for individual histologic type of tumor. Daumas-Duport et al[3] proposed a 4-tier grading system of astrocytomas, known as St. Anne/Mayo grading for astrocytomas (SAM-A). The criteria delineated for grading were however different from those of Kernohan et al.[6] A good survival correlation

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for the Daumas-Duport grading system has been reported.[8] In 1992, Schmitt and Oberwittler[16] reported a computer-aided semi-objectivized 4-step numerical classification of astrocytomas (TESTAST 268) based on five histologic and three non-histologic parameters. The advantages of this numerical classifier compared to subjective grading were standardized approach, high reproducibility and transparency of the features on which the assessment was based. Further application of quantitative morphometry for the histologic variables of TESTAST 268 classifier was found to eliminate any residual inter-observer variability.[18] A significant survival difference between grade 3 and grade 4 tumors, however, could not be observed.[16]

At present, adoption of any one of the existent classification systems by a particular center appears to be rather arbitrary. We report in this communication the results of a single center study on comparative survival evaluation along with assessment of inter-classification concordance or discordance level using Kernohan, Daumas-Duport (SAM-A), TESTAST 268 and WHO classification systems in 102 cases of adult supratentorial astrocytic tumors.

Material and Methods

A total of 102 supratentorial astrocytic tumors in adults (≥ 16 years) treated in the Department of Neurosurgery of this Institute during 15 years period (1980–1994) were included in the study. Cases with inadequate surgery, non-compliance to post-surgical radiotherapy or inadequate follow up information, and those dying due to causes unrelated to the tumor were excluded. A further 37 cases were required to be excluded when review of slides from the files of Department of Pathology showed presence of scant or necrotic tissue only or presence of a component of oligodendroglioma, ependymoma or neoplastic ganglion cells. All the patients included underwent complete or subtotal tumor excision followed by post-operative radiotherapy and had adequate follow up information available. Pilocytic astrocytomas and subependymal giant cell astrocytomas were not included for the obvious reason that their biologic behavior is different.[14]

Age, sex, site of the tumor and survival status were recorded in each case. Histologic review and evaluation were done by two of us (CS & AKK) independently, without the knowledge of the original diagnosis or clinical data including follow up information on survival. Each case was histologically typed and/or graded as per the described specified criteria of the four classification systems of Kernohan,[6] SAM-A,[3] TESTAST-268[16] and WHO.[9] Software necessary for TESTAST-268 malignancy grading was kindly provided by Prof. H.P. Schmitt (Institute of Neuropathology, University of Heidelberg, Germany). In case of discordance in the review results of two patholo-

Table 1. **Inter-classification survival comparison**

	Classification & grades	*Survival in months*			
		Range	*Mean ± s.e.*	*Median*	*95% confidence interval for median*
2	T	12.0–189.6	75.6 ± 10.3	46.8	36.0–62.4
	SAM	24.0–189.6	88.0 ± 12.3	54.0	42.0–112.8
	K	12.0–189.6	75.3 ± 10.4	46.8	36.0–62.4
	WHO	24.0–189.6	87.8 ± 12.2	54.0	39.6–112.8
3	T	6.0–90.0	25.2 ± 3.6	18.0	15.6–21.6
	SAM	12.0–51.6	26.3 ± 4.0	24.0	18.0–30.0
	K	2.4–90.0	24.9 ± 4.2	17.5	15.6–18.0
	WHO	12.0–90.0	30.6 ± 5.3	24.0	18.0–34.8
4	T	2.4–33.6	13.5 ± 1.6	12.5	9.6–15.6
	SAM	2.4–90.0	21.3 ± 2.5	15.6	14.4–18.0
	K	4.8–33.6	15.9 ± 1.2	15.5	13.2–18.0
	WHO	2.4–52.8	18.8 ± 1.9	15.6	14.4–18.0

Table 2. **Intra-classification survival for various grades**

	Classification & grades	*Survival in months*			
		Range	*Mean ± s.e.*	*Median*	*95% confidence interval for median*
T	2	12.0–189.6	75.6 ± 10.3	46.8	36.0–62.4
	3	6.0–90.0	25.2 ± 3.6	18.0	15.5–21.6
	4	2.4–33.6	13.5 ± 1.6	12.5	9.6–15.6
SAM	2	24.0–189.6	88.0 ± 12.3	54.0	42.0–112.8
	3	12.0–51.6	26.3 ± 4.0	24.0	18.0–30.0
	4	2.4–90.0	21.3 ± 2.5	15.6	14.4–18.0
K	2	12.0–189.6	75.3 ± 10.4	46.8	36.0–62.4
	3	2.4–90.0	24.9 ± 4.2	17.5	15.6–18.0
	4	4.8–33.6	15.9 ± 1.2	15.5	13.2–18.0
WHO	II	24.0–189.6	87.8 ± 12.2	54.0	39.6–112.8
	III	12.0–90.0	30.6 ± 5.3	24.0	18.0–34.8
	IV	2.4–52.8	18.8± 1.9	15.6	14.4–18.0

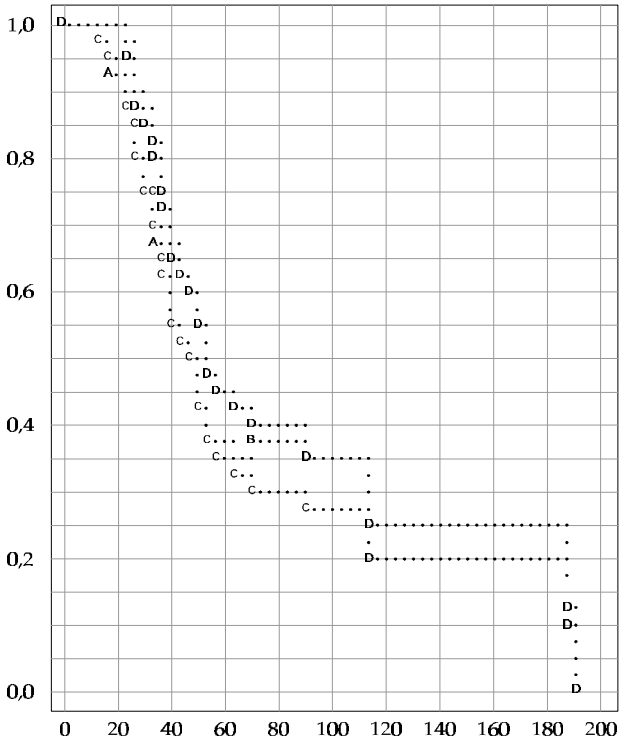

Figure 1. Showing intra-classification survival comparison for grade 2 tumors (A: Kernohan, B: SAM, C: TESTAST 268, D: WHO).

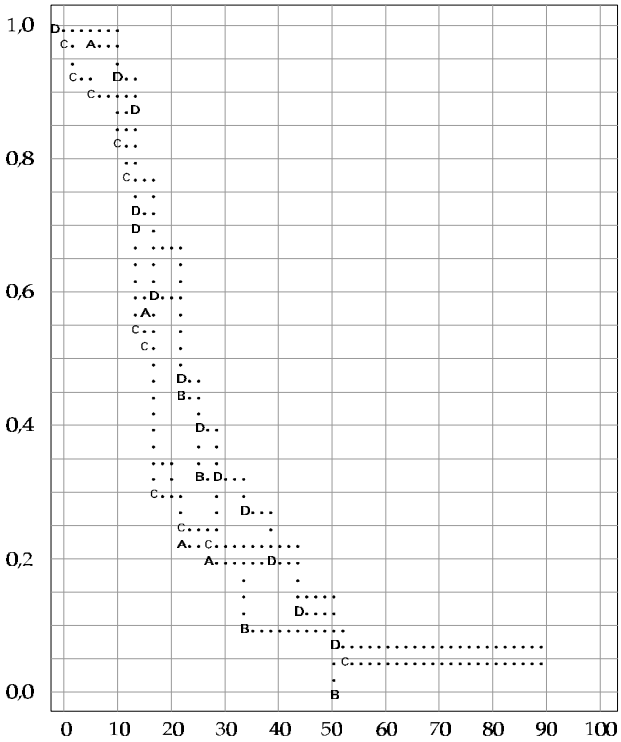

Figure 2. Showing intra-classification survival comparison for grade-3 tumors (A: Kernohans, B: SAM, C: TESTAST 268, D: WHO).

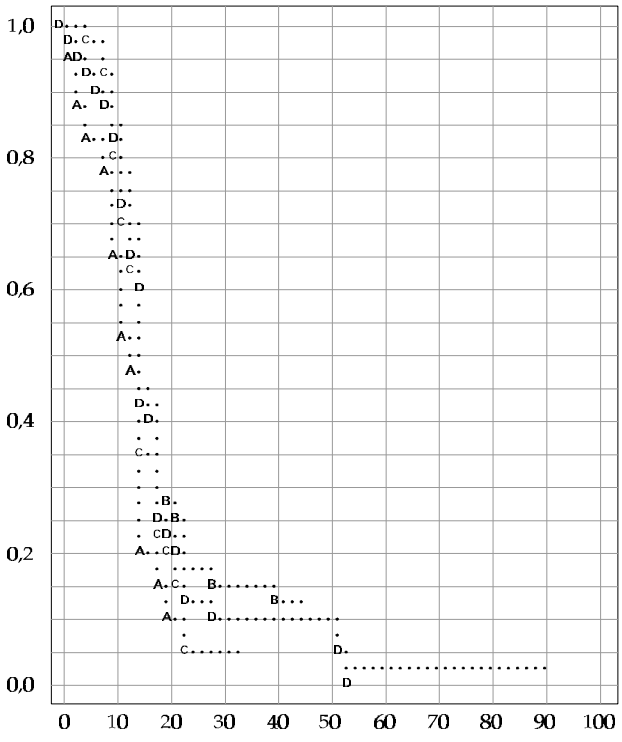

Figure 3. Showing intra-classification survival comparison for grade-4 tumors (A: Kernohans, B: SAM, C: TESTAST 268, D: WHO).

gists, the case was reviewed together with critical evaluation of the histologic features and a consensus reached after discussion.

Survival time was calculated from the date of first operation to the date of death or the most recent follow-up evaluation. The time of onset of symptoms was not taken for survival period calculation, since reliable precise information was not available from the patients in many cases. Survival curves were estimated by the Kaplan-Meier method using BMDP statistical software, release 7.0 (BMDP Statistical Software Inc., 1440 Sepulveda Blvd, Los Angeles, CA 90025, USA).

Nineteen (18.6%) were alive at last review of follow up censored at last visit. Generalised savage (Mantel–Cox) and Log rank test were used to determine any difference in the survival curves between tumor grades.

Results

Patient age at diagnosis ranged from 17 to 72 years (median: 36 years) with a male to female ratio of 2.8:1. Distribution of tumors according to site was as follows: frontal 39; temporal 23; parietal 20; frontoparietal 9; temporoparietal 5; insular region 3; frontotemporal 2 and parietooccipital 1.

WHO histological types of astrocytoma, anaplastic astrocytoma and glioblastoma multiforme were regarded

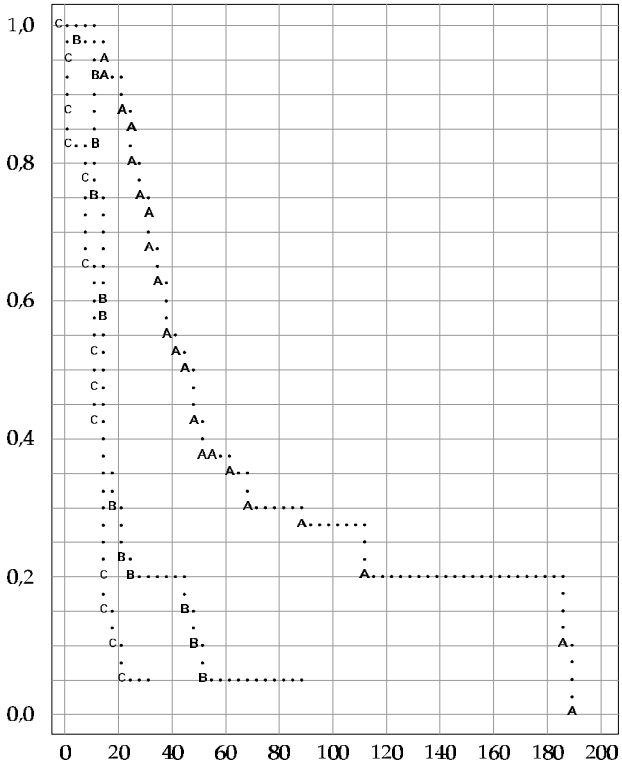

Figure 4. Showing comparative survival of grade 2 (A), 3 (B), and 3 (C) in Kernohan system.

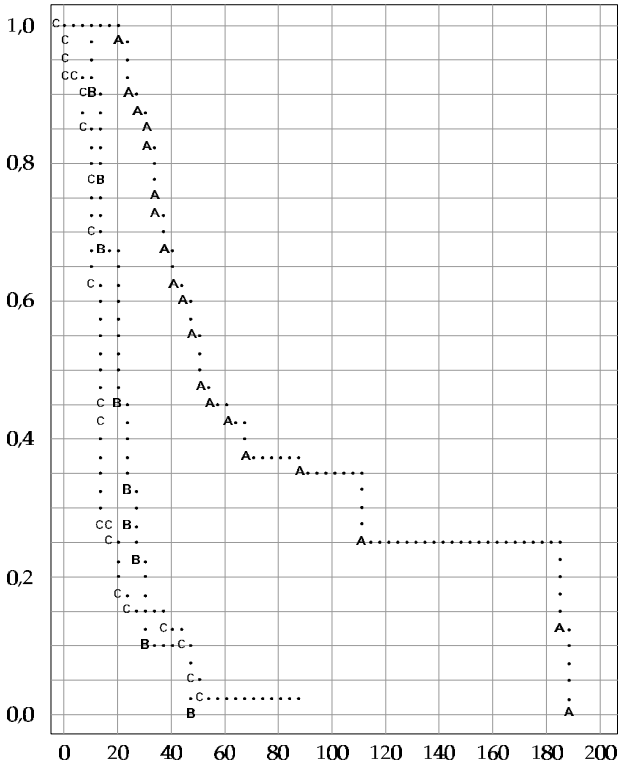

Figure 5. Showing comparative survival of grade 2 (A), 3 (B), and 4 (C) in SAM system.

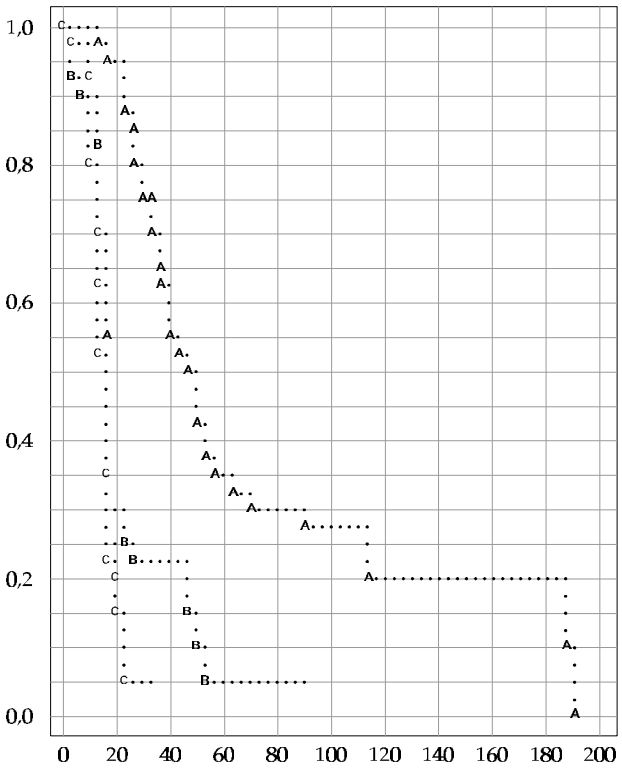

Figure 6. Showing comparative survival of grade 2 (A), 3 (B) and 4 (C) in TESTAST 268 system.

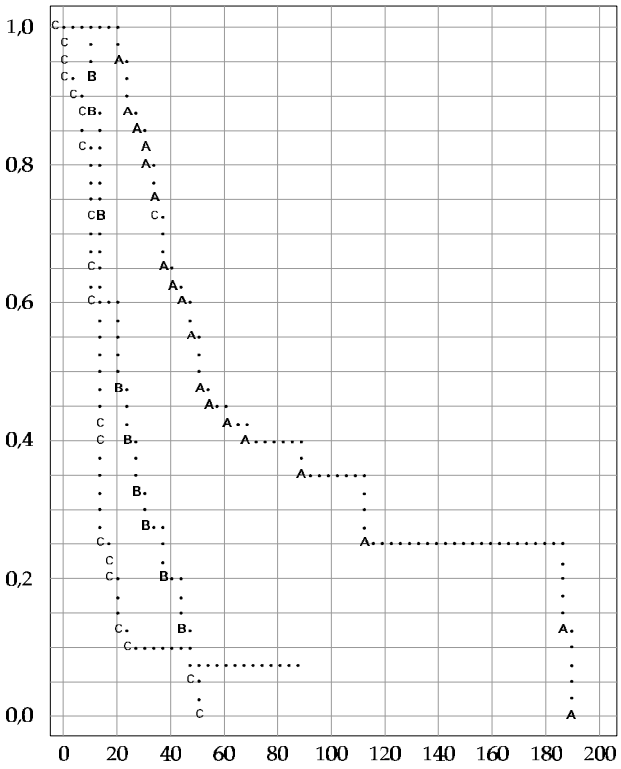

Figure 7. Showing comparative survival of grade 2 (A), 3 (B) and 4 (C) in WHO system.

Table 3. **4-system inter-classification concordance**

T	*Classification system* SAM	*K*	*WHO*	*No. of cases (n=53)*
G2	G2	G2	GII	33
G4	G4	G4	GIV	19
G3	G3	G3	GIII	1

G2: Grade 2; G3: Grade 3; G4: Grade 4

as of grades 2,3 and 4 respectively for comparative evaluation with grades of other classification systems. A single case in the entire series with 60 months survival and alive was assigned to be grade 1 according to Kernohan and SAM-A systems but belonged to grade 2 as per TESTAST-268 and WHO criteria. Rest of the 101 cases were all distributed between grades 2 to 4.

Inter-classification comparative survival in different grades is summarized in *Table 1.* and the corresponding comparative survival curves are presented in *Figure 1-3*. Similarly, summary of comparative intra-classification grade-wise survival is presented in *Table-II* and the corresponding survival curves in *Figure 4–7.* An almost identical data distribution is observed between Kernohan and TESTAST-268 systems and also between SAM and WHO systems (*Tables 1 and 2*). Median survival for grades 2 and 3 tumors were found to be 6-7 months higher in both SAM and WHO classifications versus those observed in Kernohan and TESTAST-268 systems. In grade 4, SAM, Kernohan and WHO all showed an identical median survival of 15.5 months whereas TESTAST-268 had a 3 months lower median survival of 12.5 months. Survival curve analysis (*Figure 1–3*), however, does not demonstrate any such difference amongst all four classification systems.

Intra-classification grade-wise survival analysis (*Figure 4–7*) reveals a statistically significant difference ($p < 0.01$) between grade 2 and grade 3 as well as between grade 2 and grade 4, but no difference between grades 3 and 4 in any of the classification systems.

Comparative analysis of inter-classification concordance for tumor grading revealed that out of a total of 102 cases, 53 cases (51.9%), showed an absolute grading concordance for all four classifications. While the maximum number of concordant cases belonged to grade 2, followed by grade 4, only 1 case belonged to grade 3 (*Table 3*). Twenty one cases (20.6%) showed a three classification concordance with maximum number belonging to grade 4 followed by grade 3 but only 1 case belonging to grade 2 (*Table 4*). Concordance for any two of the four classification systems was seen in 28 cases (27.5%) with maximum number of 19 cases showing grade 3/grade 4 division (*Table 5*).

Survival curve analysis of all-four-classification-concordant cases versus rest of the cases (*Figure 8*) revealed that while the difference between concordant grade 2 and grade 4 is clearly evident and statistically highly significant ($p < 0.001$), the survival curve of the cases showing any degree of discordance is similar to grade 4 except for the lower part of the curve drifting away indicating that survival distribution in approximately 15% of cases in the group might be significantly different from the survival of grade 4 patients.

Table 4. **3-system inter-classification concordance**

T	*Classification system* SAM	*K*	*WHO*	*No. of cases (n=21)*
G3	G4	G4	GIV	10
G4	G4	*G3*	GIV	4
G3	*G4*	G3	GIII	4
G3	G3	*G2*	GIII	1
G2	G3	G3	GIII	1
G2	*G3*	G2	GII	1

* Discordant grades are underlined.

Table 5. **2-system inter-classification concordance**

T	*Classification system* SAM	*K*	*WHO*	*No. of cases (n=28)*
G3	*G4*	G3	*GIV*	19
G2	*G4*	G3	GIII	1
G2	*G3*	G2	*GIII*	5
G2	*G4*	G2	*GIII*	2
G2	G1	G1	*GII*	1

* Discordant grades are underlined.

Discussion

Pathologic classification and grading of astrocytic tumors is a controversial subject. The simultaneous use of different classification systems understandably creates confusion in assessing prognosis and planning of therapy as well as interpreting the results of multi-center therapeutic trials. Hence, there is a need to evaluate the various classification systems in vogue currently in relation to their prognostic outcome in order to choose the best of them, which can then subsequently be used uniformly in all multi-center studies. The present study is a contribution in this direction.

The most important observation in this study was that similar survival curves were obtained for any one grade of tumor by all the 4 classification systems. Further, there was a significant difference in survival between grades 2 versus 3 and 4 but no difference between grades 3 and 4 by any of the classifications. Thus, it appears that if described specified criteria related to any of the classification systems is rigorously followed to, they will produce comparable and identical results. Therefore, the guiding force for any center to adopt a particular system of classification will be its

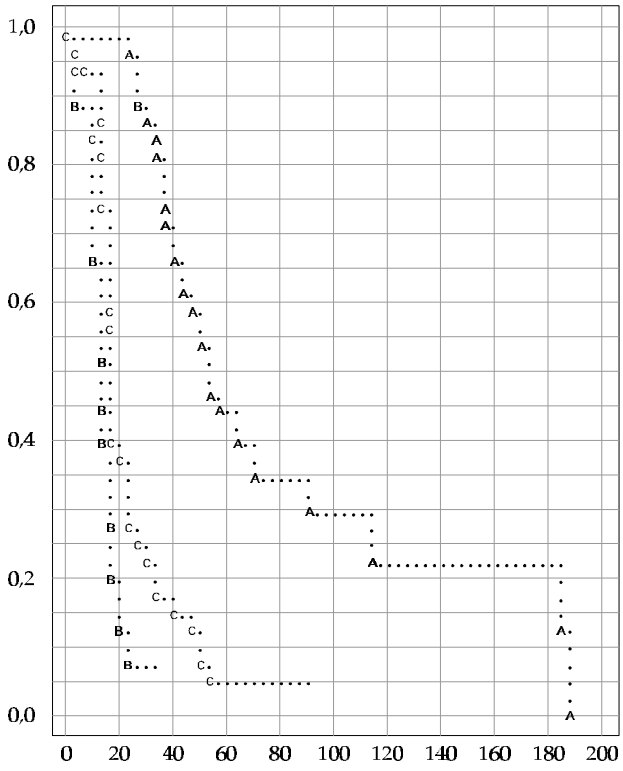

Figure 8. Showing survival comparison of all-four-classification concordant grade 2 (A) and grade 4 (B) cases versus rest of the cases without absolute 4-classification concordance (C).

simplicity and reliability of histologic feature value categorization with high degree of reproducibility.

In this regard, the Kernohan grading scheme[6] has been found difficult to apply because the criteria are often ambiguous, leading to a certain degree of uncertainty. Interpathologist discordance has been found to be maximum using this system in our earlier study[18] as well as by others.[3,4]

TESTAST-268 overcomes the subjectivity of the Kernohan system to a very great extent and thus has a higher degree of reproducibility.[18] However, numerical assessment of histologic feature values are semi-objective and thus require more time, meticulousness and some degree of experience before a consensus can be reached.

Morphometric quantitation[18] eliminates the uncertainty of semi-objectiveness but is very labour intensive and thus may not be routinely applicable in classical situations. WHO typing[9] is fairly reproducible but the drawback is the absence of any clearly objectivized histological criteria. The grading of Daumas-Duport[3] appears to be an efficient and simple method based on the presence of objective histological criteria. One of the attractions of this particular scheme is the limited number of histological features needed. Further, high rates of reproducibility have been reported.[3,8] which are attributable to the selection of easily identifiable morphologic criteria and to their simple recognition as being either present or absent, thus minimizing subjectivity to a great extent. Our present study also shows that this is the most easily adaptable, least time consuming, most unambiguous and highly reproducible system. We recommend this system for reliable comparison of prognostic and therepeutic data from various centers as this can be followed efficiently in all centers with least discordance level.

In the present study, 51.9% cases showed absolute concordance by all 4 classification systems with majority belonging to grade 2 followed by grade 4. The significance of total failure to find any significant survival difference between grades 3 and 4 by any classification system in the present study is somewhat difficult to relate. This topic is rather controversial in the literature wherein many reports[4,6,7,13,19] are in agreement with our findings but others contradict.[3,8,10,11,12,17] It is difficult to make any speculative comment on this topic now and possibly cumulative results of multi-centric end result analysis may resolve this issue in due course of time.

The slides of the all 4-classification discordant cases were re-reviewed for any possible missed histologic feature which might have been the source of discordance to some extent. The situation, however did not improve. Hopefully, additional biologic parameters like proliferative index, AgNOR counts or apoptotic rate might provide a better grading identification to this group in terms of biologic behaviour.

Lastly, the majority of the 4-classification discordant cases with a survival curve overlap with grade-4 (*Figure 8*) should actually find their place in grade-4 from the point of view of survival irrespective of the noise of any interclassification discordance. In this regard SAM-A and the WHO systems emerge as more efficient for this purpose in the present study, compared to Kernohan and TESTAST-268.

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