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Survival in Patients With Recurrent Glioma as a Measure of Treatment Efficacy: Prognostic Factors Following Nitrosourea Chemotherapy

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The assessment of efficacy of treatment in patients with recurrent glioma is notoriously difficult, and survival is the most objective endpoint. Between 1970 and 1992, a cohort of 211 patients with recurrent glioma received nitrosourea-based chemotherapy at the time of disease progression. The median survival from the start of chemotherapy was 7 months, with 30% 1-year and 10% 2-year survival probabilities. One-year survival was 22% in 147 patients with recurrent high-grade astrocytoma, 41% in 37 patients with low-grade astrocytoma and 45% in 24 patients with oligodendroglioma. Age, histological grade and Karnofsky performance status (KPS) at recurrence were independent prognostic factors for survival on multivariate analysis. Based on patients' age, tumour grade and KPS, it was possible to define three distinct prognostic groups with 1-year survival probabilities of 60, 21 and 17% ($P < 0.005$). Response to chemotherapy was difficult to assess but correlated with prognostic subgroup, with highest response rate (46%) in the most favourable group and lowest (13%) in the poor prognostic group. In patients with recurrent glioma, patient and tumour parameters are the major determinants of outcome which are identical to prognostic factors at the time of primary diagnosis. They can be used to provide prognostic information for the individual patient, and to stratify patients particularly in trials assessing the efficacy of novel treatments.

Key words: recurrent glioma, chemotherapy, prognostic factors
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INTRODUCTION

THERE ARE many treatment approaches in patients with recurrent glioma. They include either systemic chemotherapy and biological therapy, or local treatment in the form of surgery [1], irradiation (conventional external beam radiotherapy, stereotactic radiotherapy [2] or brachytherapy [3]) and intralesional chemotherapy or biological therapy [4]. The diversity of treatments in patients with recurrent glioma attests to the absence of a regimen with dramatic effectiveness and acceptable toxicity, and patients continue to have poor prognosis.

There are many new appraoches tested in phase I and II studies and often claimed as potentially effective therapy. Yet, there is no agreement on the most appropriate way of measuring the effectiveness of new treatments in recurrent glioma. Although concensus on the assessment of response has been published and includes both clinical and radiological criteria [5], such responses are difficult to measure, even in prospective studies. Problems include accurate definition of radiological response on computed tomography or magnetic resonance imaging (CT)/(MRI), particularly when discernable changes are small, and ascertaining the significance of neurological status in the context of corticosteroid therapy. The relationship of response to real anti-tumour effect and survival is also not clearly established.

As the majority of patients with recurrent glioma die of progressive tumour, survival from the time of recurrence is the most objective endpoint of effectiveness of therapy. It does not require the assessment of radiological response, particularly in the situation of surgical or radiotherapeutic interference, where radiological changes do not necessarily reflect the response to treatment. The prognostic factors which determine survival in patients with recurrent glioma have not been fully described. We report the survival results in a series of consecutive patients treated with nitrosourea-based chemotherapy at the time of recurrence at the Royal Marsden Hospital, and define the prognostic factors for survival and the relationship between survival and response.

MATERIALS AND METHODS

211 patients with progressive recurrent glioma were treated with nitrosourea-containing chemotherapy at the Royal Marsden Hospital between 1970 and 1992. All patients were observed until death or July 1992. Patient, primary disease and treatment characteristics are summarised in Table 1. Patients were aged 18–75 years (median 47) at primary diagnosis. All had histologically-verified primary tumours, graded according to the criteria of Kernohan and Sayre [6]. All were treated initially by surgery and external beam radiotherapy. At initial surgery, 32 patients had biopsy alone, 144 partial removal and 35 apparent complete macroscopic tumour removal. All received post-operative radiotherapy by planned megavoltage external beam radiation to the tumour and a 2–5 cm margin. Radiotherapy was completed at the Royal Marsden Hospital in all except 8 patients. Details of radiotherapy dose are shown in Table 1.

Disease progression was defined by both clinical and radiological criteria. All patients had symptomatic progression with worsening neurological deficit or features of raised intracranial pressure, and, in the majority of patients, it was confirmed by CT or MR. Progression-free interval (time interval from beginning of primary radiotherapy to disease progression) was less than a year in 100 patients and 1 year or more in 111.

At the time of recurrence, 37 patients underwent a further surgical procedure. 31 patients had excision, 5 had cyst aspiration and or biopsy, and 1 had insertion of a ventriculo-peritoneal shunt (Table 2). Histological grade at recurrence was available in 23 patients with astrocytoma. Progression from low- to high-grade tumour was noted in 17 cases and 5 had no change in their grade.

Table 1. Patients' and disease characteristics at the time of initial presentation, and primary treatment of 211 patients with recurrent glioma

Characteristic	Patients No.	%
All	211	100
Age at diagnosis (years)		
16–40	71	34
41–59	109	52
≥60	31	14
Sex		
Male	124	59
Female	87	41
Histology at primary diagnosis		
Oligodendroglioma	24	11
Astrocytoma		
Low-grade (I and II)	37	18
High-grade (III and IV)	147	70
Unknown grade	3	1
Extent of primary surgery		
Biopsy	32	15
Partial removal	144	68
Macroscopic "complete"	35	17
Radiotherapy dose		
35–49 Gy	5	2
50–54 Gy	57	27
55–59 Gy	131	62
60+Gy	10	5
Not known	8	4

At the time of tumour progression, 16 patients received a second course of external beam radiotherapy which included stereotactic radiotherapy in 4 [2]. Conventional fractionated radiotherapy was usually given to a dose of 40 Gy (or equivalent), 1.6–1.8 Gy daily. Chemotherapy was given at the time of further tumour progression after retreatment with surgery and radiotherapy.

At the time of progression, patients received cytotoxic chemotherapy with either nitrosourea as single-agent or as combination chemotherapy. Details of the chemotherapy regimens are shown in Table 3. 28 patients received combination chemotherapy containing platinum as well as nitrosoureas. The usual treatment policy was to give two cycles of chemotherapy followed by reassessment, and, in the absence of disease progression, continue to six courses. Fewer courses reflect withdrawal of treatment due to tumour progression. The number of courses of chemotherapy given ranged from one to 20 (median three cycles).

Other concomitant medical treatment included anti-convulsants and corticosteroids. Steroid doses were titrated for optimum improvement in neurological function and least toxicity, and were considered in the response assessment.

Response to chemotherapy was documented and assessed according to the criteria of MacDonald and colleagues [5]. Complete response (CR) was defined as neurologically stable or improved, off steroids, and complete disappearance of primary

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*Table 2. Patients' characteristics and treatment at the time of recurrence, according to initial histological grade**

Characteristic	Histology		
	HG Astro	LG Astro	Oligo
	(Number of patients)		
All	147	37	24
Age at chemotherapy (years)			
16–40	32	16	4
41–59	83	19	15
≥ 60	32	2	5
Karnofsky performance status at recurrence			
> 70%	79	13	14
≤ 70%	68	24	10
Re-irradiation at recurrence	7	6	3
Surgery at progression			
Cyst aspiration and/or biopsy	3	1	1
Excision	15	10	6
Shunt	0	1	0
No surgery	129	25	17
Chemotherapy			
Nitrosourea + platinum	18	3	7
Nitrosourea +/− other agents	129	34	17
Courses received			
< 3	71	13	7
3–6	59	15	13
> 6	17	9	4
Response to chemotherapy			
CR + PR	33	13	10
SD + PD	100	19	14
Not evaluable	14	5	0

*Grade not known in 3 patients. HG Astro, high-grade astrocytoma; LG Astro, low-grade astrocytoma; Oligo, oligodendroglioma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

lesion on CT or MRI. Partial response (PR) was defined as neurologically stable or improved, steroid dose stable or reduced, and or more than 50% regression of primary lesion on CT or nuclear magnetic resonance (NMR). Progressive disease (PD) was defined as neurological deterioration, steroid requirement stable or increased, together with a > 25% increase in the size of the tumour on CT or MRI. Stable disease (SD) was defined by exclusion. Imaging was usually performed after two cycles of chemotherapy and subsequently when clinically indicated.

Toxicity was assessed before administration of each cycle of chemotherapy and during the rest period by clinical examination, peripheral blood count and biochemistry. Clinical toxicity has been graded retrospectively. Survival was defined from the start of the first cycle of cytotoxic chemotherapy. No distinction was made between death with or due to recurrence of glioma. Survival was analysed by patient, tumour and treatment factors using log-rank actuarial methods on univariate analyses. Cox's proportional hazard model was used to identify independent variables [7].

RESULTS

Survival and prognostic factors

211 patients with glioma were considered suitable for treatment with nitrosourea-containing chemotherapy at the time of progressive recurrent disease. The median survival from the start of chemotherapy was 7 months, with 30% 1-year, 10% 2-year and 2% 5-year survival probabilities (Figure 1).

Patient, disease and treatment factors listed in Table 4 were examined for prognostic significance for survival following chemotherapy. Age, initial histological grade of tumour (Figure 2), Karnofsky performance status at recurrence, and progression-free interval were significant prognostic factors on univariate analysis.

On multivariate analysis, age, tumor grade and Karnofsky performance status at the time of chemotherapy remained independent prognostic factors (Table 4). The relative risk (RR) of death was 1.6 for patients aged 41–59 years and 2.6 for patients ≥ 60 compared to a RR of 1.0 in younger patients (aged

Table 3. Chemotherapy schedules employed

Name	Agent	Dose		Cycle (weeks)
Group A: nitrosourea + platinum				
1) BOPP	BCNU	50 mg/m²	i.v. days 1 and 2	6
	Vincristine	1.5 mg/m²	i.v. day 1	
	Cisplatinum	20 mg/m²	i.v. infusion days 1–3	
	Procarbazine	50 mg/m²	p.o. days 1–7	
2) BOP	BCNU		Scheduling same as above	6
	Vincristine			
	Cisplatinum			
3) BP	BCNU		Scheduling same as above	6
	Cisplatinum			
Group B: nitrosourea ± other agents				
1) Single agent	BCNU	100 mg/m²	Days 1 and 2	6
	CCNU	130 mg/m²	p.o. day 1	6
2) PCV	Procarbazine	100 mg/m²	p.o. days 1–14	
	CCNU	100 mg/m²	p.o. day 1	6
	Vincristine	1.5 gm/m²	i.v. day 1	

i.v., intravenous; p.o., oral

Table 4. Univariate and multivariate analysis of patient, disease and treatment factors for survival following chemotherapy

Characteristic	Number of patients	1 year survival (%)	*P* (uni)	*P* (multi)	RR
All patients	211	30	—	—	—
Sex					
Male	124	25	NS	NS	—
Female	87	31			
Age (years) at chemotherapy					
16–40	53	41			1
41–59	119	27	<0.005	<0.001	1.6
≥60	39	11			2.6
KPS at recurrence					
>70%	107	38			1
≤70%	104	16	<0.01	<0.01	1.6
Initial histological grade*					
LG Astro and oligo	61	43	<0.005	<0.001	1
HG Astro	147	22			2.0
Progression-free interval					
≤1 year	100	17	−0.005	NS	—
>1 year	111	37			

HG Astro, high-grade astrocytoma; LG Astro, low-grade astrocytoma; oligo, oligodendroglioma; uni, univariate analysis; multi, multivariate analysis; RR, relative risk; NS, non-significant; KPS, Karnofsky performance status.
*Grade not known in 3 patients.

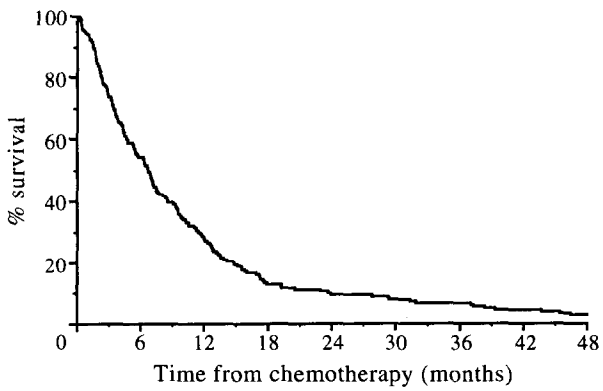

Figure 1. Actuarial survival of 211 patients with recurrent glioma, treated with chemotherapy.

16–40 years). The RR for patients with high-grade compared to low-grade tumours was 2.0. Patients with KPS ≤ 70 had RR of 1.6 compared to those with KPS > 70. Surgical decompression at the time of recurrence was not an independent prognostic factor for survival. Gender, site of tumour and type of chemotherapy regimen were also not of prognostic significance.

Patients were grouped into three prognostic categories according to the number of poor prognostic factors. These included KPS ≤ 70, high-grade histology and age > 40 years. Age > 60 years was counted as an additional poor prognostic factor. 59 patients with one or no poor prognostic factor had the best prognosis with a 1-year survival of 60%, 83 patients with two adverse factors had a 1-year survival of 21% and 69 patients with three to four factors had the worst prognosis, with only 17% surviving for 1 year ($P < 0.005$; Figure 3). The median survival was 14, 7 and 4 months, respectively, for the three groups.

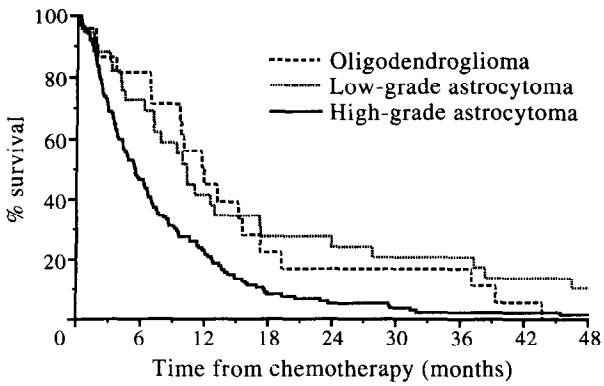

Figure 2. Actuarial survival of patients according to initial histological grade. Comparison of oligodendroglioma versus low-grade astrocytoma versus high-grade astrocytoma.

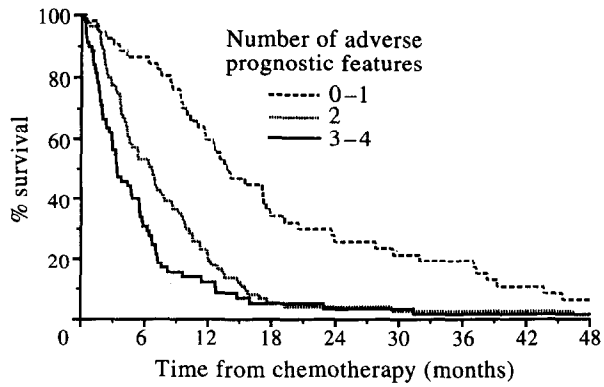

Figure 3. Actuarial survival of patients according to prognostic groups.

Prognosis by histological grade

One-year survival was 22% in patients with recurrent high-grade astrocytoma and 41% in patients with recurrent low-grade astrocytoma ($P < 0.05$). One-year survival in 24 patients treated for recurrent oligodendroglioma was 45%. Prognostic factors for survival were examined separately for both high- and low-grade tumours of astrocytic or oligodendroglial history. On univariate analysis, age was a significant prognostic factor for survival for all subsets, except low-grade astrocytomas. Karnofsky performance status and progression-free interval were only significant prognostic factors on univariate analysis in high-grade astrocytomas.

On multivariate analysis, age and performance status were significant prognostic factors for survival in patients with high-grade astrocytoma and the combined group of low-grade astrocytomas and oligodendroglioma.

Response to chemotherapy

57 of 211 patients (27%) responded to chemotherapy (CR or PR) (Table 5) based on combined clinical and radiological criteria [5]. Response rate was 23/61 (38%) in patients with low-grade tumours compared to 33/147 (22%) in patients with high-grade astrocytoma ($P < 0.05$) and 42% (10/24) in patients with recurrent oligodendroglioma. The difference in response between low- and high-grade astrocytomas did not reach statistical significance. Response was also related to age and performance status (Table 5). Separation of patients into three prognostic categories also correlated with response. There was no significant difference in response rate between different chemotherapy regimens, and the addition of cisplatinum did not result in a significantly higher response rate.

Second surgical procedure and re-irradiation

At the time of tumour progression, 10/37 (27%) patients with low-grade glioma had further tumour resection, compared with 15/147 (10%) patients with high-grade glioma. 6 of 37 (16%) patients with low-grade tumours also received a further course of radiotherapy, compared with 7/147 (5%) in patients with high-grade glioma. Second resection or re-irradiation had no prognostic significance for survival on univariate or multivariate analysis.

Treatment-related toxicity

Chemotherapy was generally well tolerated. Haematological and gastrointestinal toxicity of nitrosourea-based regimens were noted. There were no treatment-related deaths. 17 (8%) patients had WHO grade 2/3 leucopenia or thrombocytopenia which necessitated a dose reduction or delay in chemotherapy, of which only one required hospitalisation. One patient receiving BOPP regimen developed both persistent leucopenia and thrombocytopenia, and chemotherapy was discontinued. 2 other patients developed grade 3 nausea and vomiting requiring modification of the chemotherapy schedule.

DISCUSSION

The prognosis of patients with malignant glioma is poor, and an increasingly diverse range of therapeutic approaches has been adopted at the time of progression after primary therapy has failed. Treatment at recurrence includes further surgical resection, radiotherapy, chemotherapy or investigational treatments such as brachytherapy, stereotactic radiotherapy or the use of systemic or intralesional biological agents. The assessment of efficacy of conventional and new treatment modalities is complicated by the difficulty of evaluating responses on conventional CT or MR imaging, and by the difficult assessment of clinical response in patients with neurological deficit.

Survival is the most objective endpoint in the assessment of treatment efficacy as the majority of patients with recurrent glioma die from progressive recurrent tumour. However, the factors which determine survival in patients with recurrent glioma are poorly documented. Prolongation of survival has been used as an endpoint in some studies (e.g. brachytherapy), but selection of patients by favourable prognostic factors at the time of recurrence may be the most important determinant of survival rather than the efficacy of the new form of therapy tested [8].

Table 5. Response to chemotherapy

Characteristic	Response (Number of patients) CR + PR*		SD + PD	NE	P (uni)
All	57	(27%)	134	20	<0.005
Age at chemotherapy (years)					
<40	20	(38%)	28	5	
41–59	33	(28%)	73	13	<0.005
≥60	4	(10%)	33	2	
KPS					
>70	38	(35%)	61	8	<0.005
≤70	19	(18%)	73	12	
Grade					
HG Astro	33	(22%)	100	14	
LG Astro and oligo	23	(37%)	33	5	NS
LG Astro	13	(38%)	19	5	
Oligo	10	(42%)	14	—	
Prognostic groups					
Good	27	(46%)	27	5	
Intermediate	21	(25%)	56	6	<0.005
Poor	9	(13%)	51	9	

*Figures in parentheses, % response rate.
uni, univariate analysis; NE, not evaluable; NS, non-significant.

Chemotherapy has been and, at present, remains the treatment modality most widely used in patients with recurrent glioma. Nitrosoureas are considered the most effective agents, and have been used either alone or in combination. Therefore, the natural history of patients with recurrent glioma, treated with nitrosourea-containing chemotherapy, may provide a baseline for evaluating the effectiveness of new treatment modalities.

Previous studies reviewing the efficacy of a wide range of chemotherapy regimens at the time of relapse have documented response rates of 17–92%, with time to progression between 23 and 78 weeks, and median survivals of 6 and 11 months for glioblastoma multiforme and anaplastic astrocytoma [9]. However, such studies include small numbers of patients and suffer from a lack of uniformity in the response criteria where "stable disease" has variably been recorded as response or no response. Larger scale reviews are usually in the form of a summary of many small phase II studies, including cases from a number of institutions with varying inclusion criteria. It is, therefore, reasonable to present a large single-centre experience of chemotherapy in patients with recurrent glioma where the criteria for patient selection were relatively uniform and all patients considered suitable for chemotherapy were included in the analysis.

The population of patients studied was relatively heterogeneous. However, in terms of chemotherapy, all patients received a nitrosourea, either alone (CCNU or BCNU) or in combination with other agents, including vincristine and procarbazine (e.g. PCV; Table 3). The schedules reflect the agents thought to hold promise in the systemic management of glioma during the period of the study. In the mid-1980s, cisplatinum was added because of presumed activity in malignant glioma [10]. There is little evidence, at present, that combination chemotherapy is more effective than single-agent nitrosourea, with the exception of a single randomised study comparing BCNU alone with PCV in an adjuvant setting [11]. The response rate to cisplatinum alone in patients with recurrent glioma using strict response criteria is small. No additional response (data not shown) or survival benefit accrued in patients receiving cisplatinum, further questioning its effectiveness in the treatment of malignant glioma. However, a small survival benefit cannot be excluded.

Dose intensity is considered an important determinant of response and survival, and this has largely been shown in curative chemotherapy. The varying number of chemotherapy courses in this cohort of patients is not a reflection of varying dose intensity. Treatment was usually discontinued because it was not effective and reflects the short survival of this group of patients. It was, therefore, not possible to perorm a dose intensity analysis, although longer, more intensive treatment may be more effective. However, studies of marrow-ablative doses of BCNU in the primary therapy of high-grade glioma have not demonstrated a survival benefit [12].

The 1-year survival from the time of chemotherapy of 211 patients with recurrent glioma was 30%, and 2-year survival 10%. It does not represent the prognosis of all patients with recurrent glioma, as some patients, particularly those with severe disability are not suitable for any form of active treatment. Such selection undoubtedly favours less disabled, younger patients, but is representative of the type of patients referred for active treatment at the time of recurrence.

Age, histological grade and Karnofsky performance status were independent prognostic factors for survival in the whole population of patients with recurrent glioma, and these are identical to the most important prognostic factors in patients with primary disease [13–17]. Progression-free interval, which may reflect the tumour grade, was of prognostic significance only on univariate analysis.

The results highlight the importance of tumour grade in determining survival in patients with malignant glioma. The prognosis of patients with high-grade glioma at the time of recurrence remains poor, with only 22% 1-year survival. Age and performance status also remain independent prognostic factors for survival. The additional significance of progression-free interval on univariate analysis suggests that patients who remain clinically stable without progression for longer periods may have more indolent disease, where primary biopsy may have selectively sampled a high-grade component of a less aggressive low-grade tumour.

The prognosis in patients with low-grade tumours, including low-grade astrocytoma and oligodendroglioma, is marginally better with 44% 1-year survival from the time of chemotherapy. There was no difference in outcome between the two low-grade histologies. Although it would be of interest to distinguish patients who have transformed at the time of recurrence to higher grade tumour from those with recurrent low-grade glioma, too few patients were rebiopsied to provide a satisfactory answer.

Response to chemotherapy, where response rate represents either complete or partial response, is considered the principal tool in assessing the effectiveness of treatment. There is no uniform agreement on the methods of assessment, although a consensus view has been published [5]. Given the difficulty in the assessment of response in a prospective setting, it is clearly difficult to assess response retrospectively. The response data presented are only indicative of clinical and radiological response, and are subject to all the errors of such retrospective measurement. Nevertheless we have shown a correlation between response and survival, as demonstrated in many other chemotherapy studies.

It has been suggested that oligodendrogliomas are more chemosensitive than other glial tumours [18]. The response was higher in low-grade tumours (low-grade astrocytomas and oligodendrogliomas) compared to high-grade tumours, which was reflected in a survival benefit in patients with low-grade tumours. There was no difference in response or survival between low-grade astrocytomas and oligodendrogliomas.

A number of patients received combination chemotherapy. This included a variety of drugs, reflecting the agents popular at the time of treatment. Their specific efficacy has not been assessed in this study, with the exception of cisplatinum, which was used in a phase II study not previously published. Our results do not show any response or survival benefit in patients receiving cisplatinum.

In summary, we have defined the overall prognosis and the prognostic factors for survival in a large group of patients with recurrent glioma treated with nitrosourea-containing chemotherapy. The factors which determine survival are essentially those predictive of outcome in patients with primary malignant glioma. We have clearly demonstrated that patient and tumour factors are powerful determinants of outcome, and future design of prospective studies, assessing new treatments in recurrent disease, should incorporate stratification by prognostic factors. This is particularly important when survival is used as the objective endpoint. Knowledge of the influence of such prognostic factors may also be used to guide the clinician in selecting patients for appropriate treatment protocols, either within or outside clinical studies.

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DNA Content as a Predictor of Clinical Outcome in Soft Tissue Sarcoma Patients

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The prognostic relevance of cellular DNA content has been shown for a variety of human malignancies. However, only a few studies concerning soft tissue sarcomas have been published. Biopsies of 81 patients with soft tissue sarcomas, referred for primary or secondary surgery, were analysed by flow cytometry to determine cellular DNA content of tumours. Most patients (60/81) already had one or more local recurrences at the time of first presentation at Essen University. The median age of the patients was 45 years (range 14–79). 44 (54%) patients had euploid and 37 (46%) had aneuploid tumours. Age, sex, and tumour localisation (trunk versus extremity) were equally distributed between euploid and aneuploid sarcoma patients. The median follow-up was 69 months (range 9–312). The median survival time for euploid and aneuploid tumours was 84 and 30 months, respectively ($P < 0.0005$). In the univariate analysis, ploidy, S-phase percentage, localisation and tumour grading were significant predictors of survival, whereas in the multivariate analysis, only DNA content and tumour localisation were independent prognostic variables for survival.

Key words: sarcoma, ploidy, prognostic factor
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INTRODUCTION

HUMAN SOFT tissue sarcomas consist of a histologically and prognostically, very heterogeneous group of tumours. Distant metastases occur in approximately 50% of patients and remain the major cause of death in soft tissue sarcoma patients [1–5]. The considerable morbidity of currently available adjuvant chemotherapeutic regimens, including high doses of doxorubicin and ifosfamide, appears to be unreasonable in the subgroup of patients, who have a good prognosis by local treatment alone. Therefore, identifying patients with a high risk of distant