THE VALUE OF POSTOPERATIVE RADIOTHERAPY OF PRIMARY SPINAL CORD GLIOMA

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SUMMARY

Forty patients with spinal cord gliomas, irradiated postoperatively between 1976 and 1994 at the Department of Radiation Oncology of Maria Skłodowska-Curie Memorial Centre in Kraków, were retrospectively reviewed. Twenty seven (67%) patients were classified as those with ependymomas, and 13 (33%) with astrocytomas. Thirty six patients were irradiated because of non radical excision, in 4 cases indication for radiotherapy was high grade histology. The overall actuarial survival rates at 5 and 10-years were 74% and 71%, respectively. The 10-year relapse free survival was 69%. Multivariate analysis showed that only age, histology and neurological function were correlated with survival time. Patients under 30 years of age, with ependymoma, and with very good, good or moderate neurological function carried the best prognosis.

Key words: spinal cord glioma, radiotherapy, prognostic factors.

INTRODUCTION

Primary tumours of the spinal cord are rare and account for about 7% of adult central nervous system neoplasms [1,2]. Gliomas occur in 22% of all primary spinal tumours, of these 63% are ependymomas, 25% are astrocytomas and 7% are glioblastomas [3].

The management of spinal cord glioma is still unclear. The treatment of choice is surgical resection with preservation of neurologic function. [4-8]. Because of their infiltrative nature, the excision of spinal glioma can be difficult to achieve. Complete surgical resection is potentially curative. It is generally accepted that postoperative irradiation is suggested when macroscopic or microscopic residual tumour persists [3,9-18]. The radiosensitivity of the spinal cord limits the dose of radiation that can be given to the tumour. Most authors recommend a dose of 45-55 Gy delivered with conventional fraction doses. For patients with high grade gliomas, localised at the level of thoracic or lumbar spinal cord, who have permanent transverse meyolopathy application of doses higher or equal 60 Gy, has also been an option [18,19].

MATERIAL AND METHODS

Records of 40 patients with spinal cord gliomas, irradiated postoperatively between 1976 and 1994 at the Department of Radiation Oncology of Maria Skłodowska-Curie Memorial Centre in Kraków, were retrospectively reviewed. The parameter monitored to determine clinical response to therapy was neurological function (according to Shirato scale – *Tab. 1*) [18].

Tab. 1. Classification of neurological functions according to Shirato [18].

Assessment	Neurological function
Excellent	Intact or minimal neurological deficit, no functional impairment
Good	Mild neurological deficit, ambulating without braces or aids, no functional impairment
Fair	Moderate neurological deficit, ambulating with braces and/or aids, significant functional impairment
Poor	Quadriplegic or paraplegic, wheelchair dependent, significant functional impairment

There were 16 female (40%) and 24 male (60%) patients with a median age of 33 years (range: 16-57). Pain was the most common presenting symptom at pretreatment examination, followed by motor weakness, sensory loss and sphincter dysfunction. The median length of symptoms, prior to diagnosis, was 36 months (range: 1 month to 150 months). Initial radiological investigation consisted of myelogram alone in 34 cases (85%), myelogram and CT in 2 cases (5%), CT in 2 cases (5%) and MRI in 2 cases (5%). The distribution of sites of involvement was as follows: cervical spinal cord - 2 patients (5%), thoracic - 11 patients (32%) and cauda equina - 21 patients (34%). In 6 patients (15%), a multifocal spinal disease was observed. All patients underwent surgical resection aimed at removing as much tumoral tissue as possible with preservation of neurologic function. Thirty five surgical resections (88%) were considered as subtotal, 4 (10%) as gross total resection and 1 (2%) as biopsy alone. The distribution of histologic types in the group studied was as follows: 27 ependymomas (67%), 13 astrocytomas (33%). In 33 (82.5%) cases histology grade was available.

Before radiotherapy, performance status and neurological function were assessed. Karnofsky's score was superior or equal to 80% in 6 cases (15%), 70%-50% in 32 cases (80%) and 40% or less in 2 cases (4%). Neurologic function was assessed as very good in 3 patients (8%), good in 12 patients (30%), moderate in 14 patients (35%) and poor in 11 patients (27%)

All patients were treated with megavoltage external beam radiotherapy, energies used including cobalt (1.25 MV) and 9 MV photons. Thirty six patients were irradiated because of non radical excision; in 4 cases indication for radiotherapy was high grade histology. The total dose ranged from 24 to 75 Gy (mean: 51.13 Gy), delivered with daily fractions of 1.5-6 Gy (*Tab. 2*). The direct posterior field in 36 patients (90%) or posterior oblique fields with wedges in 4 patients (10%) were used. The treatment volume covered the residual tumour or the site of the tumour removal with a margin of 3 cm. Doses above 55 Gy were used in patients who already had poor motor function status, with tumour location in the thoracic or lumbar spinal cord. In those cases no deterioration of neurological function was apparent.

Tab. 2. Range of total and fraction doses in the analysed group.

Total dose	Fraction dose	No of patients	%
25 – 45 Gy	2.5 - 6 Gy	8	20
>45 – 55 Gy	1.5 – 3 Gy	22	55
>55 Gy	2 – 3 Gy	10	25

Survival was measured from the first day of radiotherapy. The survival was estimated by the Kaplan-Meier method [20]. Prognostic factor analysis included univariate and multivariate analysis. The Kaplan-Meier method and log rank test were used for univariate analysis; the Cox regression model was used for multivariate analysis [21,22].

RESULTS

The treatment was generally well tolerated. All patients completed their course of radiation therapy.

After radiotherapy, 23 patients (58%) showed improvement in neurological function, in 15 cases (37%) neurological function was assessed as steady. In 2 (5%) cases neurological function became worse due to progression of the tumour.

Survival

The overall actuarial survival rates at 5 and 10-years were 74% and 71%, respectively (*Fig. 1*). The 10-year relapse free survival was 69% (*Fig. 2*).

The following characteristics were associated with improved patient survival by univariate analysis: age <=30; very good, good and moderate neurological function before radiotherapy; ependymoma histology; and tumour location in cauda equina (test log rank p<=0.05, *Figs. 3-6*). Gender and total dose had no influence on prognosis. There was no assessment of tumour grade due to small subgroups.

Results of univariate analysis of prognostic factors are presented in *Tab. 3*. Multivariate analysis showed that only age, histology and neurological function were correlated with the survival time. Patients under 30 years of age, with ependymoma, and with very good, good or moderate neurological function carried the best prognosis. The definitive results of the Cox model are given in *Tab. 4*.

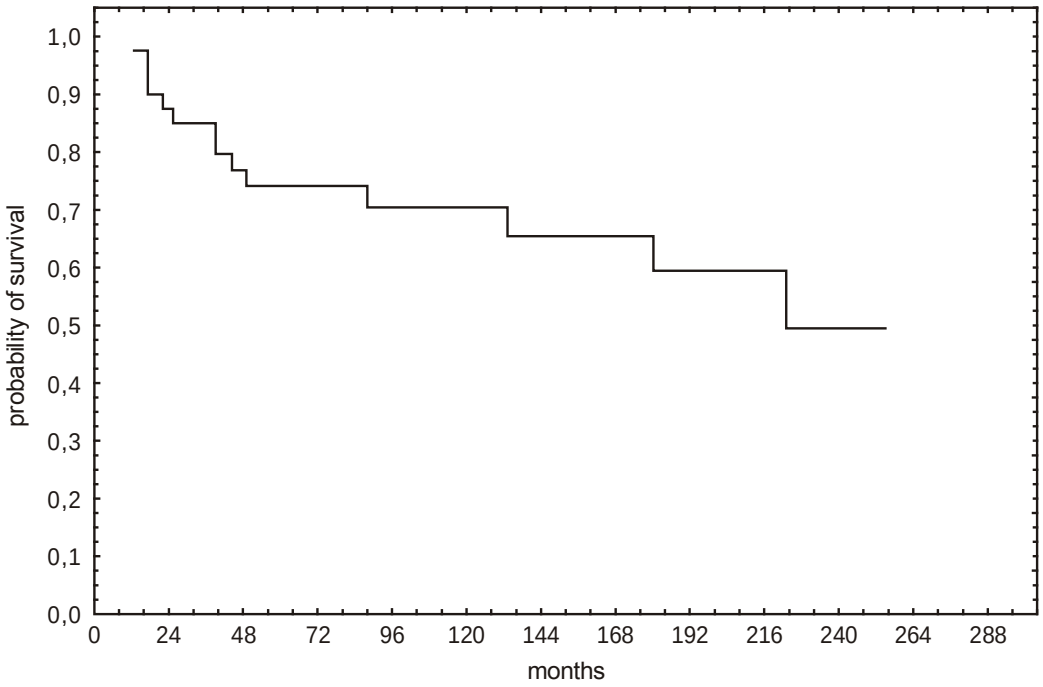

Fig. 1. Overall survival of 40 postoperatively irradiated patients with spinal cord gliomas.

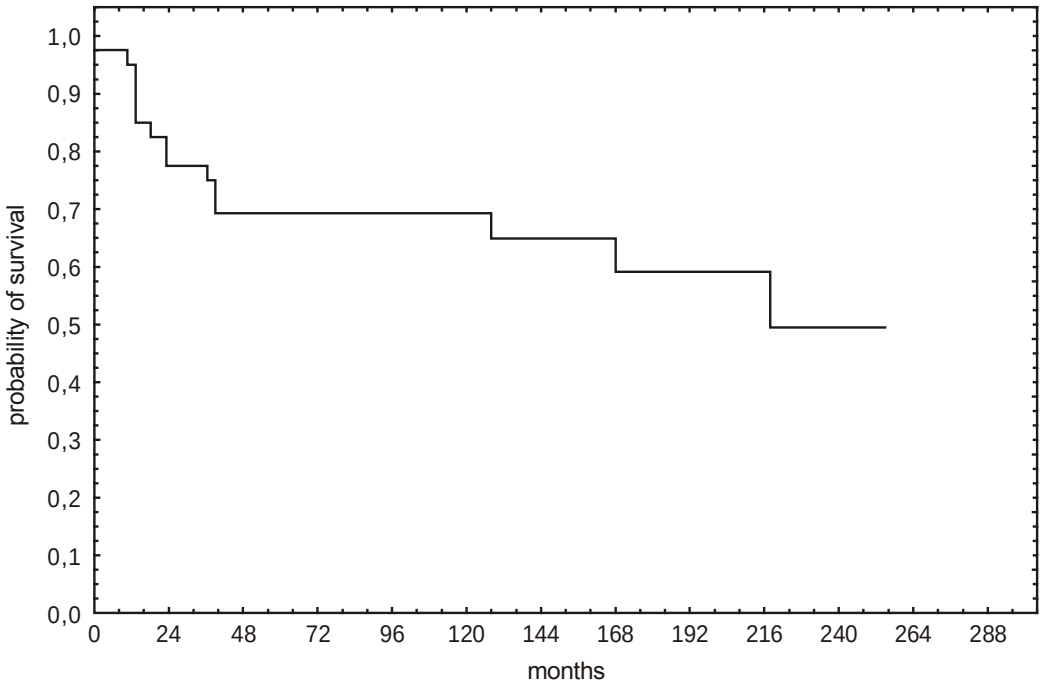

Fig. 2. Relapse free survival of 40 postoperatively irradiated patients with spinal cord gliomas.

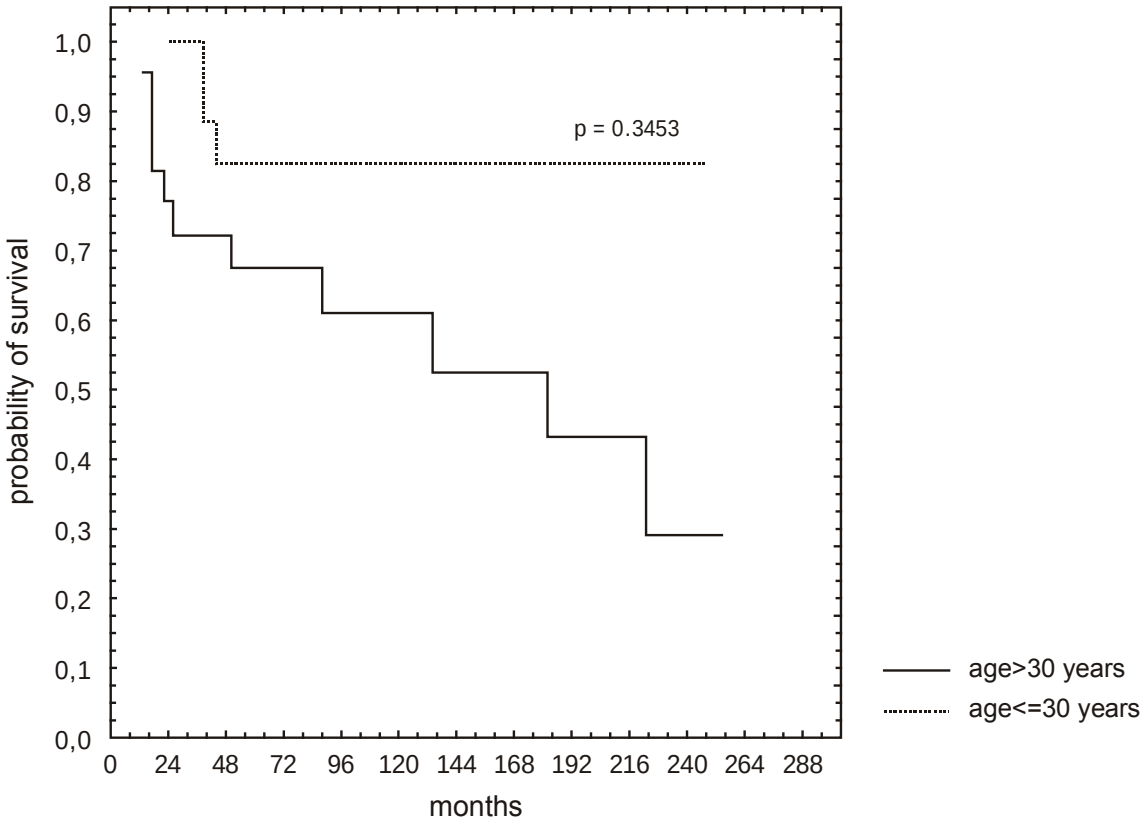

Fig. 3. Overall survival of 40 postoperatively irradiated patients with spinal cord gliomas according to age.

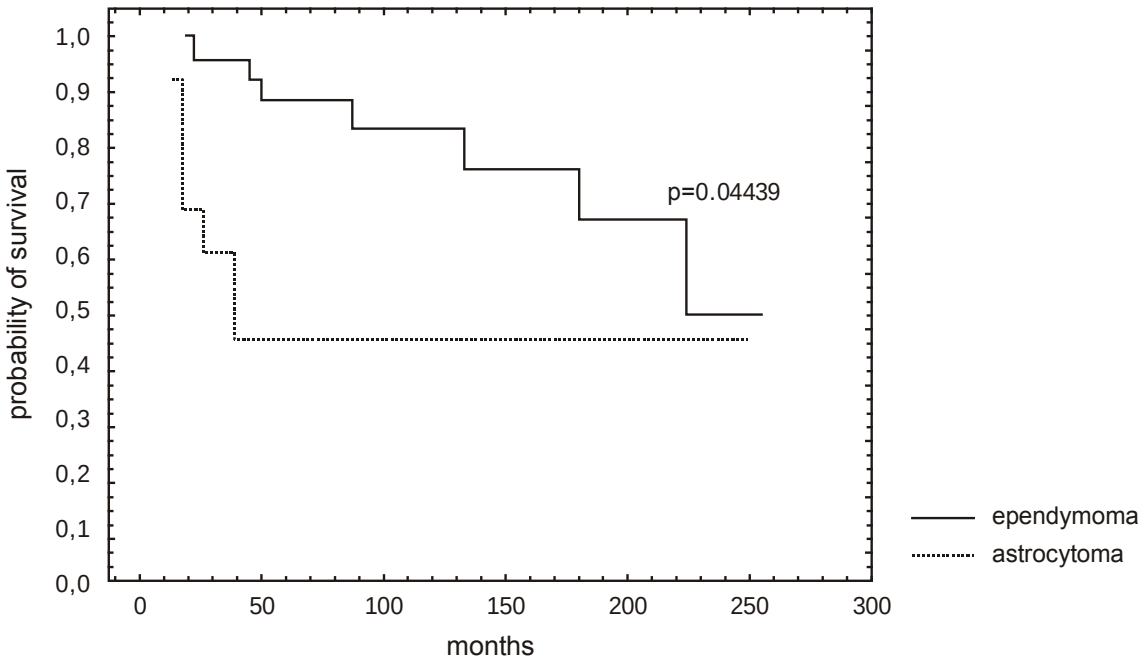

Fig. 4. Overall survival of 40 postoperatively irradiated patients with spinal cord gliomas according to histology.

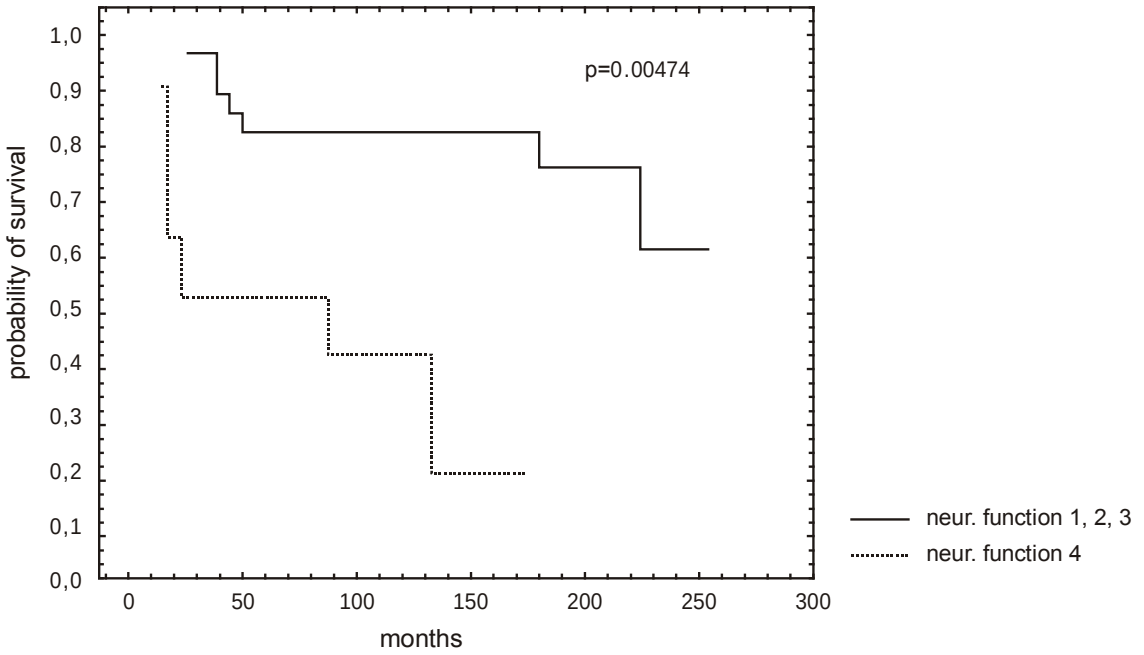

Fig. 5. Overall survival of 40 postoperatively irradiated patients with spinal cord gliomas according to neurological function (Shirato scale).
neur. function 1,2,3 very good, good, moderate neurological function
neur. function 4 poor neurological function

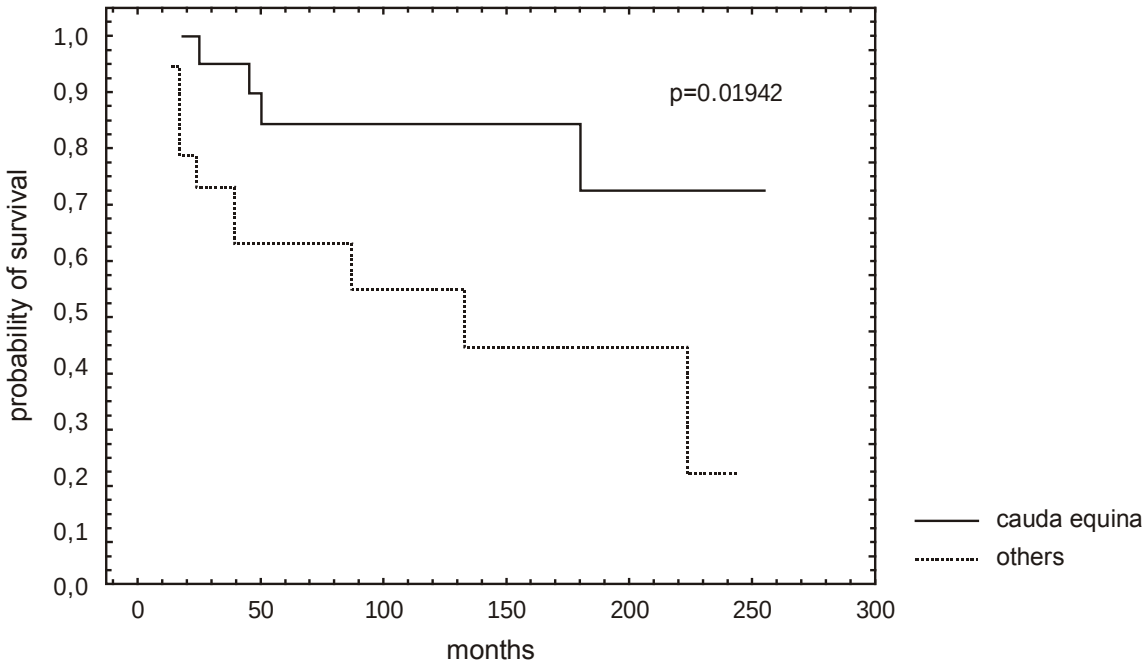

Fig. 6. Overall survival of 40 postoperatively irradiated patients with spinal cord gliomas according to localisation.

Tab. 3. Univariate analysis of prognostic factors in 40 patients with spinal cord glioma.

Factors	Relative risk	p	Actuarial 10-year survival	p
Age				
<=30 n=18	1.00	-	82%	0.03453
>30 n=22	8.13	0.011413	61%	
Gender				
male n=24	1.00	-	75%	0.89432
female n=16	1.07	0.894151	65%	
Neurological function				
very good, good, moderate n=29	1.00	-	82%	
poor n=11	4.14	0.024456	42%	0.00474
Localisation				
cauda equina n=21	1.0	-	84%	
others n=19	3.67	0.028589	55%	0.01942
Histology				
ependymoma n=27	1.00	-	84%	
astrocytoma n=13	3.01	0.041276	46%	0.04439
Total dose				
>45 Gy n=32	1.0	-	78%	
<= 45 Gy n=8	2.01	0.212003	50%	0.18279

Tab. 4. The definitive Cox model in 40 patients with spinal cord glioma.

Factor	Relative risk	P-value	Confidence interval
Histology			
ependymoma	1.00	-	2.11-35.53
astrocytoma	8.65	0.002761	
Age			
<=30	1.00	-	1.60-41.30
>30	8.13	0.011413	
Neurological function			
very good, good, moderate	1.00	-	1.20-14.28
poor	4.14	0.024456	

Recurrences

Clinical progression was observed in 15 patients (37%), in all cases the failure was observed at the primary site. In 3 cases it was documented by myelogram, in 4 cases by CT, in one case by MRI and in 7 cases assessed only by neurological examination. The median time to recurrence was 20 months (range: 1-217 months). Four patients underwent second operation, one combined therapy - surgery and chemotherapy and one - chemotherapy. Nine patients received only symptomatic treatment.

DISCUSSION

Numerous prognostic factors have been reported in spinal cord gliomas such as

age, performance status, neurological function, length of symptoms, tumour histology, grade, location and stage.

Our results indicate that histology and age are the principal variables determining the survival of patients with spinal cord gliomas.

The actuarial 10-year survival rates were 84% and 46% respectively, in patients with ependymoma and astrocytoma (p=0.04439). Patients with low grade ependymoma have an excellent survival rate, while patients with astrocytoma, even of low grade, have a less favourable outcome. These findings agree with many other reports [9-11,18,23-25]. Shirato et al present 5-year actuarial survival rates in ependymal tumour and those in astrocytic tumour 96% and 50%, respectively (p=0.007) [18].

The actuarial 10-year survival rates were 82% and 61%, respectively, in patients aged 30 or under and those over 30 (p=0.03453). In the series of 52 patients with spinal cord gliomas reported by Rodriges et al., 5-year cause-specific survival rates were, respectively, 100% in patients aged 18 or under compared to 56% in patients over 18 (p=0.03) [3]. Huddart et al. found 5-year overall survivals of 80%, 64% and 38% in patients under 16, those between 16 and 39, and those over 40, respectively (borderline statistical significance p<0.10) [26]. On the other hand, there are a few reports which did not find differences in the survival rates depending on age [16,17,24].

Also the parameters of neurological state showed prognostic influence on the survival in the multivariate analysis of our series. The actuarial 10-year survival rate was 82% in patients with very good, good and moderate neurological function and 42% in patients with poor neurological function (p=0.00474). These findings agree with other reports [23,27]. Neurological function is directly connected with stage and length of the disease, and tumour location. Neurological status is better in patients with a low stage disease and those with tumour located in the cauda equina. Duration of symptoms is shorter in this group compared to patients with poorer neurological function, which allows recovery of neurological function after treatment. An attempt has been made to explain the favourable prognosis in younger patients with good neurological function by better tolerance of treatment: surgery as well as radiotherapy.

In our material, univariate analysis showed that tumour location was a statistically significant prognostic indicator. The actuarial 10-year survival rates were 84% and 55%, respectively, in patients with tumour of cauda equina and other sites (p=0.01942). This is consistent with the study of Garcia who found that patients with tumours of cauda equina had significantly better survival than those with tumours at other locations [9]. Explanation for this observation includes greater concentration of function per unit volume of the spinal cord in comparison with cauda equina.

In the presented series, gender had no influence on prognosis, which is in agreement with the results of Rodrigues et al. [3]. However, some authors have observed that female patients have statistically significant survival advantage over male patients [24,26].

The treatment of choice for spinal cord glioma is surgery. After radical excision postoperative radiotherapy is not indicated because of a low local recurrence rate [4,5,7,8]. Complete resection should not be attempted however, if more extensive surgical excision would result in unacceptable neurologic deficit. With modern surgical techniques, ependymomas are relatively easy to excise completely [5,25,28]. Total resection of astrocytoma is usually difficult because its margin from the normal spinal cord is poorly defined as compared with ependymoma. The extent of surgery does not influence significantly the survival of patients with astrocytic spinal cord tumours [3,8,10,12,23].

Combined surgery and postoperative radiotherapy in patients with spinal cord glioma make it possible to obtain long-term survival. Review of the literature confirms that postoperative irradiation is beneficial in patients with biopsied or subtotally excised spinal cord glioma [3,9-18,25,26]. The doses required for the optimal management of spinal cord gliomas are not well established due to the rarity of this tumour type. Most

authors recommend doses of 45-50 Gy, conventionally fractionated. In the series presented by Cohen and Shirato, some patients received a total dose of 60 Gy and higher, but because of the small number of patients no dose response relationship to establish a control rate has been recorded [18,19]. The patients treated in this way had a high grade glioma at the level of the thoracic or lumbar spinal cord and already showed permanent poor motor function.

In the present series no significant differences in the survival retes were found in patients who were treated with a dose lower than 45 Gy, when compared with those treated with 45 Gy or more. This is consistent with most of the publicshed results. It should be noted, however, that interpretation of dose response data in small retrospective series is not reliable.

The high incidence of local failure, despite total dose in the range of 45-50 Gy, indicates a need for more effective therapy. Strategies to increase dose delivered with acceptable levels of late toxicity should be investigated. Hyperfractionated irradiation for spinal cord tumours offers the ability to elevate total dose and maintain the same level of late effects. The use of novel radiotherapy techniques such as: 3-D treatment planning, dynamic conformal RT, and stereotactic RT might improve local control. The systemic therapy can also be considered in patients with high-grade tumours. It is possible that combination of radiotherapy and chemotherapy in this group will result in more favourable outcomes.

CONCLUSION

1. Combined surgery and postoperative radiotherapy in patients with spinal cord glioma result in 5-year and 10-year overall actuarial survival rates in 74% and 71% of cases, respectively.
2. Age, histology (astrocytoma vs. ependymoma) and neurological function before radiotherapy were significant variables determining the survival of patients with spinal cord glioma. Patients under 30 years of age, with ependymoma, and with very good, good or moderate neurological function carried the best prognosis.

REFERENCES

1. Wood EH, Berne AS, Taveras JM. The value of radiation therapy in the management of intrinsic tumors of spinal cord. Radiology 1954;63:11-22.
2. Kurland LT. The frequency of intracranial and intraspinal neoplasms in the resident population of Rochester, Minesota. J Neurosurg 1958;15:627.
3. Rodrigues GB, Waldron JN, Wong CS, Laperriere NJ. A retrospective analysis of 52 cases of spinal cord glioma managed with radiation therapy. Int J Radiat Oncol Biol Phys 2000;48:837-42.
4. Cooper PR, Epstein F. Radical resection of intramedullary spinal cord tumors in adults. Recent experience in 29 patients. J Neurosurg 1985;63:492-9.
5. McCormick PC, Torres R, Post KD, Stein BM. Intramedullary ependymoma of the spinal cord. J Neurosurg 1990;72: 523-32.
6. Epstein FJ, Farmer JP, Freed D. Adult intramedullary astrocytomas of the spinal cord. J Neurosurg 1992;77:355-9.
7. Sawaya R. Neurosurgery issues in oncology. Curr Opin Oncol 1991;3:459-66.
8. Guidetti B, Mercuri S, Vagonzi R. Long term results of the surgical treatment of 129 intramedullary spinal gliomas. J Neurosurg 1981;54:323-30.
9. Garcia DM. Primary spinal cord tumors treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 1985;11:1933-9.
10. Linstad DE, Wara WM, Leibel SA, Gutin PH, Wilson CB, Sheline GE. Postoperative radiotherapy of primary spinal cord tumors. Int J Radiat Oncol Biol Phys 1989;16:1397-403.
11. Chun HC, Schmidt-Ullrich RK, Wolfson A, Tercilla OF, Segerman RH, King GA. External beam radiotherapy for primary spinal cord tumors. J Neurooncol 1990;9: 211-7.

12. Sandler HM, Papadopulos SM, Thornton AF Jr, Ross DA. Spinal cord astrocytomas: results of therapy. Neurosurgery 1992;30:490-3.

13. Whitaker SJ, Bessel EM, Ashley SE, Bloom HJ, Bell BA, Brada M. Postoperative radiotherapy in the management of spinal cord ependymoma. J Neurosurg 1991;74:720-8.

14. Wen BC, Hussey DH, Hitchon PW, Schelper RL, Vigliotti AP, Doornbos JF, et al. The role of radiation therapy in the management of ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 1991;20:781-6.

15. Nishio S, Morioka T, Fujii K, Inamura T, Fukui M. Spinal cord gliomas: management and outcome with reference to adjuvant therapy. J Clin Neurosci 2000;7: 20-3.

16. Abdel-Wahab M., Corn B, Wolfson A, Raub W, Gaspar LE, Curran W, et al. Prognostic factors and survival in patients with spinal cord gliomas after radiation therapy. Am J Clin Oncol 1999;22:344-51.

17. McLaughlin MP, Buatti JM, Marcus RB, Maria BL, Mickle PJ, Kedar A. Outcome after radiotherapy of primary spinal cord gial tumors. Radiat Oncol Investig 1998;6: 276-80.

18. Shirato H, Kamada T, Hida K, Koyanagi J, Iwasaki Y, Miyasaka K, et al. The role of radiotherapy in the management of spinal cord glioma. Int J Radiat Oncol Biol Phys 1995;33:323-8.

19. Cohen AR, Wisof JH, Allen JC, Epstein F. Malignant astrocytomas of the spinal cord. J. Neurosurg 1989;70:50-4.

20. Kaplan ME, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.

21. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;35:1-39.

22. Cox DR. Regressions models and life tables. J Royal Stat Assoc 1972;34: 187-229.

23. Innocenzi G, Salvati M., Cervoni L, Delfini R, Cantore G. Prognostic factors in intramedullary astrocytomas. Clin Neurol Neurosurg 1997;99:1-5.

24. Jyothirimayi R, Madhavan J, Nair MK, Rajan B. Conservative surgery and radiotherapy in the treatment of spinal cord astrocytoma. J Neurooncol 1997;33: 205-11.

25. Schild SE, Nisi K, Scheithauer BW, Wong WW, Lyons MK, Schomberg PJ. The results of radiotherapy for ependymomas: the Mayo Clinic expirience. Int J Radiat Oncol Biol Phys 1998;42:953-8.

26. Huddart R, Traish D, Ashley S, Moree A, Brada M. Management of spinal astrocytoma with conservative surgery and radiotherapy. Br J Neurosurg 1993;7:473-81.

27. Malis LI. Intramedullary spinal cord tumors. Clin Neurosurg 1978;25:512-39.

28. Ohata K, takami T, Gotou T, El-Bahy K, Morino M, Maeda M, et al. Surgical outcome of intramedullary spinal cord ependymoma. Acta Neurochir (Wien) 1999; 141:341-6.