TABLE 3. Prognostic Factors for Recurrence-Free Survival (RFS) in Patients with Synovial Sarcoma of the Soft Tissues

Variable	5-Year RFS Rate (%)	n (%)	*P* Value
Age			0.27
<20 years	50	8 (26.7)	
≧20 years	72	22 (73.3)	
Gender			0.95
Male	67	12 (40.0)	
Female	63	18 (60.0)	
Site			0.08
Distal	89	13 (43.3)	
Proximal	53	17 (56.7)	
Size			0.74
≦5 cm	70	12 (40.0)	
5–10 cm	67	10 (33.3)	
>10 cm	57	8 (26.7)	
Surgical margin			0.26
Adequate	75	16 (53.3)	
Inadequate	57	14 (46.7)	
Depth			0.48
Superficial	50	5 (16.7)	
Deep	68	25 (83.3)	
Stage			0.53
IA	83	6 (20.0)	
IB	100	2 (6.7)	
IIB	80	8 (26.7)	
III	67	3 (10.0)	
IV	46	11 (36.7)	
Adjuvant therapy			0.13
None	88	8 (26.7)	
CTX and/or RTX	56	22 (73.3)	
Internal septa			0.89
Positive	63	10 (33.3)	
Negative	67	20 (66.7)	
Cyst			0.74
Positive	60	19 (63.3)	
Negative	69	11 (36.7)	
Calcification			0.87
Positive	65	22 (73.3)	
Negative	67	8 (26.7)	
Hemorrhage			0.46
Positive	57	16 (53.3)	
Negative	75	14 (46.7)	
Fluid-fluid levels			0.77
Positive	75	5 (16.7)	
Negative	64	25 (83.3)	
Triple signal pattern			0.08
Positive	50	13 (43.3)	
Negative	83	17 (56.7)	
Enhancement			0.36
Homogeneous	71	5 (16.7)	
Heterogeneous	40	25 (83.3)	

Note: CTX, chemotherapy; RTX, radiotherapy.

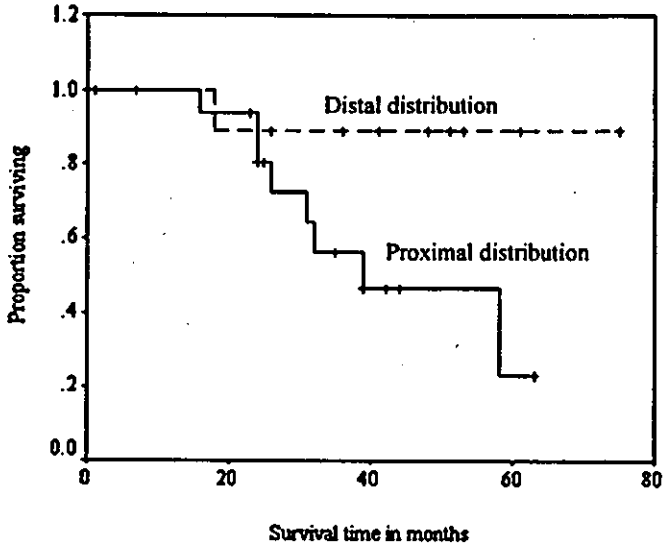

FIGURE 6. Influence of tumor site on the disease-free survival (DFS) in 30 patients with synovial sarcoma of the soft tissues ($P < 0.05$).

scribed that the areas of low signal intensity on T1-weighted images and high signal intensity on T2-weighted images also corresponded to viable portions.[10] Although tissue specimens revealed a biphasic nature within the tumors, no apparent correlation was found between the signal intensity on MR images and the fibrous content of the pathologic specimens.

The limitation of our study is that, given the limited number of patients and limited follow-up, multivariate analysis of the prognostic value of clinical and radiologic findings could not be performed. Whether CT and MR imaging parameters will add original information to the existing prognostic

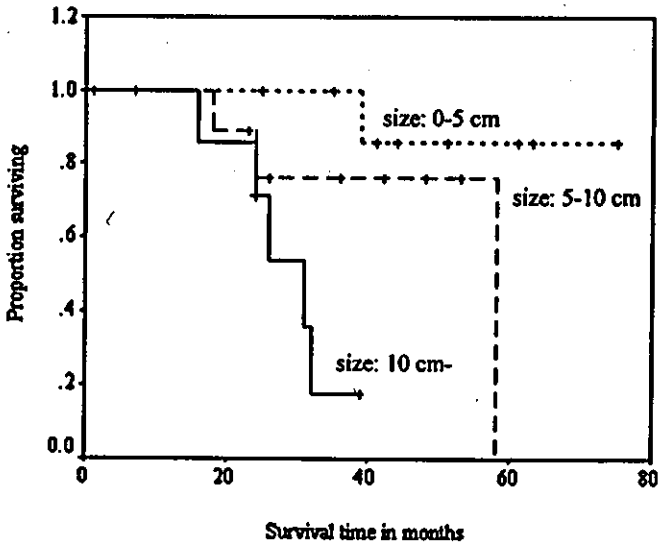

FIGURE 7. Influence of tumor size on the disease-free survival (DFS) in 30 patients with synovial sarcoma of the soft tissues ($P < 0.01$).

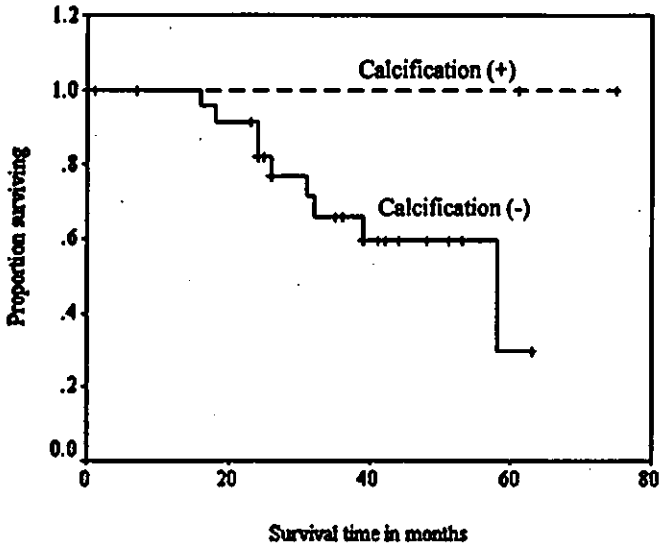

FIGURE 8. Influence of calcification on the disease-free survival (DFS) in 30 patients with synovial sarcoma of the soft tissues ($P < 0.01$).

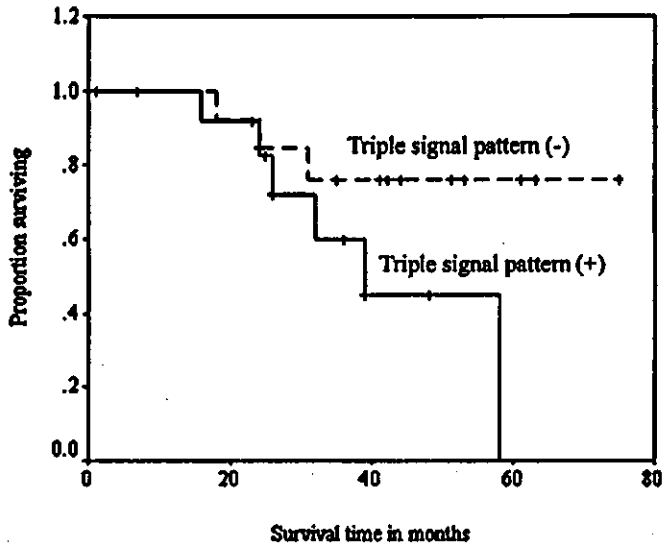

FIGURE 10. Influence of triple signal pattern on the disease-free survival (DFS) in 30 patients with synovial sarcoma of the soft tissues ($P < 0.05$).

variables requires further evaluation in an ongoing long-term study. Of several imaging findings, our results suggested that tumor size could help distinguish between low- and high-grade tumors. However, there was no association between tumor size and clinical outcome by univariate analysis. A retrospective study of 56 patients by Oda et al[22] suggested that large tumor size and extensive tumor necrosis are adverse prognostic factors. Blacksin et al[13] reported that one-third of synovial sarcomas approximately less than 5 cm in diameter had benign characteristics. Our relatively small sample size might affect the statistical analysis.

In conclusion, this study shows that CT and MR imaging findings can assist in distinguishing between low- and high-grade tumors in patients with synovial sarcoma of the soft tissues. Although these imaging findings cannot be considered specific for synovial sarcoma of the soft tissue, an awareness of the typical morphologic appearance may aid in predicting survival.

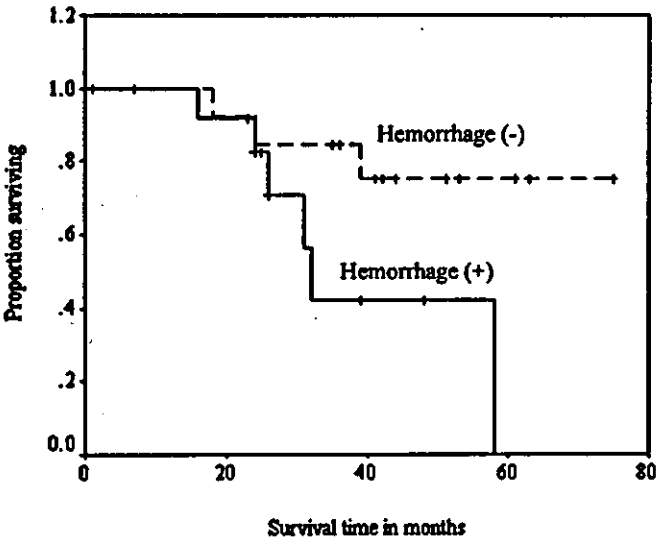

FIGURE 9. Influence of hemorrhage on the disease-free survival (DFS) in 30 patients with synovial sarcoma of the soft tissues ($P < 0.05$).

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Prognostic Significance of MRI Findings in Patients with Myxoid–Round Cell Liposarcoma

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Prognostic Significance of MRI Findings in Patients with Myxoid–Round Cell Liposarcoma

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OBJECTIVE. The aims of this study were to determine the prognostic significance of MRI findings in patients with myxoid–round cell liposarcomas and to clarify which MRI features best indicate tumors with adverse clinical behavior.

MATERIALS AND METHODS. The initial MRI studies of 36 pathologically confirmed myxoid–round cell liposarcomas were retrospectively reviewed, and observations from this review were correlated with the histopathologic features. MR images were evaluated by two radiologists with agreement by consensus, and both univariate and multivariate analyses were conducted to evaluate survival with a median clinical follow-up of 33 months (range, 9–276 months).

RESULTS. Statistically significant MRI findings that favored a diagnosis of intermediate- or high-grade tumor were large tumor size (> 10 cm), deeply situated tumor, tumor possessing irregular contours, absence of lobulation, absence of thin septa, presence of thick septa, absence of tumor capsule, high-intensity signal pattern, pronounced enhancement, and globular or nodular enhancement. Of these MRI findings, thin septa ($p < 0.05$), a tumor capsule ($p < 0.01$), and pronounced enhancement ($p < 0.01$) were associated significantly, according to univariate analysis, with overall survival. Multivariate analysis indicated that pronounced enhancement was associated significantly with overall survival ($p < 0.05$).

CONCLUSION. Contrast-enhanced MRI findings can indicate a good or adverse prognosis in patients with myxoid–round cell liposarcomas.

Liposarcomas are classified into well-differentiated, myxoid, round cell, and pleomorphic subtypes. Myxoid liposarcomas are the most common subtype of liposarcoma, occurring in the extremities of adults. They are considered low-grade sarcomas with a low risk of metastasis and are associated with prolonged survival [1–5]. On the other hand, round cell liposarcomas are considered high-grade sarcomas with a higher likelihood of metastasis and mortality due to disease [1–5]. Recent studies reveal that myxoid and round cell liposarcomas belong to a continuous histopathologic spectrum characterized by a chromosome translocation t(12;16)(q13;p11) resulting in the fusion transcript of the *TLS* and *CHOP* genes [6–9]. However, diagnosis and prognostic predictions can often be complicated by lesions that contain admixed morphologic components of myxoid and round cell subtypes.

The characteristic MRI features of myxoid–round cell liposarcomas are attributable to the predominantly myxoid matrix of the tumor. Tumors appear on T2-weighted MR images as encapsulated tumors with signals that are hyperintense compared with the surrounding structures [10–14]. On contrast-enhanced studies, they often show marked or heterogeneous enhancement with nonenhanced areas corresponding to myxoid material [13, 14]. As expected from the fact that the histopathologic spectrum from myxoid to round cell liposarcomas is continuous, these tumors show considerable diversity on imaging. Therefore, it is important to review the reliability of MRI features for characterizing myxoid–round cell liposarcomas. The objectives of this study were to determine the prognostic significance of MRI findings in patients with myxoid–round cell liposarcomas and to clarify which MRI features best indicate tumors with adverse clinical behavior.

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Materials and Methods

Patients

We reviewed materials from 36 patients with myxoid–round cell liposarcomas, all of whom who were registered in our pathology files. The clinical details, including follow-up information, were obtained by reviewing all the medical charts. None of the patients was lost to follow-up, which began on the date of primary surgery. The median duration of follow-up was 33 months and ranged from 9 to 276 months. The time to death due to any cause was recorded to determine the overall survival rate.

MRI Studies and Pathologic Correlations

MRI was performed using one of two 1.5-T systems (Horizon, General Electric Medical Systems, Milwaukee, WI; or Visart, Toshiba Medical Systems, Tokyo, Japan). Either the spin-echo or the fast spin-echo technique was used to obtain T1-weighted images (TR range/TE range, 460–720/12–27) in one or more planes (coronal or axial). T2-weighted images (TR range/TE_{eff} range, 3,500–6,000/96–112; echo-train length, 8–12) with flow compensation and presaturation superiorly and inferiorly were then obtained in one or more planes using a body coil. The images were obtained with a field of view of 30–40 cm, an image matrix of 128 × 256, and a slice thickness of 6–10 mm. Gadopentetate dimeglumine was administered IV, and T1-weighted images were obtained in one or more planes with (n = 20) or without (n = 16) fat suppression.

Two radiologists reviewed the MR images, and the findings were reported as a consensus opinion. The lesions were judged according to size, location, depth (superficial or deep), type of margin and contours, internal architecture, presence of a tumor capsule, signal characteristics on T1- and T2-weighted images, and homogeneity (homogeneous or heterogeneous). A superficial tumor (dermal or subcutaneous tumor) was located exclusively above the superficial fascia without invasion of the fascia, whereas a deep tumor was located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. The signal characteristics were described as isointense or hyperintense relative to the signal intensity of skeletal muscle. The extent (none and weak or pronounced), pattern (globular and nodular or diffuse), and homogeneity of gadolinium-based enhancement were also recorded. Globular and nodular enhancement corresponded to spotty enhancement (range, 3–10 mm) within the mass on contrast-enhanced MR images. Septal structures were categorized as thin (uniform linear structures ≤ 2 mm) or thick (focally thickened linear structures > 2 mm). Tumors containing areas with high-intensity characteristics on both T1- and T2-weighted MR images were considered positive for a high-intensity signal pattern.

Histologic slides of all the patients' tumors were reviewed for diagnosis by an expert pathologist. Immunohistochemical staining was performed in all cases to confirm the diagnosis or tumor type according to the classification system described by Enzinger and Weiss [1]. In this study, the histologic grade of a tumor was determined using a three-grade system established by Hasegawa et al. [15–17]. According to this system, myxoid–round cell liposarcomas are assigned a grade of 1, 2, or 3. Grade 1 tumors (n = 12, 33.3%) are considered low-grade tumors, grade 2 tumors (n = 14, 38.9%) are intermediate-grade tumors, and grade 3 tumors (n = 10, 27.8%) are high-grade tumors (n = 24, 66.7%). Excised specimens were available for review or for mapping correlation with images. Pathology reports were reviewed for descriptive comments characterizing the necrosis and myxoid-round cell tumor components of the lesions.

Statistical Analysis

Patients' demographics and imaging characteristics were compared using Wilcoxon's rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorized variables. Univariate analysis was performed by comparing survival curves generated using the Kaplan-Meier method and carrying out log-rank tests. The relative risk of each variable subjected to multivariate analysis was estimated using a Cox proportional hazards model. All analyses were conducted using SPSS software version 11.0J (Statistical Package for the Social Sciences, Chicago, IL) for Windows (Microsoft, Redmond, WA). Differences and correlations at a p value of less than 0.05 were considered statistically significant.

Results

Twenty-one (58.3%) of the 36 patients were men and 15 were women (41.7%). The mean age at diagnosis was 47 years, and the patients ranged in age from 17 to 87 years. The tumors were located on the lower extremities in 31 patients (86.1%) and the trunk in five (13.9%). The mean tumor size was 9.6 cm, and 16 tumors (44.4%) were larger than 10 cm. Thirty-one tumors (86.1%) were situated deeply, and five (13.9%) were superficial. The surgical procedures consisted of wide excision, amputation, or disarticulation. Surgical margins were confirmed to be adequate at pathology in 28 patients (77.8%). Marginal or intralesional excision with inadequate margins were found in eight (22.2%). Additional treatment included chemotherapy in five patients (13.9%), radiotherapy in nine (25.0%), and both in seven (19.4%).

Metastases occurred in 11 (30.6%) of the 36 patients; the location of metastasis was the peritoneal cavity in five patients (13.9%); soft-tissue in five (13.9%); lung in three (8.3%); and bone, liver, retroperitoneum, and mediastinum in one (2.8%). Eight (38.0%) of the 21 patients who received additional treatment had metastasis subsequently. Twelve (33.3%) of the 36 patients developed local recurrences. Three patients (8.3%) with inadequate excision had local recurrence. Four patients (11.1%) with local recurrence underwent additional therapy.

Ten (27.8%) and 26 (72.2%) of 36 tumors had regular and irregular tumor contours, respectively (Figs. 1–4). Sixteen tumors (44.4%) showed lob-

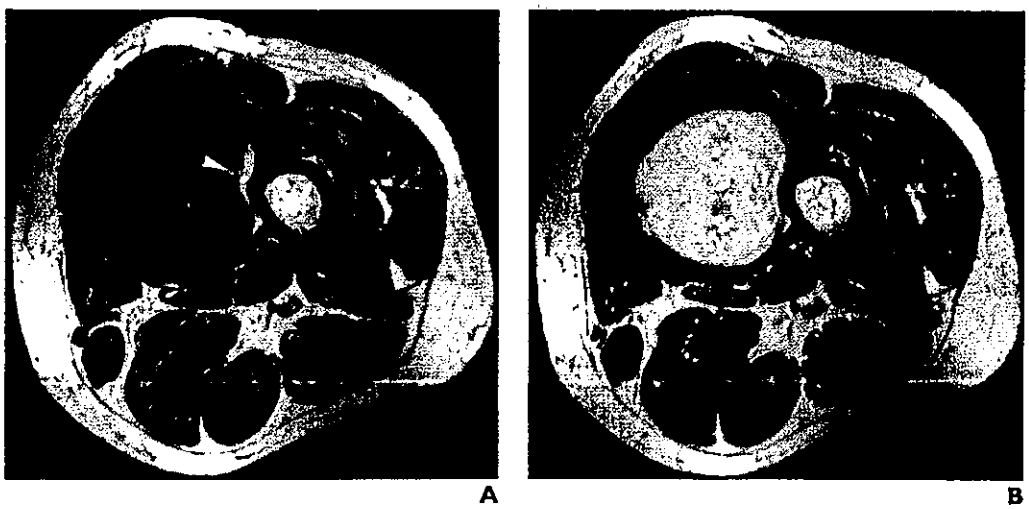
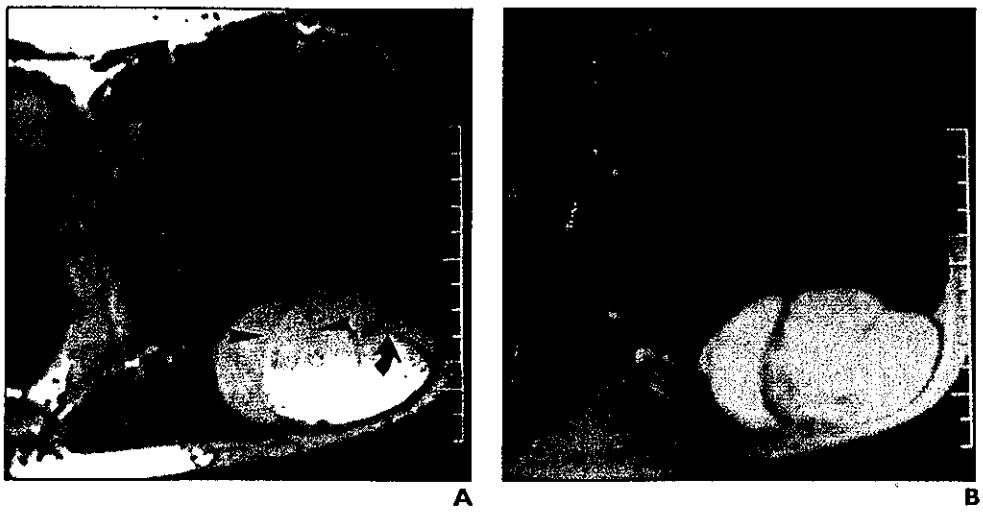


Fig. 1.—38-year-old woman with low-grade myxoid–round cell liposarcoma in left thigh.
A, T1-weighted spin-echo MR image (TR/TE, 720/20) shows tumor has regular contours with small amount of fat signal in periphery (*arrowhead*).
B, Contrast-enhanced T1-weighted spin-echo MR image (720/20) shows diffuse enhancement of tumor.



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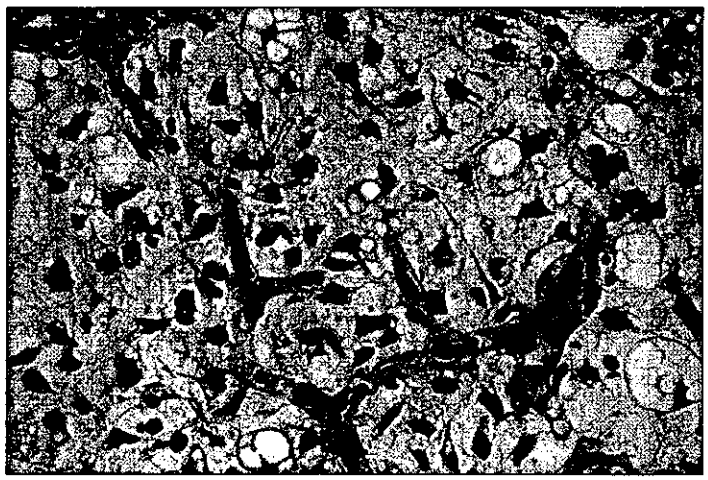

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Fig. 2.—62-year-old man with low-grade myxoid–round cell liposarcoma in left buttock.
A, Axial T2-weighted fast spin-echo MR image (TR/TE, 3,500/100) shows septate appearance of lesion. Linear structures of low intensity contained thick septa (*arrow*) and thin septa (*arrowheads*).
B, Axial fat-saturated contrast-enhanced T1-weighted spin-echo MR image (720/20) shows tumor of high intensity with slight enhancement of septa.
C, Photomicrograph of specimen shows paucicellular myxoid liposarcoma with less than 25% round cell components has dispersed small round or short spindled cells and multivacuolated lipoblasts within abundant myxoid matrix and plexiform vascular network. (H and E, ×200)

ulated morphology. On MR images, thin and thick septa (Fig. 2) were identified in 31 (86.1%) and 10 (27.8%) tumors, respectively. On T1-weighted MR images the signals of the tumors relative to those of muscle were hyperintense ($n = 15$), isointense ($n = 12$), or hypointense ($n = 9$). Tumors showed predominantly increased signal intensity compared with that of the skeletal muscle on T2-weighted MR images. The images showed the tumor as having a heterogeneous appearance with thin or thick septa of low intensity. High-intensity signals similar to subcutaneous fatty tissue (high-intensity signal pattern) were found in 15 tumors (41.7%) on both T1- and T2-weighted MR images (Figs. 1 and 4).

On contrast-enhanced MR images, pronounced enhancement (Fig. 4) located mostly at the peripheries of the lesions was present in 22 tumors (61.1%). Globular and nodular enhancement (Figs. 3 and 4) was found mostly in the centers of the lesions of 16 patients (44.4%), whereas diffuse enhancement (Fig. 1) was seen in six lesions (16.7%). Contrast-enhanced MR images also revealed that 23 tumors (63.9%) had homogeneously enhanced tumor capsules (Fig. 3).

All tumors were characterized microscopically by a prominent plexiform vascular pattern admixed with an abundant myxoid matrix. The extent of cellularity ranged from slight to moderate, and the lesions were composed of small uniform, round, or spindle-shaped hyperchromatic cells. Tumor necrosis was found on microscopic observation in 12 cases (33.3%). The necrotic areas varied in degree, but most tumors contained only a small amount of necrotic areas that were difficult to identify on MR images.

Statistically significant MRI findings that favored a diagnosis of intermediate- or high-grade tumor were large tumor size (> 10 cm) ($p < 0.01$), deeply situated tumor ($p < 0.05$), tumor possessing irregular contours ($p < 0.001$), absence of lobulation ($p < 0.001$), absence of thin septa ($p < 0.05$), presence of thick septa ($p < 0.01$), absence of tumor capsule ($p < 0.001$), high-intensity signal pattern ($p < 0.01$), pronounced enhancement ($p < 0.001$), and globular and nodular enhancement ($p < 0.001$). The presence of thin septa or a tumor capsule indicates low-grade tumor. Irregular contours were found in only 10 high-grade tumors (58.8%). All the low-grade tumors had a capsule, thin septa, and a high-intensity signal pattern. The odds ratios for a specific finding favoring a diagnosis of intermediate- or high-grade tumor are shown in Table 1. The multiple logistic regression model showed that irregular contour and thick septa were the most significant predictors of intermediate- or high-grade tumors, with an odds ratio of 13.8 for both (95% confidence interval [CI], 1.5–128.8; $p < 0.05$).

At the last follow-up, 10 (27.8%) of the 36 patients had died of their disease and four (11.1%) were alive with metastatic disease. The 5- and 10-year survival rates were 80.5%

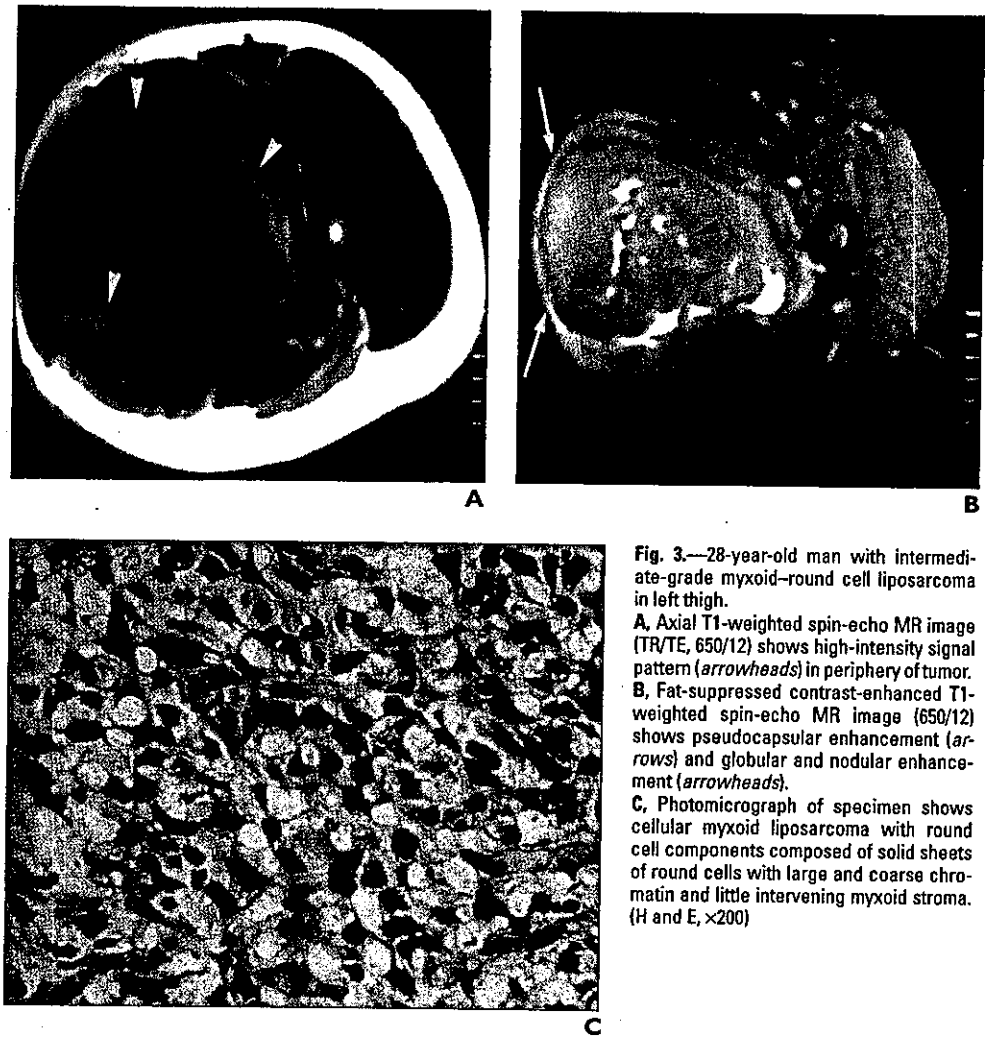


Fig. 3.—28-year-old man with intermediate-grade myxoid–round cell liposarcoma in left thigh.
A, Axial T1-weighted spin-echo MR image (TR/TE, 650/12) shows high-intensity signal pattern (*arrowheads*) in periphery of tumor.
B, Fat-suppressed contrast-enhanced T1-weighted spin-echo MR image (650/12) shows pseudocapsular enhancement (*arrows*) and globular and nodular enhancement (*arrowheads*).
C, Photomicrograph of specimen shows cellular myxoid liposarcoma with round cell components composed of solid sheets of round cells with large and coarse chromatin and little intervening myxoid stroma. (H and E, ×200)

and 72.4%, respectively. The univariate analysis showed that thin septa ($p < 0.05$), tumor capsule ($p < 0.01$), and pronounced enhancement ($p < 0.01$) were significantly associated with overall survival (Table 2). The multivariate analysis revealed that pronounced enhancement was the most significant adverse prognostic factor (Fig. 5) with a relative risk of 7.3 (95% CI, 1.5–35.1; $p < 0.05$).

TABLE 1 Odds Ratio for Features Favoring Diagnosis of Intermediate- or High-Grade Myxoid–Round Cell Liposarcoma

Feature	Odds Ratio	95% CI
Size > 10 cm	9.0	2.6–30.9
Lobulation absent	21.0	8.3–126.5
Thick septa present	20.3	2.1–188.7
Pronounced enhancement present	34.7	3.72–324.1
Globular and nodular enhancement present	9.0	2.0–41.3

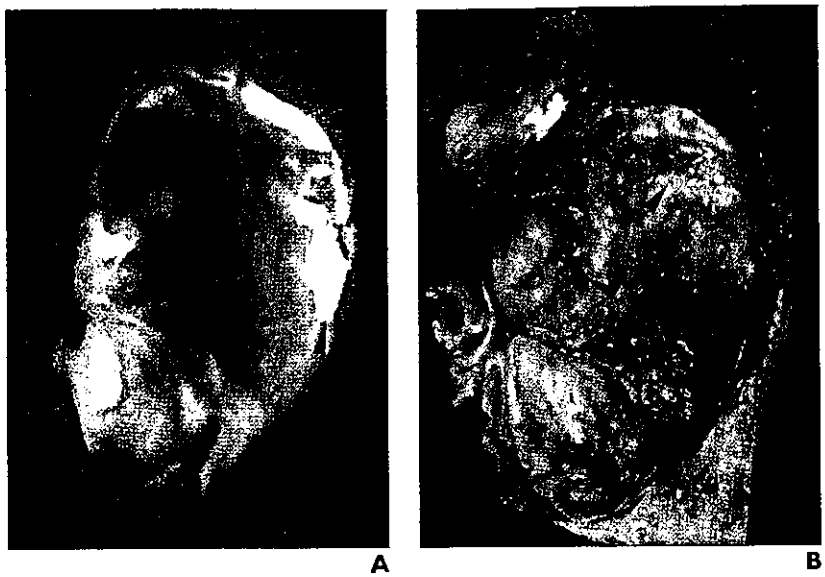
Note.—CI = confidence interval.

Discussion

In this study, we documented the prognostic significance of MRI features in patients with myxoid–round cell liposarcomas. Univariate analysis revealed that the presence of thin septa, a tumor capsule, and pronounced enhancement had a significant correlation with overall survival. Multivariate analysis showed that, of these variables, pronounced enhancement on contrast-enhanced MR images was the most influential adverse prognostic factor. This MRI finding of enhancement correlated with the round cell–component content on pathologic specimens. The prognostic importance of the round cell component has been acknowledged in previous studies [18–20]. From a practical viewpoint, detection of this enhancement pattern on contrast-enhanced MR images in myxoid–round cell liposarcomas is useful for predicting their behavior.

The amount of necrosis has been reported to be correlated with clinical outcome [21–25]. Spontaneous tumor necrosis identified in four (4%) of 95 patients with myxoid–round cell liposarcomas was correlated with increased risks of metastasis and death [18]. In our study, we did not evaluate the relationship between the presence of tumor necrosis and patient prognosis, because most tumors accompanied by necrosis in our study contained only a small amount of necrotic areas that were difficult to identify on MR images.

On contrast-enhanced MR images, pronounced enhancement was located mainly at the periphery of the lesion in 61.1% of the pa-



A B

C

Fig. 4.—69-year-old man with high-grade myxoid–round cell liposarcoma in left thigh.
A, Sagittal contrast-enhanced T1-weighted spin-echo MR image (TR/TE, 600/15) shows globular and nodular enhancement (*arrows*) and pronounced enhancement (*arrowheads*) predominantly at tumor periphery.
B, Photograph of macroscopic specimen of same tumor as in **A** shows heterogeneous tumor components (*arrowheads*).
C, Photomicrograph shows that specimen is composed of solid sheets of uniform round cells with large and coarse chromatin. (H and E, ×200)

tients, and globular and nodular enhancement occurred at the lesion center in 44.4%. These two patterns of enhancement were characteristic of intermediate- or high-grade tumors. Round cell components were reported to be located at the peripheries of lobules; adjacent to fibrous septa extending through the tumor; and surrounding large vessels, particularly in tumors with only a small amount of round cell components [7, 8]. Thus, these two enhancement patterns may be reliable imaging findings for detecting round cell components within tumors. In one study, despite a small sample size, researchers showed that patients ($n = 5$) who initially had a tumor with 5% or greater round cell components had a significantly higher incidence of metastasis or death from disease than those ($n = 7$) who initially had a tumor with less than 5% round cell components [18]. In a study of 24 patients with round cell components composing 25% or more of the tumor, round cell components were associated significantly with a lower survival rate [19]. However, the correlation between the quantity of round cell components and the clinical outcome may depend on the difficulty in quantifying the round cell components at transitional areas at microscopic observation.

There was no significant difference between the risks of an adverse outcome in patients with myxoid and transitional areas without round cell components and those with myxoid areas alone [19]. The pathologic variables responsible for differences among observers in identifying round cell components are considered to be numerous and include inaccurate criteria for tissue processing and selection of the assessment area within the spectrum of myxoid–round cell liposarcomas [20]. Our results suggest that contrast-enhanced MR images can assist in detecting round cell component content within the entire tumor and assist in the distinction of low-grade and of intermediate- or high-grade myxoid–round cell liposarcomas.

In previous reports [26–29], the descriptions of the enhancement patterns identified on MR images included little enhancement or a few patterns (i.e., heterogeneous, homogeneous, no enhancement). However, the end points selected in these prior studies depended simply on the pathologic diagnosis of "myxoid liposarcoma," and the investigators were unaware of the lineage of "myxoid–round cell liposarcoma" as a disease entity. The results of our study are based on a definite diagnosis of myxoid–round cell liposarcoma, and we stress that

TABLE 2 MRI Findings and Univariate Analysis of Survival for Patients with Myxoid–Round Cell Liposarcoma

MRI Findings	No. (%) of Cases	5-Year Survival Rate (%)	p^a
Size (cm)			0.10
≤ 10	20 (55.6)	84.2	
> 10	16 (44.4)	56.8	
Depth			0.26
Superficial	5 (13.9)	100	
Deep	31 (86.1)	66.7	
Contour			0.27
Regular	26 (72.2)	71.2	
Irregular	10 (27.8)	62.5	
Lobulation			0.19
Absent	20 (55.6)	59.8	
Present	16 (44.4)	85.2	
Thin septa			0.02
Absent	5 (13.9)	26.7	
Present	31 (86.1)	77.1	
Thick septa			0.47
Absent	26 (72.2)	66.7	
Present	10 (27.8)	72.3	
Tumor capsule			< 0.01
Absent	13 (36.1)	16.6	
Present	23 (63.9)	83.1	
Pronounced enhancement			< 0.01
Absent	14 (38.9)	100	
Present	22 (61.1)	54.9	
Globular and nodular enhancement			0.91
Absent	20 (55.6)	78.4	
Present	16 (44.4)	66.8	
High-intensity signal pattern			0.71
Absent	21 (58.3)	72.4	
Present	15 (41.7)	69.1	

[a]Log-rank test.

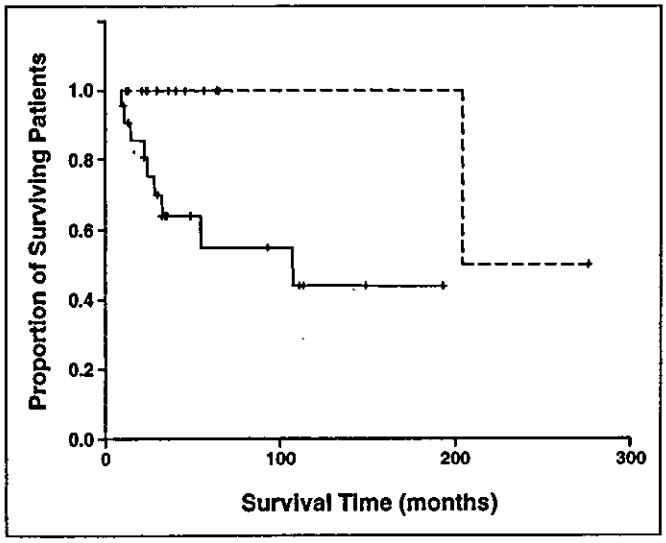


Fig. 5.—Graph shows Kaplan-Meier survival curve according to presence (*solid line*) or absence (*dashed line*) of pronounced enhancement on contrast-enhanced MR images for 36 patients with myxoid–round cell liposarcomas.

the presence of globular and nodular or pronounced enhancement identified on MRI is a finding suggestive of intermediate- or high-grade tumor and reflects the amount of round cell components in the tumor, which strongly affects patient outcome.

The presence of linear or amorphous hyperintense foci behaving like fatty tissue on T1-weighted MR images has been reported to be a pattern suggestive of myxoid liposarcoma [27]. Myxoid–round cell liposarcoma often consists of multiple histologic subtypes in the same lesion. We observed a high-intensity signal pattern in 15 low-grade tumors, and this finding was consistent with immature fatty tissue or the fat components of the tumors. Immature spindle cells lacking obvious fat genesis may be seen next to multivacuolated lipoblasts. Although MRI is sensitive enough to detect minute fat deposits or immature fatty components, our univariate analysis showed no significant association between high-intensity signal pattern on MR images and survival [28, 29].

In summary, the spectrum of MRI findings in myxoid–round cell liposarcomas is continuous. MRI findings can assist in the distinction between low-grade and intermediate- or high-grade myxoid–round cell liposarcomas. MRI findings that favored a diagnosis of intermediate- or high-grade tumor included large (> 10 cm) size of tumor, deeply situated tumor, tumor possessing irregular contours, absence of lobulation, absence of a tumor capsule, absence of thin septa, presence of thick septa, high-intensity signal pattern, pronounced enhancement, and globular and nodular enhancement. The presence of thin septa or a tumor capsule indicates low-grade tumor. Imaging features associated with overall survival were thin septa, a tumor capsule, and pronounced enhancement. Multivariate analysis showed that pronounced enhancement on MRI is the most significant factor in predicting an adverse prognosis for patients with myxoid–round cell liposarcoma.

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5. SRT（Stereotactic Radiotherapy）

5.1　はじめに

定位放射線照射（Stereotactic irradiation；STI）とは、厚生労働省がん研究助成金阿部班により以下のように定義されている。すなわちNarrow beamを用いて線量を集中的に照射させる技術のうち、①患者あるいはそれに連結された座標系において照射中心を固定精度内におさめるシステムであること、②定位型手術枠を用いた方法、または着脱式固定器具を用いた方法であること、③照射装置の照射中心精度が1mm以内であること、④治療中を通じて上記固定精度を保つこと、といった条件を満たす放射線治療とされている。通常の放射線治療に比較し、標的病変周囲の正常組織の線量を極力減少させつつ病巣に高線量を集中させる治療である。定位放射線照射は、ガンマナイフに代表される1回で照射する定位手術的照射(Stereotactic radiosurgery；SRS）と、分割照射する定位放射線治療(Stereotactic radiotherapy；SRT)に区別される。SRSの裏付けとなっているのはLars Leksellらの、治療体積が小さければ逆比例して耐容線量が上がり高線量1回投与が可能となる"という理論である。一方で、SRTは分割照射により治療可能比（＝正常組織の耐容線量/腫瘍の治癒線量）が高まるという、放射線生物学上の理論を背景としている。1回線量や照射回数などの治療スケジュールが腫瘍により理想的に設定可能であるが、精度がSRSより劣る可能性があり、さまざまな工夫が精度管理のためになされている。本稿では、SRTについて放射線生物学的特長と精度管理および臨床応用について述べる。

5.2　放射線生物学よりみた定位放射線治療

細胞死の主たる原因はDNAの二重鎖切断と考えられている。光子は物質を構成する原子と反応し高速電子を放出する。この高速二次電子がDNAの原子を直接電離したり励起して切断を起こす(直接作用)。二次電子は生体の水分子と反応し、反応活性の非常に高いラジカルを生成しDNAを損傷する（間接作用)。腫瘍細胞と正常細胞の両者で同様に障害されるDNAであるが、修復機構が正常細胞で機能するのに対し、腫瘍細胞では充分機能しないことが分割照射の利点の一つとされる。すなわち、1.5～3Gy程度の比較的低線量を照射した場合、生じたDNAのダメージを正常細胞は修復するが、腫瘍細胞は修復できず、死に至ることが期待され、分割照射が放射線治療では通常用いられている。腫瘍に大線量を照射する放射線治療としては、子宮頸癌における腔内照射や頭頸部癌に対する組織内照射のような小線源治療が良好な治療成績をあげている。しかし、近接するリスク臓器の照射線量増加により直腸炎や膀胱炎、下顎骨壊死などの副作用発症が増加することもよく知られており、放射線生物学的検討が行われてきた[2]。Linear-Quadratic model（LQ model)においては照射線量と生物学的効果は、一次的(linear）要素と二次的（quadratic）要素および回復により説明される。さらに、生物学的効果を比較する目的として使用されるbiological effective dose（BED）を用いることにより[3]、異なる線量・分割回数の治療方法の比較が可能である。分割照射の場合は照射間隔が1日以上であると完全回復と考えられるので、BED＝D（1＋d/(α＋β))、D＝総線量、d＝1回線量と表現される。α/β値は個々の組織・臓器の障害に固有の値であり、実験的に多数報告されている。正常組織の急性反応のα/β値は大きく、急性反応は1回線量の大きさにはあまり依存しないとされる。一方、正常組織の急性反応のtarget cellsは分割照射中にも再生(repopulation)するため、治療期間の延長は急性反応を軽減する。急性反応は1週間当たりの合計線量がその反応の強弱を決定する。遅発性放射線反応のα/β値は小さく、遅発性反応の1回線量の大きさに対する感受性は急性反応に比較し高いとされる。中枢神経系では正常組織の早期反応や腫瘍に対する治療効果（early effect）についてはα/β値は10Gy前後とされ、遅発性反応（late effect）についてはα/β値は2Gy前後が用いられることが多い。SRSのような1回線量が10Gyを超える放射線治療において、このようなモデルの応用に関しては議論のあるところではあるが、他に確立されたモデルがないため、このモデルによりSRSとSRTの放射線生物学的検討がなされている。

茂松らによる検討では[4]、SRSにおける腫瘍辺縁での照射線量が20Gyであった場合、1回2Gyの標準分割照射に換算すると正常組織の早期反応や腫瘍に対する治療効果（early effect）についてはα/β＝10を用いると50Gy相当、遅発性反応（late effect）についてはα/β＝2を用いると110Gy相当となる。SRSでは

表 7.5.1 Larson らによる対象の形態と病理学的特徴よりみた治療方法の選択

Category	Pattern	特徴	代表的疾患	放射線治療
Category A	Late-responding target embedded within late-responding normal tissue	標的病変は正常組織に複雑に入り組んで存在	AVM	標的病変と正常組織が同様の線量で照射される
Category B	Late-responding target surrounded by late-responding normal tissue	標的病変と正常組織の境界が比較的明瞭	Meningioma	標的病変に集中した照射が可能
Category C	Early-responding target embedded within late-responding normal tissue	標的病変と正常組織の境界は不鮮明	Low grade astrocytoma	標的病変の辺縁では正常組織と同様の線量で照射される
Category D	Early-responding target surrounded by late-responding normal tissue	標的病変と正常組織の境界は比較的明瞭	Metastatic brain tumor	標的病変に集中した照射が可能

腫瘍の2～3mm外側では線量分布上15Gy程度の線量に低下するとしても約60Gy相当となり、この範囲に重要なリスク臓器となる神経組織などが近接すると問題となってくる。

茂松らは神経組織などリスク臓器の近接の有無により理想的なスケジュールを検討している[4]。すなわち、低リスク群では1回2Gyの標準分割照射で60Gy照射した場合のearly effectを考慮し、これを凌駕する照射スケジュールとして4分割以上の、6.9Gy×7回、6.1Gy×9回、5.1Gy×12回などを提示している。高リスク群では近接する正常組織の障害を回避するために照射線量の低減が図られるが、通常分割照射で50Gy程度の照射が行われているが、これを凌駕する照射スケジュールとして12分割以上の、3.7Gy×12回、3.1Gy×16回、2.9Gy×18回などを提示している。SRTにおける照射スケジュールは、そのmodelの確立と検証を通してさらに検討が必要な課題である。

TokuueらはSRT単独で治療し、1年以上の経過観察を行った転移性脳腫瘍64例、頭蓋底浸潤6例、原発性脳腫瘍10例の計80例を検討し、3例の有害反応を認めたと報告している[5]。2例は再々照射例であり、3例中2例は保存的治療で、1例は壊死除去術後に軽快していた。照射野径が大きい症例（4cm）および1回線量が多い症例（7.5Gy）で有害反応が出現していることを指摘している。現在われわれは通常6Gy×7回、腫瘍径が大きい場合や視神経や脳幹などリスク臓器に近接している場合4Gy×13回の治療スケジュールを用いている。このスケジュールによる転移性脳腫瘍の局所制御率は他の報告と同等の92%であり、急性期の副作用は認めていない。

分割照射において他に検討すべき問題点としては、放射線生物学的には腫瘍の再増殖や再酸素化という要素がある。低酸素細胞は放射線感受性が低く、分割照射により低酸素細胞が再酸素化されれば治療上は有利となるが、治療期間が数週間と延長すると再増殖も考慮する必要が生じてくる。

5.3 対象の形態と病理学的特徴よりみた治療方法の選択

Larsonらは定位放射線照射の対象となる病変を、その性質や形態により表7.5.1のように分類している[6]。Larsonらはglioblastomaをcategory Dに分類したがglioblastomaでは周囲の浮腫が広範に広がり、その中に腫瘍細胞が存在すると考えられ、Category Cに分類すべきという指摘がある。Category Aでは病変と正常組織が同様に照射されるがα/β値も正常組織と同様であり、Category Bでは分割回数増加によりBEDが低下するため、両者では分割照射の有用性はリスク臓器が近接する場合などに限られると考えられる。Category CおよびCategory Dでは病変のα/β値＝10であり分割照射によりBEDが上昇し、特にCategory Dでは照射線量が増大できることよりSRTの有用性が考えられている。

5.4 精度管理

STIでは治療システムの正確性（accuracy）と精度（preciseness）が問題であり、システムとしてQuality assurance（QA）が必要とされる[7]。すなわち、病巣の位置を三次元的に定めるlocalization、患者の位置を正確に設定するalignment、および治療計画と計画に一致した照射を行うdose deliveryである。

SRTの場合は定位フレームの使用が問題となり、侵襲的方法以外にさまざまに工夫された非侵襲的システムが開発されている。光学的ナビゲーションを応用し

たラジオカメラシステムもその一つである。フロリダ大学で開発された本システムは[8]、バイトプレート式ローカライズシステムと光学式ナビゲーションを組み合わせたシステムである。上顎に直接固定するバイトプレートを使用することにより、侵襲式ヘッドリングを使用した場合と同等の精度を得ている。SRSに比較しSRTでは治療期間を通じてのQAを必要とするため、重要な課題である。

治療装置の幾何学的精度の管理はSTI全体の重要な課題であるが、SRTでは、システムとしてのQAがより必要となり、治療期間を通じ一般の放射線治療に加え、SRTを行うこととなるため、精度管理システムの構築が必要であり時間と手間が問題となる。

5.5　血管性病変

脳内動静脈奇形（Arteriovenous malformation；AVM）の治療には手術や塞栓術とともに、STIが施行される。STIは手術の困難な部位でも比較的安全に治療できるという利点があり、完全閉塞率も2～3年で80～90%と高い[9~12]。しかし閉塞まで時間を要し、大きな病変の治療では出血や脳浮腫などの副作用が問題となる。閉塞率や副作用に関しては病変の大きさや線量が関与していると考えられている。Flickingerらによると351症例の治療後3～11年目の評価で血管造影上73%、MR上86%の閉塞率であったと報告している[9]。この報告では多変量解析により辺縁線量が閉塞に有意な因子として指摘され（$p < 0.0001$）、dose-response関係が示されている。副作用のリスクに関しては手術難易度・治療成績に基づいたSpetzler's grading systemがあり、大きさや部位（eloquent area）、流出静脈の経路により評価しており、STIにおいても参考とされている[13,14]。SRSによるAVM治療後の有害反応に関し、Flickingerらは Post-radiosurgery injury expression (PIE) score および Significant Postradiosurgery Iinjury Expression (SPIE) scoreを発表している[15,16]。部位別に神経症状を伴ったMRIでの信号変化の発生頻度が異なることを指摘している（表7.5.2）。橋がもっとも危険であり中脳、基底核、視床のSRSによる脳壊死のリスクが高いことが示されている。治療方法を検討する際に部位により慎重な治療が必要である。SRTは分割照射により治療効果比が高まる可能性を期待し、SRSではリスクが高いと判断される症例など選択された症例に対し検討されている。青山らによると北海道大学附属病院の場合、①病変が大きい場合（2.5 cmあるいは10 ccを超える）、②視神経に近接している場合やeloquent areaにある場合、③標的病変が著しい不整形の場合に用いられている[17]。AVMの治療におけるSTIの評価は長期観察例の検討が現在進行中であり、今後より有効で副作用の少ない治療の確立のための努力が続けられている。

表7.5.2　Flickingerらによる AVM に対する SRS 治療例の location-risk score

部位	PIE score	SPIE score
Frontal	1	0.00
Temporal	2	1.89
Intraventricular	4	3.72
Parietal	2	4.83
Cerebellar	2	4.87
Corpus callosum	4	5.99
Occipital	3	6.04
Medulla	4	6.96
Thalamus	4	7.71
Basal ganglia	3	8.01
Pons / midbrain	4	10.00

PIE = Postradiosurgery Iinjury Expression score.
SPIE = Significant Postradiosurgery Iinjury Expression score

5.6　原発性脳腫瘍

原発性脳腫瘍において最も頻度の高い神経膠腫に関しては、STIの応用がさまざまな方法で試みられている[18~20]。悪性神経膠腫の再発形式の検討では、局所再発が多いことが指摘されており、小線源治療[21,22]やSTIによる追加照射が検討されている。STIは小線源治療や術中照射に比較し、標的体積に合わせた治療計画が可能であり線量分布の適正化においても自由度が高いと考えられる。さらにSRTは、放射線生物学的に治療可能比の向上が期待されるが、これは臨床試験により証明される必要がある[23]。追加照射が可能な症例は全身状態や腫瘍の大きさ、占拠部位などで選択された比較的予後良好群に属している可能性があり[24]、STIの意義を検討するためには充分に検討された前向き臨床試験による評価が必要である。Glioblastomaを対象にRadiation Therapy Oncology Group（RTOG）において施行されたchemoradiation（60 Gy/30Fr＋BCNU）±SRS（腫瘍径により15～24 Gy）の第Ⅲ相試験（RTOG9305）や、chemoradiation（50Gy/25Fr＋BCNU）＋SRT boost（腫瘍径により5または7 Gy×4）の第Ⅱ相試験（RTOG BR-0023）の治療成績の検討により悪性神経膠腫に対するSTIの応用について新たな知見が期待される。

髄膜腫はLarsonらの分類でcategory Bを代表する

疾患であり、SRSにより優れた治療成績が報告されている[25,26]。Flickingerらによると10年局所制御率が93.2%と報告されており[26]、医学的な理由で手術困難な症例や腫瘍占拠部位により手術が困難な症例において、手術に代わる可能性が報告されている[25]。しかし、海綿静脈洞近傍の髄膜腫に対するSRSの報告では、19ヵ月の経過観察において視神経交叉の線量が8 Gyを超過した症例17例中4例で視力障害を認めている[27]。1回線量が視神経障害に関する重要な因子であるという指摘もあり[28]、視神経や脳幹などが近接する場合はSRTが検討される。

聴神経腫瘍に対してはSRSによる良好な治療成績が報告されており、長期の経過観察結果で照射後手術を受ける必要のない有効症例が98%であったと報告されている[29]。

5年後の神経機能温存率は顔面神経79%、三叉神経73%、聴力51%であった。神経のダメージには1回線量や照射される神経の長さが関係するという指摘もあり、顔面神経や三叉神経麻痺、聴力低下のリスクの軽減を目的としてSRTがさまざまな施設で検討されているが、最適な治療スケジュールは確立していない。

下垂体腺腫の放射線治療ではその占拠部位より視神経と側頭葉の有害反応が問題となる。術後早期の照射の意義は明らかでなく、予後良好と思われる症例では再燃時の照射が妥当とされている[30]。ホルモン産生腫瘍の場合は補助療法の選択肢もあり、放射線治療の適応は限られる。多くの施設では術後照射として2 Gy×25回の通常分割照射が選択されているが、われわれは視神経と側頭葉の線量低減を目的としてSRTを応用している。Mitsumoriらは48例の下垂体腺腫の治療結果をSRS (18例) とSRT (30例) で比較検討している[31]。ホルモン値の正常化に要した期間はSRS 8.5ヵ月に対し、SRT 18ヵ月とSRT群で時間を要しており、3年後の局所制御率はSRS 100%に対しSRT 85.3%であった。しかし中枢神経系の副作用のない症例を検討すると3年でSRS 72.2%に対しSRT 100%であった。SRT群で副作用が高率であったことよりSRTを推奨している。

5.7 転移性脳腫瘍

転移性脳腫瘍は癌による死亡の主な原因の一つであると共に、脳の圧迫による神経障害が発生するため、癌患者のQOLを著しく低下させる原因の一つとなる。転移性脳腫瘍の多くは辺縁明瞭で周囲組織への浸潤傾向が少なくCTやMRIにより比較的小さい時期に発見されることも多いため、STIのよい対象となっている。脳転移の治療は、全脳照射と手術に加え定位放射線照射の登場により、その選択の多様性と妥当性に関する検討がさまざまに行われている。RTOG (Radiation Therapy Oncology Group) では、手術適応とならない1～3個の転移性脳腫瘍に対して、全脳照射と全脳照射＋SRSの333例のランダム化比較試験を行った (RTOG9508)[32]。全体の生存期間の中央値は全脳照射5.7ヵ月vs全脳＋SRS 6.5ヵ月と有意差を認めなかった。しかし、1個の場合は全脳照射4.9ヵ月に対して、全脳＋SRS群が6.5ヵ月であった。6ヵ月時点でのKPS改善・維持割合も全脳照射27%に対し全脳＋SRS 43%とSRS併用群が良好であったと報告している。全脳照射は、頭蓋内の新病変出現と病巣辺縁よりの再発対策として併用されてきたが、Flickingerらは全脳照射により局所制御率は向上するが生存期間の延長はもたらさないとし[33]、Sneedらは定位放射線照射後に新病変が出現した際に全脳照射を追加することを提唱している[34,35]。定位放射線照射に全脳照射を組み合せるか否かに関しては、必要性およびその意義についての結論は出ていない。

Larsonらの分類でCategory Dに分類される転移性脳腫瘍では、分割照射によりBEDが上昇し照射線量が増大できることからSRTの有用性が考えられている。また、病巣の大きさや神経組織などリスク臓器の近接の有無、標的病変が著しい不整形の場合はSRTのよい適応となると考えられる。診断や治療方法の進歩により、脳転移と診断される症例においても数年以上の長期生存が増加しており、緩和的放射線治療の意義にも変化が認められている。従来は、短期間で1回高線量のスケジュールによる治療で、治療後早期に効果的な症状緩和が得られ最小限の急性期有害反応にとどまるShort Term Palliationが主体であった。しかし長期生存例の増加はより効果的な高い総線量によるRadical Palliationの必要性をもたらし、さらに症状出現の予防を考慮したProphylactic Palliationの検討を必要としている。SRTはRadical Palliationとして、局所制御率の向上に寄与する可能性が考えられている。転移性脳腫瘍に対する最適な照射スケジュールは明らかとなっていないが、組織型や大きさ、占拠部位を考慮した照射スケジュールの変更が必要であろう。

5.8 おわりに

STIの応用は、AVMや転移性脳腫瘍のみならず原発性脳腫瘍を含むさまざまな病態で検討されている。今

後適切な臨床試験の実施により治療方法の選択に関する情報の増加が期待されるが、症例の状況や推測される予後などを考慮した適切なインフォームドコンセントのもと、治療方針の選択がなされる必要がある。

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ORIGINAL PAPER

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Primary central nervous system lymphoma in Japan 1995–1999: changes from the preceding 10 years

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Abstract *Purpose*: Previously, we conducted a nationwide survey of primary central nervous system lymphoma (PCNSL) treated between 1985 and 1994 in Japan. In the present study, we conducted further investigations of PCNSL patients treated between 1995 and 1999 to clarify possible changes with time in the clinical features, treatment, and outcome of this disease. *Methods*: Thirteen Japanese institutions were surveyed, and data on 101 patients with histologically-confirmed PCNSL were collected. These data were compared with those of 167 patients treated at the same institutions between 1985 and 1994. *Results*: Regarding patient and tumor characteristics, the proportion of patients with good performance status (PS) was significantly higher in the group treated during 1995–1999 than in that treated during 1985–1994, but other characteristics were not significantly different. Regarding treatment, more patients in the more recent period (66%) received systemic chemotherapy than those in the preceding period (53%, $P = 0.049$). For all patients, including those who did not complete radiotherapy, the median survival time was 17 months and 30 months in patients treated between 1985 and 1994 and those treated between 1995 and 1999, respectively, and the 5-year survival rate was 15% versus 31% ($P = 0.0003$). In both patient groups, higher age and tumor multiplicity were associated with poor prognosis in multivariate analysis. In patients treated between 1995 and 1999, those who received systemic chemotherapy showed significantly better prognosis than those who did not ($P = 0.0049$), but the difference was not significant in multivariate analysis ($P = 0.23$). *Conclusions*: The high survival rates observed in the present survey are comparable with those of recent prospective studies employing intensive chemoradiotherapy. The improvement in prognosis appeared to result, at least in part, from the increase in the proportion of patients with better PS. Since the clinical feature and treatment outcome of patients with PCNSL can thus change with the era, historical control data should not be used in comparing different treatment modalities.

Keywords Brain neoplasm · Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy

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Introduction

Primary central nervous system lymphoma (PCNSL) is increasing and is becoming one of the most important tumors in neuro-oncology. Radiation therapy has been the standard treatment for PCNSL until recently, but the outcome of patients treated by radiation alone has not necessarily been satisfactory (Shibamoto et al. 1990; Reni et al. 1997; Hayabuchi et al. 1998; Nelson 1999). More recently, the use of high-dose methotrexate (MTX)-containing chemotherapy before radiation appeared to have gained some success in obtaining

long-term survival (Glass et al. 1994; Blay et al. 1998; Brada et al. 1998; Abrey et al. 2000; Ferreri et al. 2000; O'Brien et al. 2000; Reni et al. 2001; Bessel et al. 2001; Caldoni & Aebi 2002; DeAngelis et al. 2002). However, there has been no randomized trial suggesting the superiority of the combined modality treatment over radiation therapy alone, and a recent study by a German group suggested a high rate of progressive disease during treatment with 6 courses of 8 g/m^2 of MTX (Herrlinger et al. 2002). Therefore, the benefit of high-dose MTX appears to remain uncertain. Since the clinical features of PCNSL appear to be changing with time, it may not be reasonable to consider that combined MTX-containing chemotherapy and radiation is superior to radiation alone, by comparing the results of combined treatment with the historical control data in patients treated by radiation therapy alone.

Previously, Hayabuchi et al. (Hayabuchi et al. 1998) conducted a nationwide survey of PCNSL in Japan treated between 1985 and 1994. The findings on 466 patients were previously published. Considering the increasing importance of this disease, we organized a research group consisting of 13 institutions to carry out both retrospective and prospective studies on PCNSL. As a first study of this group, we collected data on PCNSL patients treated between 1995 and 1999 at these institutions. In addition to analyzing these data on 101 patients, we compared the data with those on 167 patients from the previous survey treated between 1985 and 1994 at the same institutions, to investigate changes in the clinical feature, treatment modality, and outcome between these eras.

Materials and methods

Subjects of the present survey were patients with histologically-proven PCNSL who received radiation therapy between 1995 and 1999. Those who did not complete the planned radiotherapy were included. Clinical characteristics, treatment and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 101 patients were collected from 13 institutions. For comparison, data on 167 patients treated in the preceding 10 years, i.e., between 1985 and 1994, at the same institutions were obtained from the data source of the previous nationwide survey (Hayabuchi et al. 1998) and were analyzed. Data regarding tumor size (maximum diameter at diagnosis and before radiation therapy) was asked for in the present survey, which had not been done in the previous survey. As often happens with such a survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, and were categorized as follows: (A) cyclophosphamide, vincristine, and prednisolone (COP) or COP plus doxorubicin (CHOP/VEPA); (B) intravenous methotrexate (MTX) alone or MTX-containing regimens. The drugs included in regimen A had often been used in combination with MTX, and such regimens were categorized into this group; (C) cytarabine plus procarbazine; (D) nitrosourea-containing regimens. Some of the drugs in regimen A had been used in combination with nitrosoureas, and such regimens were included in this group. When MTX had been used in combination, the regimen was categorized into group B; (E) cisplatin plus etoposide; and (F) Single use or combination of miscellaneous other agents not included in the above groups. For analysis of treatment results, regimens C–F were grouped together. Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test.

Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups, and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using a computer program, Stat View Version 5 (SAS institute, Cary, NC, USA).

Results

Table 1 shows patient, tumor, and treatment characteristics in the two groups treated between 1985 and 1994 and between 1995 and 1999. There were more patients with better WHO performance status (PS) score in the group treated between 1995 and 1999 than in the

Table 1 Patient, tumor, and treatment characteristics

Characteristic		1985–1994	1995–1999	*P*
Gender	Male/female	97/70	67/34	0.20
Age (years)	<60/≥ 60	83/84	53/48	0.71
	Median (range)	60 (15–84)	59(15–84)	
Performance status	0–2/3,4	69/95	60/41	0.0078
Lactate dehydrogenase	Normal/high	49/34	50/30	0.75
B symptom	Yes/no	16/133	11/81	0.83
Phenotype	B/T	75/8	79/6	0.59
Tumor number	Single/multiple	103/63	56/43	0.44
Maximum tumor diameter	At diagnosis	–	3 (1.5–9)	
Median (range) (cm)	Before radiation	–	3 (0–9)	
Radiotherapy	Completed/not completed	158/9	97/4	0.77
Radiation field	Whole brain/partial brain	146/21	92/9	0.43
Spinal radiation	Yes/no	15/152	4/97	0.15
Total dose (Gy)	<50/≥50	54/113	28/73	0.49
	Median (range)	50 (2–70)	50 (6–80)	
Whole-brain dose (Gy)	<40/≥40	70/97	42/59	1.0
	Median (range)	40 (0–54)	40 (0–60)	
Chemotherapy	Yes / no	78/70	65/34	0.049

Table 2 Chemotherapy regimens (COP cyclophosphamide, vincristine and prednisone, CHOP/VEPA COP plus doxorubicin)

Regimen	1985–1994	1995–1999
COP, CHOP/VEPA	35 (45%)	25 (38%)
Methotrexate-containing regimens	18 (23%)	27 (42%)
Cytarabine and procarbazine	0	7 (11%)
Nitrosourea-containing regimens	13 (17%)	2 (3%)
Cisplatin and etoposide	8 (10%)	4 (6%)
Miscellaneous drugs	4 (5%)	0

group treated in the preceding 10 years, but the other patient and tumor characteristics did not differ significantly between the two groups. Radiotherapy characteristics were similar between the two groups. During both study periods, more than 85% of the patients were treated with whole-brain irradiation with or without focal boost, and the median total and whole brain doses were 50 Gy and 40 Gy, respectively. Whole spinal irradiation was employed in less than 10% of the patients. On the other hand, more patients seen between 1995 and 1999 received systemic chemotherapy than those seen between 1985 and 1994 (66% vs 53%, $P = 0.049$). Table 2 shows chemotherapy regimens used in the two groups. The use of MTX-containing regimens appeared to be increasing recently. However, a high dose of MTX (> 2 g/m^2 per administration) was used in only 14 patients (14% of all patients) treated between 1995 and 1999.

Figure 1 shows overall survival curves for all patients in the two groups. Patients in the present survey had significantly better survival rates than those in the previous survey ($P = 0.0003$); median survival time was 30 vs 17 months, and the 3-year survival rate was 46% vs 24%. The 5-year survival was 31% and 15%, respectively. Table 3 summarizes survival data in the two groups according to potential prognostic factors. In both study periods, patients with ages < 60 years, PS 0–2, or a single tumor showed significantly higher survival rates. Patients with normal lactate dehydrogenase (LDH) levels or without B symptom had better prognoses than those with high LDH level or with B symptom, respectively, in the group treated between 1995 and 1999, but not in those treated during 1985–1994.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (and died soon) were excluded. In patients treated between 1985 and 1994, those who received partial-brain radiation, spinal radiation, or whole-brain dose < 40 Gy showed better prognoses, but these phenomena were not observed in patients treated between 1995 and 1999. Figure 2 shows survival curves according to the treatment modality, i.e., radiation alone vs radiation plus chemotherapy. In patients treated between 1985 and 1994, the two groups showed similar prognoses. In patients treated between 1995 and 1999, however, those who received radiation plus chemotherapy showed significantly better survival than those who received radiation alone. Among these patients, 61% of the

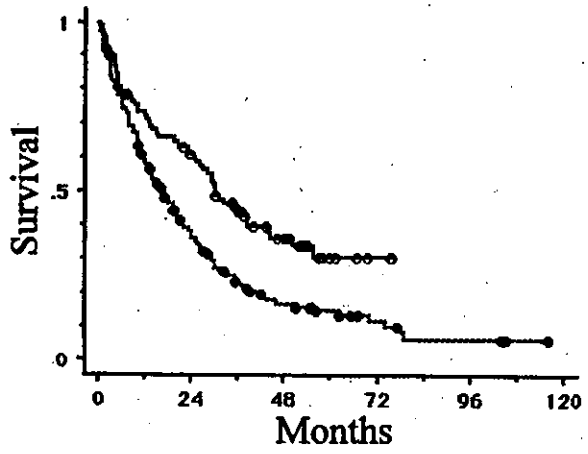

Fig. 1 Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (____O____). The difference was significant ($P = 0.0003$)

patients who received radiochemotherapy were younger than 60 years, but 39% of those treated with radiation alone were younger than 60 years ($P = 0.050$). Similarly, 64% of the patients who received radiochemotherapy had a PS 0–2, but 55% of those treated with radiation had a PS 0–2 ($P = 0.50$). Figure 3 shows survival curves according to the chemotherapy regimens. In patients treated between 1985 and 1994, there was no significant difference in survival curves according to the regimens. On the other hand, there was an overall difference in those treated between 1995 and 1999 ($P = 0.018$). Patients receiving MTX-containing regimens showed better survival than those treated with CHOP/VEPA or COP ($P = 0.0071$).

Multivariate analyses were performed for potential prognostic factors, which were significant in univariate analyses (Table 4). Factors concerning the radiation field and spinal radiation were not included because of the small number of patients in one of the groups. In both patient groups treated during 1985–1994 and 1995–1999, age and tumor number were suggested to be significant prognostic factors. PS and LDH level did not reach statistical significance. The radiation dose to the whole brain and chemotherapy did not prove significant in patients treated between 1985 and 1994, and in those treated between 1995 and 1999, respectively.

Discussion

The most significant finding of this study appears to be that patients treated between 1995 and 1999 showed a significantly better prognosis than those treated between 1985 and 1994. Comparison of the patient and tumor characteristics revealed that there were more patients with better PS between 1995 and 1999 than between 1985 and 1994. This may be due to the earlier diagnosis of the disease in recent years and improvement in gen-