Table 2. *Continued*

Variables	*n*	1-year survival (%)	2-year survival (%)	3-year survival (%)	*P* value
Mitotic index					
0 or 1 or 2	32	96.9	96.9	87.2	0.0006
3	35	81.7	62.2	56.0	
Glut-1 overexpression					
(−)	19	94.1	94.1	94.1	0.0292
(+)	48	87.2	74.7	65.0	
MIB-1 grade					
1 or 2	17	100.0	100.0	83.3	0.0311
3	50	85.2	72.1	67.0	
Mitotic grade					
1 or 2	19	94.7	94.7	94.7	0.0198
3	48	86.7	72.9	62.1	

SR, surgical resection; AC, adjuvant chemotherapy; RT, radiotherapy; Glut-1, glucose transporter protein 1.

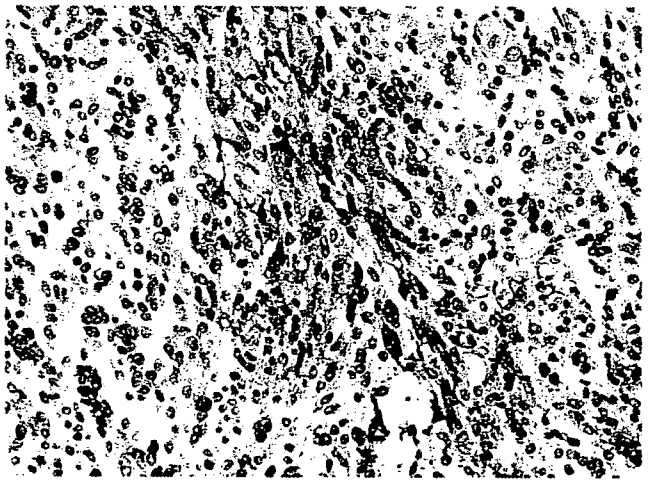

Figure 1. Immunohistochemical analysis of Glut-1. Intensity of Glut-1 staining score: 0 (0%), 1 (1–9%). Histologic diagnosis was pleomorphic malignant fibrous histiocytoma. Glut-1, glucose transporter protein 1.

the presence of local recurrence or metastasis and treatment modality. On the basis of univariate analysis, it was found that Glut-1 overexpression was significantly associated with poor OS ($P = 0.029$, Fig. 4).

Multivariate analysis shows that the presence of metastasis is associated with significantly poor OS ($P = 0.031$, Table 4) than those without metastasis. It also shows that the anatomical site (trunk or extremity), the presence of metastasis, treatment without surgical resection, tumor size, treatment modality, tumor differentiation, necrosis, mitotic index, MIB-1 grade and Glut-1 overexpression were not independently associated with OS. When we excluded the presence of metastasis from variables, mitotic index was significant

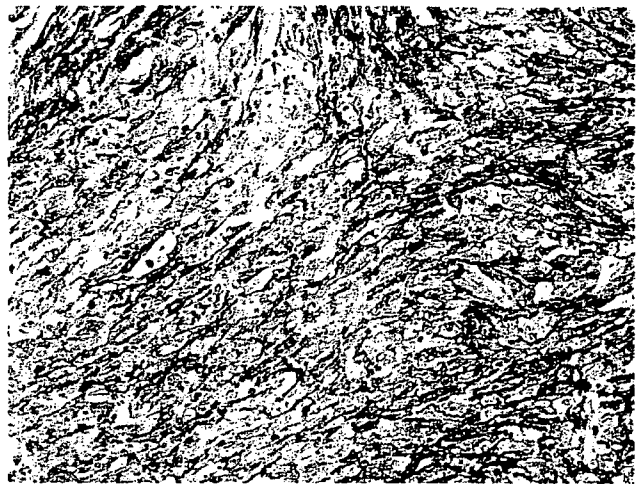

Figure 2. Immunohistochemical analysis of Glut-1. Intensity of Glut-1 staining score: 2 (10–29%). Histologic diagnosis was pleomorphic malignant fibrous histiocytoma.

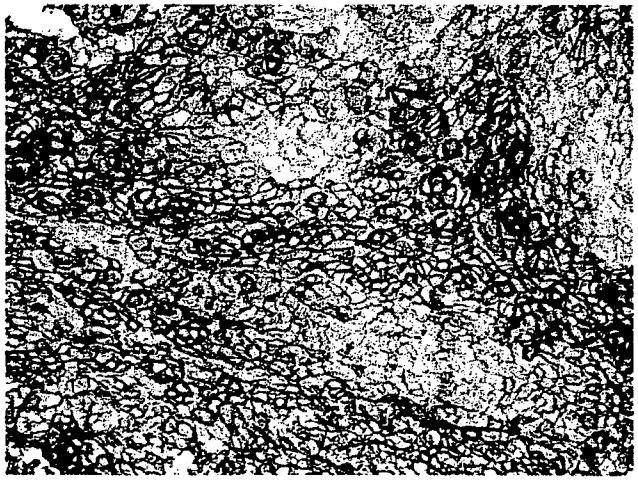

Figure 3. Immunohistochemical analysis of Glut-1. Intensity of Glut-1 staining score: 3 (>30%). Histologic diagnosis was synovial sarcoma.

indicator of poor OS [hazard ratio, 8.709; 95% confidence interval 1.980–38.319; $P = 0.004$).

DISCUSSION

This study suggests three notable features. First, Glut-1 overexpression is a possible adverse prognostic factor similar to the presence of metastasis, treatment without surgical resection, tumor differentiation, necrosis, mitotic index and MIB-1 grade. Secondly, the presence of metastasis is independently associated with poor prognosis in multivariate analysis. Thirdly, there is significant correlation between Glut-1 intensity and MIB-1 grade. Our study is the first that focusing on the relations between Glut-1 expression and prognosis in patients with bone and soft-tissue sarcomas.

Glut-1 expression has been investigated in a variety of tumors (12–14), however, its expression in bone and

Table 3. MIB-1 grade and Glut-1 intensity

MIB-1 grade	Glut-1 intensity			
	0	1	2	3
1	3 (4)	4 (6)	0	0
2	0	4 (6)	1 (1)	5 (7)
3	0	8 (12)	7 (10)	35 (52)

The numbers of the parentheses are percentages.

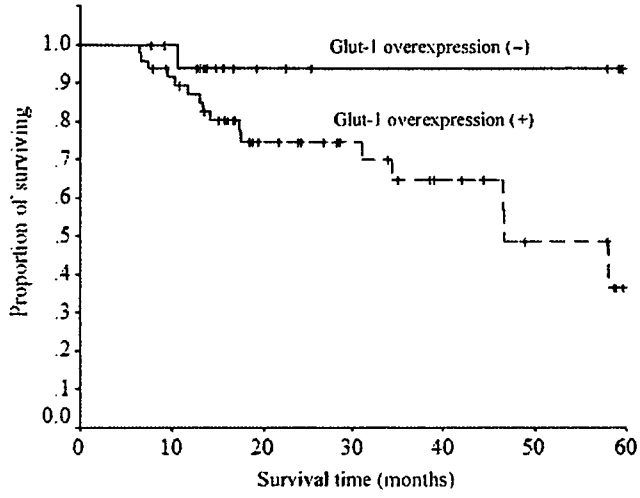

Figure 4. Kaplan–Meier estimated overall survival by Glut-1 overexpression. Patients with Glut-1 overexpression were associated with poor overall survival compared with patients without Glut-1 overexpression.

soft-tissue sarcomas has rarely studied. The aim of this study was to determine whether the intensity of Glut-1 expression in a tumor could serve as a surrogate marker of the survival. On the basis of this study, it was found that Glut-1 overexpression is associated with OS in the univariate analysis. However, it is unknown whether Glut-1 overexpression is more predictive of OS than other variables. Therefore, the immunohistochemical results support the significance of Glut-1 expression as a biomarker of poor prognosis in patients with bone and soft-tissue sarcomas. Glut-1 antibody is achieved easily and inexpensively, and Glut-1 staining can be done as a part of routine pathologic procedure.

Our results suggested that glucose transport by Glut-1 plays an important role in progression of bone and soft-tissue sarcoma. Besides, glucose transport and metabolism provide crucial prognostic information, they have the potential of being future treatment targets. Inhibition of glucose transport is investigated in some cancer cells, for example, inhibition of glucose transport by cytochalasin-B presented increased gemcitabine-induced apoptosis in hepatoma cells (30). Investigation about the inhibition of glucose transport in bone and soft-tissue sarcomas is challenges for the future.

Table 4. Multivariate analysis of overall survival (OS)

	B	SE	Wald	HR	95% CI	*P*-value
Metastasis	0.632	0.293	4.671	1.882	1.061–3.340	0.031

SE, standard error; HR, hazard raio; CI, confidence interval.

Glut-1 expression is the common mediator of glucose uptake in malignant tumors (12–14). However, Glut-1 immunostaining was absent in three tumors (4%) in our study: two well-differentiated liposarcomas and a clear cell chondrosarcoma. Glucose transporter proteins other than Glut-1 exist and expresses in various histologic kinds of malignant tumor (31). It is possible that Glut-1 negative tumors would have been positive for other glucose transporters.

The present study had limitations. Follow-up duration of our study is relatively short to calculate patient OS. Whether Glut-1 overexpression adds original information to several prognostic variables requires a further evaluation in an ongoing long-term study. Glut-1 overexpression has a poor prognostic significance in the univariate analysis. This finding to some extent validates our study population because Glut-1 is an excellent indicator of tumor grade and one of the most important prognostic factors in patients with soft-tissue sarcomas treated with combination therapy. However, Glut-1 overexpression was not independently associated with poor prognosis in our study. Short duration of follow-up in our study may affect the results of multivariate analysis. Treatment regimens and duration were not the same for all the patients. Since combination therapy in our study is eligible for patients with bone and soft-tissue sarcomas, this might be biased with the study analysis.

In conclusion, Glut-1 overexpression could be a negative prognostic factor in patients with bone and soft-tissue sarcomas. These findings support the concept of pretherapeutic stratification with Glut-1 immunostaining to identify high-risk patients and propose a more risk-adapted approach of treatment in patients with bone and soft-tissue sarcomas.

FUNDING

This work was supported in part by grants from Scientific Research Expenses for Health and Welfare Programs and the Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

References

1. Hasegawa T. Yamamoto S. Yokoyama R, Umeda T, Matsuno Y, Hirohashi S. Prognostic significance of grading and staging system using MIB-1 score in adult patients with soft tissue sarcoma of the extremities and trunk. *Cancer* 2002;95:843–51.

2. Kulander BG, Polissar L, Yang CY, Woods JS. Grading of soft tissue sarcomas: necrosis as a determinant of survival. *Mod Patho.* 1989;2:205–8
3. Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U, Vaupel P. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. *Cancer Res* 1996;56: 4509–15.
4. Airley RE, Phillips RM, Evans AE, Double J, Burger AM, Feibig HH., et al. Hypoxia-regulated glucose transporter Glut-1 may influence chemosensitivity to some alkylating agents: results of EORTC (First Translational Award) study of the relevance of tumour hypoxia to the outcome of chemotherapy in human tumour-derived xenografts. *Int J Oncol* 2005;26:1477–84.
5. Griffiths EA, Pritchard SA, Welch IM, Price PM, West CM. Is the hypoxia-inducible factor pathway important in gastric cancer? *Eur J Cancer* 2005:41:2792–805.
6. Hockel M, Vaupel P. Biological consequences of tumor hypoxia. *Semin Oncol* 2001;28:36–41.
7. Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S, et al. Overexpression of Glut-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma. *Cancer* 2003;97:1015–24.
8. Kato H, Takita J, Miyazaki T, Nakajima M, Fukai Y, Masuda N, et al. Correlation of 18-F-fluorodeoxyglucose (FDG) accumulation with glucose transporter (Glut-1) expression in esophageal squamous cell carcinoma. *Anticancer Res* 2003;23:3263–72.
9. Younes M, Lechago LV, Somoano JR, Mosharaf M, Lechago J. Wide expression of the human erythrocyte glucose transporter Glut1 in human cancers. *Cancer Res* 1996;56:1164–7.
10. Airley R, Loncaster J, Davidson S, Bromley M, Roberts S, Patterson A, et al. Glucose transporter glut-1 expression correlates with tumor hypoxia and predicts metastasis-free survival in advanced carcinoma of the cervix. *Clin Cancer Res* 2001;7:928–34.
11. Airley RE, Loncaster J, Raleigh JA, Harris AL, Davidson SE, Hunter RD, et al. GLUT-1 and CAIX as intrinsic markers of hypoxia in carcinoma of the cervix: relationship to pimonidazole binding. *Int J Cancer* 2003:104:85–91.
12. Younes M, Brown RW, Stephenson M, Gondo M, Cagle PT. Overexpression of Glut1 and Glut3 in stage I nonsmall cell lung carcinoma is associated with poor survival. *Cancer* 1997:80:1046–51.
13. Haber RS, Rathan A, Weiser KR, Pritsker A, Itzkowitz SH, Bodian C, et al. GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis. *Cancer* 1998;83:34–40.
14. Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R, et al. GLUT-1 expression in ovarian carcinoma: association with survival and response to chemotherapy. *Cancer* 2001:92:1144–50.
15. Green FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, et al. *AJCC Cancer Staging Manual.* 6th edn. New York: Springer 2002.
16. Sobin LH, Wittekind C. UICC TNM Classification of Malignant Tumours. 6th edn. New York: Wiley 2002.
17. Fletcher CDM, Unni KK, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon, France: IARC Press 2002.
18. Hasegawa T, Yamamoto S, Nojima T, Hirose T, Nikaido T, Yamashiro K, et al. Validity and reproducibility of histologic diagnosis and grading for adult soft-tissue sarcomas. *Hum Pathol* 2002:33:111–5.
19. Haberkorn U, Bellemann ME, Brix G, Kamencic H, Morr I, Traut U, et al. Apoptosis and changes in glucose transport early after treatment of Morris hepatoma with gemcitabine. *Eur J Nucl Med* 2001:28:418–25.
20. Medina RA, Owen GI. Glucose transporters: expression, regulation and cancer. *Biol Res* 2002;35:9–26.