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Clinical Study

Does extent of surgery influence outcome for astrocytoma with atypical or anaplastic foci (AAF)? A report from three Radiation Therapy Oncology Group (RTOG) trials

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Abstract

103 patients with the diagnosis of AAF were identified from the RT/BCNU arms of 3 RTOG malignant glioma trials. Pre-treatment tumor size was < 5 cm for 48% and ≥ 5 cm for 52%, and tumor sites were frontal lobe in 55%, temporal in 25%, and parietal in 16%. Surgery consisted of biopsy for 30%, partial resection for 56%, and total resection for 14%. Extent of surgery correlated with age, with 81% of patients < 40 undergoing partial/total resection vs. 60% of those over 40 ($P = 0.019$).

The median survival time (MST) of patients undergoing partial/total resection was 49 mo., vs. 18 mo. for those biopsied only ($P = 0.002$). Patients with frontal location had longer MST than those with non-frontal lesions (MST: 49 vs. 25 mo., $P = 0.047$), while no survival difference was apparent by univariate analysis of tumor size. Multivariate analysis demonstrated that only younger age, frontal location, and smaller tumor size correlated significantly with extended survival. Extent of surgery was not predictive.

The close correlation between young age and extensive surgery obscures the survival advantage for greater surgery seen with univariate analysis. Smaller tumor size and frontal location favorably influence outcome even when adjusted by age.

Introduction

Standard therapy for adults with supratentorial malignant gliomas consists of an operative procedure followed by cranial irradiation (RT) with or without chemotherapy [1, 2]. Efforts to improve patient outcome achievable with this approach have emphasized modifications in the delivery of RT (altered fractionation, brachytherapy, or radiation sensitizers) [3–7] or in the intensification of available chemotherapy [8–10]. Less systematic attention has been directed toward improvements possible through modifications in neurosurgical technique. While there have been notable technical advances in the surgical approach to malignant glial tumors, including stereotactic surgery, perioperative cortical sensory and motor mapping, and computer-assisted laser resection [11–14], the ability of radical surgical resection to extend patient survival time has not been conclusively established [15]. While several reports have identified more extensive resection and/or less post-operative residual tumor with longer survival, it remains uncertain whether this advantage is due to the neurological improvement possible with tumor decompression or to the reduction in tumor volume achieved prior to RT and chemotherapy [16–19]. These reports have not stratified the favorable outcome observed with greater tumor resection by all variables likely to also influence outcome, including age, tumor size, tumor location, and performance status.

In 1983 J.S. Nelson *et al.*, demonstrated that the presence of one or more foci of coagulation necrosis was of greater prognostic value in distinguishing outcome among supratentorial malignant gliomas than the degree of cellular anaplasia used in the systems developed by Broders or Kernohan *et al.* In a centrally verified review of 503 surgical specimens from the Radiation Therapy Oncology Group (RTOG) 74-01/Eastern Cooperative Oncology Group (ECOG) 1374 treatment protocol, the authors demonstrated an eight month median survival time (MST) for patients with foci of necrosis, i.e., glioblastoma multiforme (GBM), and a 28 month MST for patients with malignant gliomas without necrosis, called astrocytomas with atypical or anaplastic features (AAF) [20]. Burger *et al.*, confirmed that tumor necrosis was the principal pathologic criteria influencing survival among 1140 reviewed cases on 3 Brain Tumor Study Group (BTSG) trials [21]. Current cooperative group trials for malignant glioma stratify patients according to this pathologic distinction, and GBM patients have constituted 80–85% of accrual to malignant glioma protocols within RTOG clinical trials since 1974 [2, 3, 22].

The purpose of this report is to determine whether more extensive surgical resection influences survival among a consistently treated and histologically verified cohort of patients with AAF.

Materials and methods

Patient selection

Patients under evaluation in this report were those AAF cases entered on treatment arms assigned to receive BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) chemotherapy and either once-daily or hyperfractionated (1.2 Gray [Gy] BID) RT on one of three RTOG protocols for malignant glioma. Primary treatment outcome reports of these three trials have been previously published [2, 3, 22]. The three studies, RTOG 74-01/ECOG 1374, RTOG 79-18, and RTOG 83-02, accrued adult patients with biopsy-proven, supratentorial malignant gliomas. Central pathology review was conducted by one of the authors (JSN). To be considered analyzable for the present study, each case had to have central pathology review, and evaluable tumor size, and known extent of surgery (biopsy only, subtotal resection, or total resection). There were 589 such analyzable cases on the RT and BCNU arms of these three studies, of whom 103 were AAF (18%) and 486 GBM (82%). These 103 AAF cases form the subject of this analysis.

Radiation therapy guidelines

Breakdown by treatment arm in each respective study is shown in Table 1. Seventeen of the 626 patients treated on RTOG 74-01/ECOG 1374 had AAF lesions and received whole brain RT to 60 Gy in 1.8 to 2.0 Gy daily fractions. There were 20 analyzable AAF patients on RTOG 79-18, and all received whole brain RT to 60 Gy in 1.8 to 2.0 Gy daily fractions. The total doses of hyperfractionated RT assigned to the 66 AAF patients treated on RTOG 83-02 is shown in Table 1. The initial RT target volume for the initial 57.6 Gy was the primary tumor and surrounding edema with a 2 cm margin and the remaining RT treatment included

Table 1. Cases accrued and analyzed by study and treatment. All patients received BCNU chemotherapy

Study	RT dose	# Pts confirmed AAF
RTOG 74-01/ ECOG 1374	60 Gy	17
RTOG 79-18	60 Gy	20
RTOG 83-02	64–81 Gy	66
Total		103

the primary tumor with a 2.5 cm margin. The RT treatments were delivered in 1.2 Gy fractions twice daily with an interfraction interval of 4 to 8 hours. Because of a limited follow-up period, patients enrolled in the two accelerated hyperfractionated arms of 1.6 Gy BID were excluded from this analysis.

Chemotherapy guidelines

All 103 patients received BCNU 80 mg/m^2 for three consecutive days during the first week of radiation therapy and then every eight weeks. Dose modifications were made based on hematological toxicity, and treatment was discontinued in the presence of progressive disease or declining neurological performance status.

Statistical methods

Differences in patient characteristics between groups were evaluated with the Pearson chi-square test for differences in proportions [23]. A stepwise Cox proportional hazards model was used to test for significance of the factors: age; KPS; extent of surgery; and tumor size [24]. Covariates were included into the model using the maximum partial likelihood ratio test. Survival was measured from the start of therapy and plotted as a step function using product limit estimates [25]. Tests for differences in survival were performed using the log-rank statistic.

Table 2. Patient characteristics

Characteristic	N = 103	(%)
Tumor size		
< 5 cm	50	(48)
5–10 cm	47	(46)
≥ 10 cm	6	(6)
Tumor location		
Frontal	57	(55)
Temporal	26	(25)
Parietal	16	(16)
Other	4	(4)
Age		
< 40	48	(46)
40–59	42	(41)
≥ 60	13	(13)
Karnofsky performance status		
< 50	4	(4)
60–70	18	(17)
80–100	78	(76)
Not recorded	3	(3)
Extent of surgery		
Biopsy only	31	(30)
Partial resection	58	(56)
Total resection	14	(14)

Results

Patient characteristics

The 103 AAF patients were grouped according to tumor size, tumor location, age, performance status, and extent of surgery in Table 2. Pre-treatment tumor size was < 5 cm for 48% and ≥ 5 cm for 52%, and tumor sites were frontal lobe in 55%, temporal in 25%, and parietal in 16%. Forty-six percent of patients were under age 40, 41% were ages 40 to 59, and 13% were over age 60. Karnofsky performance status (KPS) was evaluated as 80–100 in 76% of patients, 60–70 in 17%, and 50 or less in 4%. Surgery consisted of biopsy for 30%, partial resection for 56%, and total resection for 14%.

Table 3 shows the distribution of the patient characteristics of age, KPS, and tumor site according to pre-operative tumor size. No significant difference in the distribution of these factors was evident between those patients with tumors less than or greater than 5 cm. In Table 4, patients are divided between those who underwent biopsy vs. those having either a subtotal or total resection. Extent of surgery did correlate with age, with 81% of patients < 40 years of age undergoing partial/total resection vs. 60% of those over 40 ($P = 0.019$). Twenty-six percent of the biopsy-only patients were over age 60 vs. 7% in the group undergoing either total or subtotal resection. A greater proportion of the biopsy-only patients had tumors less than 5 cm than those undergoing more extensive surgery, 61 vs. 43% ($P = 0.09$).

Survival

The median survival time (MST) for all 103 AAF patients was 36 months, with 1, 2, 3, and 5 year survival rates of 80%, 60%, 50%, and 37%, respectively. No difference in survival is seen between the 50 patients with tumors < 5 cm vs. the 53 patients with tumors ≥ 5 cm, with MST's of 38.9 and 30.2 months, respectively (Table 5). A significant survival difference between patients with tumors with frontal lobe location versus those of non-frontal sites, with MST's of 49.3 and 25.1 months, respectively ($P = 0.047$). When survival is partitioned by extent of surgery, a significant advantage is seen for the patients undergoing subtotal or total resection compared to the biopsy-only patients, with MST's of 49.3 vs. 18.3 months, respectively ($P = 0.0023$). The findings are shown in Figs 1 and 2.

Multivariate analysis

Table 6 presents the outcome of a stepwise Cox proportional hazards model analysis. There were 96 cases with full information necessary for this analysis. Age, tumor size, and primary site were the covariates most predictive for survival, with KPS having marginal significance. In this multivariate analysis, extent of surgery was not a significant predictor of survival. The three factors most strongly correlated with extended survival in this analysis were age < 40, frontal location, and tumor size < 5 cm.

Discussion

The goals of initial neurosurgical intervention for adults with a suspected malignant glioma include: (a) establishment of a tissue diagnosis; (b) decompression of mass effect when present; and (c) aggressive tumor resection. While the importance of the first two goals is unchallenged, the benefit of aggressive cytoreductive surgery remains less certain. Prior reviews of the role of aggressive surgery have usually included all adults with malignant gliomas, a group generally consisting of 80–85% GBM and 15–20% AAF cases. Because of striking differences between these histologies in respon-

Table 3. Distribution of patient characteristics according to tumor size

	< 5 cm (50 pt)		≥ 5 cm (53 pt)	
	#	(%)	#	(%)
Tumor location				
Frontal	25	(50)	32	(60)
Temporal	14	(28)	12	(23)
Parietal	9	(18)	7	(13)
Other	2	(4)	2	(4)
Age				
< 40	20	(40)	28	(53)
40–59	23	(46)	19	(36)
≥ 60	7	(14)	6	(11)
Karnofsky performance status				
< 50	2	(4)	2	(4)
60–70	11	(22)	7	(13)
80–100	36	(72)	42	(79)
Not recorded	1	(2)	2	(4)
Extent of surgery				
Biopsy only	19	(38)	12	(23)
Partial/total resection	31	(62)	41	(77)

Table 4. Distribution of patient characteristics according to extent of resection

	Biopsy only (31 pt)		Subtotal/total resection (72 pt)	
	#	(%)	#	(%)
Tumor location				
Frontal	15	(48)	42	(58)
Temporal	7	(23)	19	(26)
Parietal	6	(19)	10	(14)
Other	3	(10)	1	(3)
Age				
< 40	9	(29)	39	(54)
40–59	14	(45)	28	(39)
≥ 60	8	(26)	5	(7)
Karnofsky performance status				
< 50	1	(3)	3	(4)
60–70	8	(26)	10	(14)
80–100	21	(68)	57	(79)
Not recorded	1	(3)	2	(3)
Tumor size				
< 5 cm	19	(61)	31	(43)
≥ 5 cm	12	(39)	41	(57)

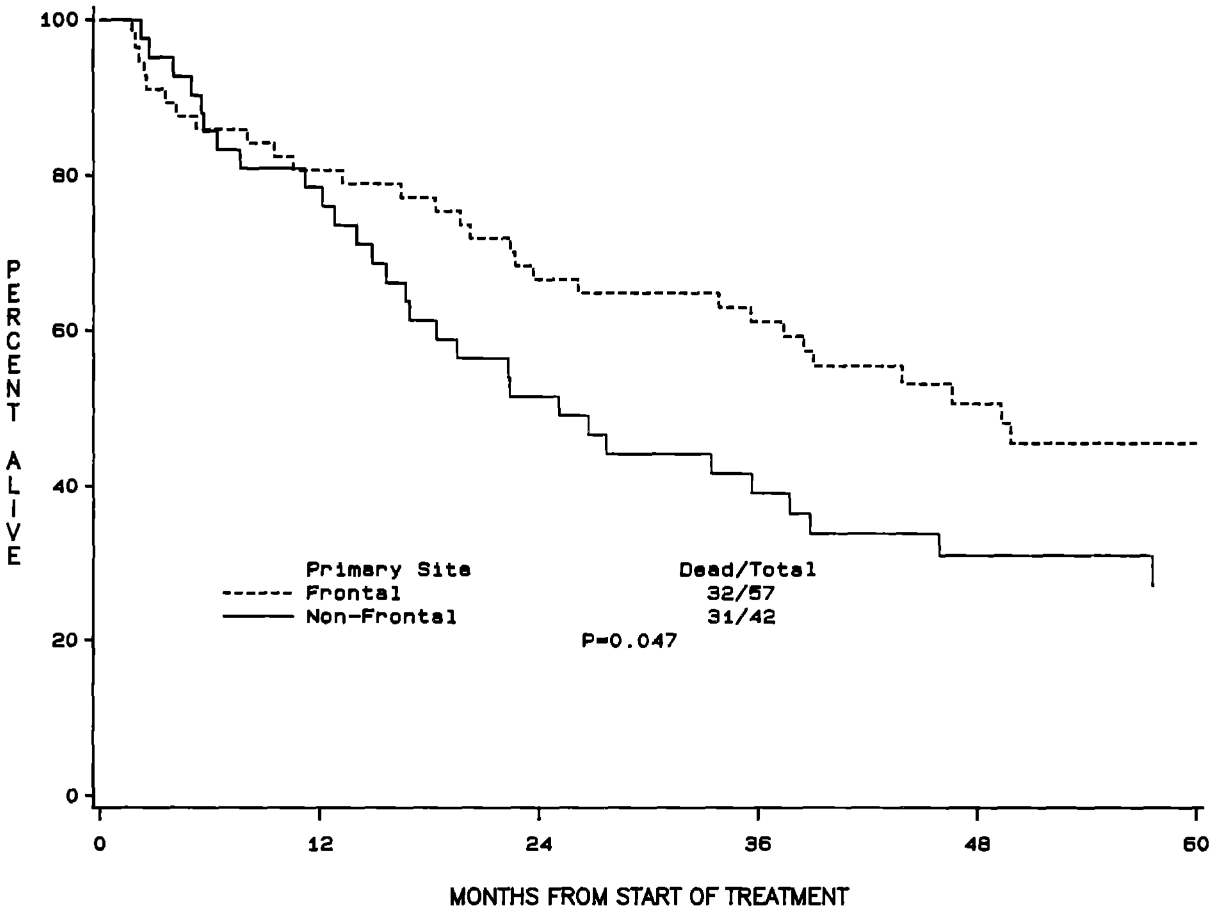

Fig. 1. Survival according to tumor location: Frontal lobe versus non-frontal lobe.

siveness to non-surgical therapy and in prognosis, it was hypothesized that the potential benefit of surgery may differ as well. For these reasons, an inde-

Table 5. Survival by tumor size

Time (mo)	< 5 cm		≥ 5 cm	
	% Alive	# at risk	% Alive	# at risk
0	100	50	100	53
12	82	40	77	41
24	61	30	58	31
36	53	23	47	22
48	43	17	40	14
Dead/Total	29/50		38/53	
Median	38.9 mo		30.2 mo	
				$P = 0.31$

Table 6. Proportional hazards model analysis for survival

Covariate	Coefficient	*P* value
Age (< 40, 40–59, ≥ 60)	0.9315	< 0.0001
Karnofsky perf status (80–100, ≥ 70)	0.5323	0.0742
Tumor size (< 5 cm, ≥ 5 cm)	0.6965	0.0096
Tumor location (Frontal, temporal, parietal)	0.7397	0.0003
Extent of surgery (Biopsy, subtotal/total resection	***	0.5688

*** Coefficient not calculated for *P* values > 0.10.

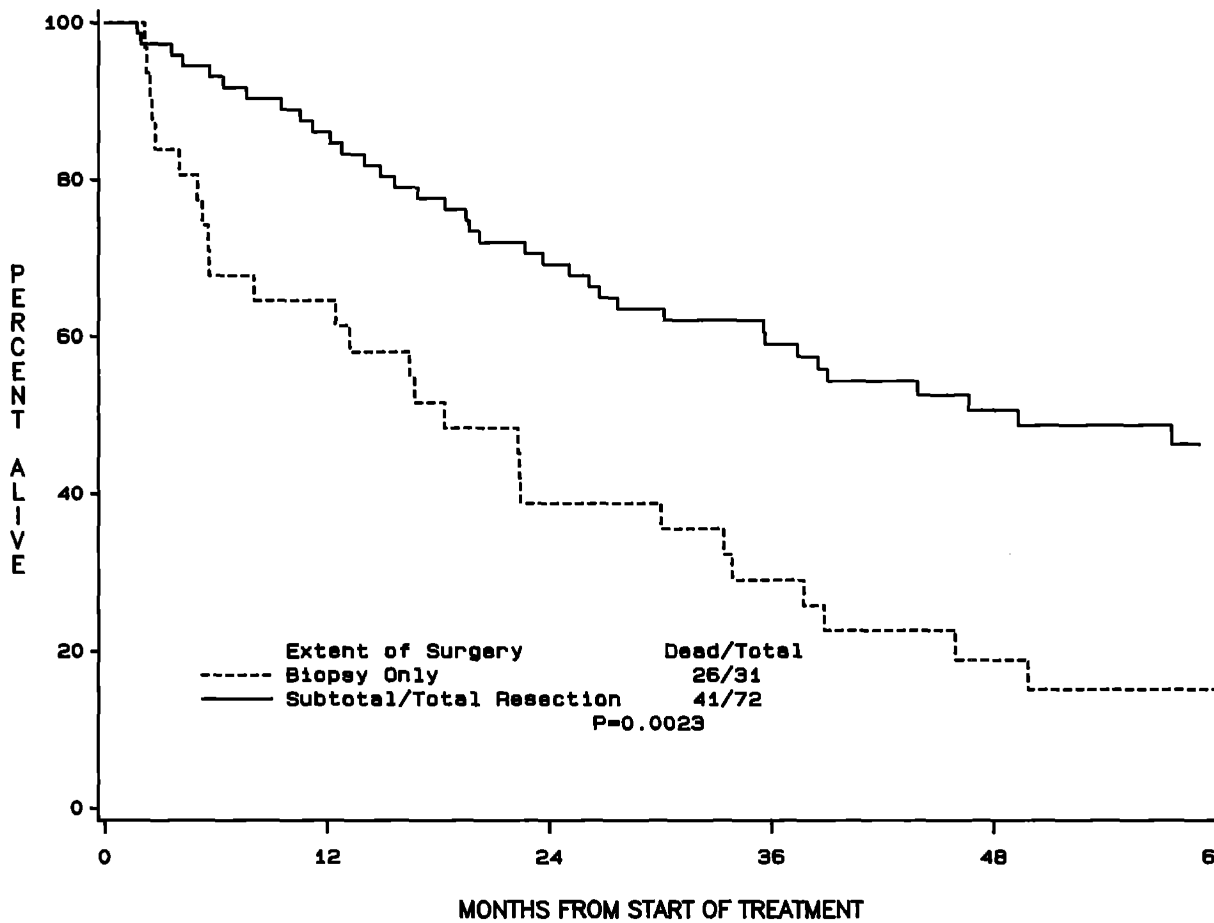

Fig. 2. Survival according to extent of surgery: Subtotal/total resection versus biopsy.

pendent analysis of AAF patients treated with RT and BCNU on recent RTOG protocols has been performed.

Since the demonstration that needle biopsy via a burr-hole is a reliable and relatively safe technique of establishing the tissue diagnosis of a glial tumor [11], this approach has been used for cases in which significant tumor resection is unlikely. With the improvement in such operative techniques as computer-assisted stereotaxic laser resection and cortical localization via sensory-evoked potential mapping [12, 13], aggressive surgical resection of deep-seated malignant gliomas situated in neurologically important locations is more possible. In reviews of both institutional and cooperative group experiences with malignant gliomas, conclusions regarding the influence of aggressive surgery on survival are conflicting. Reports noting a positive correlation include those by Stenning *et al.* [26], Gehan and Walker [27], Chang *et al.* [2], Ammirati *et al.* [28], and Vick *et al.* [29]. Those observing no significant relationship between extent of surgery and survival include studies by Fulton *et al.* [4], Eyre *et al.* [30], and Nelson *et al.* [22]. For a malignancy in which pre-treatment patient characteristics influence survival more strongly than treatment-related factors, such discordance is not surprising.

Several factors could explain these differing conclusions, including the method of determining extent of surgery, failure to perform a stepwise proportional hazards model analysis, or the selection of variables for such an analysis. In a review of patients enrolled on BTSG 80-01, Wood *et al.* defined extent of surgery by both the size of the tumor area on a post-operative CT slice and by the percentage of tumor removed. A significant survival advantage was observed among patients with the smallest residual tumor area on CT scans, however, no significant survival difference was noted according to the percentage of tumor removed [31]. In a multivariate analysis among 417 malignant glioma patients entered on Medical Research Council (MRC) studies, Stenning *et al.* observed a significant survival benefit to more extensive surgery [26]. However, the Kernohan and Sayre tumor grading system was used and was not found useful in discriminating outcome. Neither the BTSG nor the MRC studies entered tumor location into their multivariate analysis.

Only one prior study has reported survival outcome by extent of surgery among a significant number of AAF patients with centrally verified pathology. D.F. Nelson *et al.* reviewed survival among 94 patients with AAF treated with 60–70 Gy cranial irradiation (RT) with and without BCNU chemotherapy on 3 consecutive RTOG trials. Twenty-five patients were included in both the Nelson study and the present report. A multivariate analysis including age, KPS, and extent of surgery (biopsy, partial excision, total excision) revealed that extent of surgery had greater influence on survival than either age or KPS [32]. Neither tumor size nor location were considered in that analysis. With the addition of these two variables to the Cox regression analysis, the present study does not confirm that extent of surgery is independently predictive of extended survival. Despite a significant survival difference between those patients undergoing biopsy vs. partial/total resection (MST: 18 vs. 49 mo), the strong association between age and extent of surgery appears to obscure the influence of surgery on survival.

Smaller tumor size and frontal location were noted in this study to favorably influence survival among AAF patients, even when age is considered. While tumor size is prognostically important in most malignancies and included as a staging criteria, its importance in malignant gliomas, and specifically AAF, is poorly documented. Neither tumor size or location have been used to stratify patients in prior malignant glioma trials, and neither variable was used by the MRC in a recent attempt to define a prognostic index for malignant gliomas [26]. Wood *et al.* did not find pre-operative tumor size to be predictive of survival among 510 patients (80% GBM) on a BTSG trial [31]. Tumor location, which can be categorized by specific lobe, lobar vs. nonlobar, central vs. noncentral, or dominant vs. nondominant hemisphere, has been found by several investigators to be unassociated with patient outcome [4, 22, 33]. While both Jelsma and Bucy [34] and Hildebrand *et al.* [6] observed better survival for patients with noncentral vs. central gliomas, only Brihaye *et al.* had observed a survival difference according to lobar location [35]. As in the present report, they noted the best survival among cases with a frontal location.

There are two differing conclusions regarding surgical resection and AAF that can be derived from the present report. It could be concluded that, despite the results of a Cox analysis, the pronounced survival difference by extent of surgery verifies that aggressive resection does influence survival. The strong association between age and surgery could be related to the decision to treat younger patients more aggressively and older patients with a more conservative operative approach. In developing such an approach, the operative therapy offered to younger patients results in greater prolongation of survival than that performed on older patients.

The contrary conclusion is that age is such a powerful predictor of response to cranial RT and BCNU that any variable associated with young age, such as aggressive resection, would appear favorable in a univariate analysis. This view is lent support by the observations of Hoshino *et al.*, who used a bromodeoxyuridine (BUdR) labeling index technique to define the relative proliferative potential of both AAF and GBM tumors [36]. It was observed that age was independently predictive of BUdR labeling index for both highly and moderately anaplastic astrocytoma patients but not for glioblastoma multiforme cases. This suggests that histologically similar AAF tumors may have differing degrees of biological malignancy, as evidenced by the BUdR labeling index, and that age is the best predictor of this index. The lower proliferative potential of AAF tumors in younger patients may be a more important determinant of their extended survival than the details of either their surgical and non-surgical therapies. While it is logical to assume that maximal cytoreductive surgery of AAF tumors should be attempted whenever feasible, the influence of this approach on survival remains unclear.

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