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ABSTRACT

Cytogenetic analyses have not only provided important information on the pathogenesis of soft tissue tumors but, by disclosing distinct chromosomal rearrangements in different histopathological entities, it has also come to serve as a valuable diagnostic tool. Little is known about the potential prognostic impact of cytogenetic features detected in these tumors. A total of 239 benign and 222 malignant soft tissue tumors with clonal chromosome aberrations were subdivided according to general karyotypic features, such as degree of complexity and ploidy level, and rearrangements of specific chromosomal regions. The cytogenetic variables were analyzed regarding clinical outcome, using time to metastasis as the end point. Selected variables were then compared with established clinicopathological predictors of metastasis development. When the entire material was considered, 167 of 268 investigated cytogenetic variables were associated with clinical outcome. Focusing on the subset of 151 patients with high-grade sarcoma, 17 variables were identified that, besides grade and size, were associated with increased risk of metastasis development. A final Cox regression analysis identified five independent cytogenetic predictors of adverse outcome: breakpoints in chromosome regions 1p1, 1q4, 14q1, and 17q2, and gain of regions 6p1/p2. An increasing effect on metastatic risk was seen with increasing involvement of the selected cytogenetic variables, even when different histopathological types were studied separately. We conclude that cytogenetic data provide independent prognostic information in soft tissue sarcomas. Furthermore, our results point to specific areas of the genome harboring genes that may influence the metastatic potential of sarcoma cells.

INTRODUCTION

Soft tissue tumors constitute a heterogeneous group of tumors that clinically run the gamut from totally benign lesions to highly malignant neoplasms. This clinical variability is reflected in the recognition of >100 histopathological entities, and it is well known that histogenetic type and malignancy grade are associated with clinical outcome (1). To identify those patients requiring more extensive surgery and/or adjuvant radio- or chemotherapy, it is, thus, essential to classify and grade the tumors correctly. However, despite increasingly sophisticated means of classifying these tumors, some are difficult to distinguish, and even among well-characterized tumors of a specific histotype, the clinical course may vary. Hence, several other prognostic factors have been evaluated, some of which, e.g., tumor size and depth, as well as tumor necrosis, have proven valuable (2–6).

Since the early 1980s, cytogenetic analyses have provided a wealth of information on the genetic constitution of benign and malignant soft tissue tumors. Clearly nonrandom patterns of karyotypic changes, be they balanced translocations, such as the t(12;16)(q13;p11) and t(X;18)(p11;q11) in myxoid liposarcomas and synovial sarcomas, respectively, or characteristic chromosomal imbalances, such as ring chromosomes in dermatofibrosarcoma protubersans, have been identified in each histological entity studied in sufficient detail to permit conclusions.3 The finding of tumor-specific karyotypic patterns in some types has not only been instrumental for the elucidation of tumorigenic rearrangements at the DNA level but has also provided the clinician with a diagnostic tool for a group of neoplasms that often present differential diagnostic dilemmas. Whereas the diagnostic usefulness of cytogenetic analysis is undisputed, little is known about the possible prognostic impact of acquired chromosome rearrangements in soft tissue tumors.

The present investigation was undertaken by the international CHAMP study group to investigate whether the karyotypic features alone, irrespective of histotype, grade or other clinicopathological parameters, could be used to identify soft-tissue-tumor patients with an increased risk to develop metastases. More specifically, we focused on the clinical outcome in patients with tumors classified as high-grade sarcomas, to evaluate the prognostic impact of chromosomal aberrations in this clinically important subset of patients.

MATERIALS AND METHODS

Patients. The study included 467 patients with primary benign (n = 239) and malignant (n = 228) soft tissue tumors with abnormal karyotypes that had been analyzed in Lund, Sweden, and Leuven, Belgium, between 1984 and 1997. For seven patients, all of whom had grade 2 or 3 sarcomas, no information on metastasis development at diagnosis or later stages, could be retrieved, and they were, hence, removed from further analysis. Nine-tenths of the patients had been treated at the musculoskeletal tumor centers in Lund and Leuven. Sarcoma patients were regularly followed for the detection of local recurrence or distant metastasis. No patients had received preoperative radiotherapy. Not all of the patients with benign tumors were followed by regular clinical examinations; follow-up times for these patients were calculated as the time between surgery and compilation of the database for this study, when we checked their medical status.

All of the tumors had been evaluated by the CHAMP group pathologists by use of recut sections, immunohistochemistry, and, when available, electron microscopy. Diagnostic criteria for the various histological types and subtypes were as reported previously (7–12). Malignancy grading (three-grade scale) was based on consensus decision among the CHAMP pathologists. The distribution of patients according to sex, age, and tumor location, size, depth, grade, and histotype is provided in Table 1.

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4 The abbreviations used are: CHAMP, Chromosomes and Morphology; ISCN, International System for Human Cytogenetic Nomenclature; NOS, not otherwise specified.
**RESULTS**

**Impact of Clinical Variables on Metastasis Development.** Considering metastasis development in the 151 patients with grade 2 or 3 sarcomas, a significant effect was found for malignancy grade \((P = 0.002)\), tumor size \((P = 0.01)\), tumor depth \((P = 0.01)\), gender \((P = 0.02)\), and histotype \((P = 0.02)\), but not for age or tumor location (Table 1). Tumor size was dichotomized into \(<5\) cm and \(\geq 5\) cm, because the effect on metastasis development was similar for \(5–10\) cm and \(10–cm\) tumors (data not shown). In the Cox regression analyses including malignancy grade and each of the other statistically significant clinicopathological variables, size and depth turned out to be significant, but in the ensuing trivariate Cox analysis, size and depth were not significant (Table 2).

**Impact of Cytogenetic Variables on Metastasis Development.** Considering all of the 460 patients with end point data, the majority (167 of 268) of the cytogenetic variables showed a significant effect on metastasis development. In line with this finding, karyotypic complexity was found to be a strong prognostic factor (Fig. 1A). When analyzing only patients with grade 2 or 3 sarcomas, and

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*Table 2: Prognostic effects of malignancy grade, tumor size, and tumor depth on the hazard of metastasis development*

<table>
<thead>
<tr>
<th>Bivariate analyses</th>
<th>Trivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Grade: 3 vs. 2</strong></td>
<td></td>
</tr>
<tr>
<td>2.8 (1.5–5.1)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Size: ≥5 vs. &lt;5 cm</strong></td>
<td></td>
</tr>
<tr>
<td>2.6 (1.2–5.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Depth: deep vs. superficial</strong></td>
<td></td>
</tr>
<tr>
<td>2.9 (1.2–6.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*No. of patients (no. of patients with metastasis) in each combined prognostic category were as follows: [grade 2, size <5 cm, superficial(s)], 1(10); [2, ≥5, s], 5(1); [2, <5, deep (d)], 4(0); [2, ≥5, d], 4(16); [3, <5, s], 1(2); [3, ≥5, s], 7(3); [3, <5, d], 10(6); [3, ≥5, d], 8(8). Size was unknown for 4(3) patients and depth was unknown for 2(1) patients; all of these patients had grade 2 tumors.

HR, hazard ratio estimate; CI, confidence interval; P, obtained from Wald’s test.

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*Not included in the analysis.*

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*Table 1: Summary of clinicopathological features and incidence of metastasis in the total material of 460 soft tissue tumor patients with follow-up data and in the subset of 151 patients with grade 2 and 3 sarcomas*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients with metastasis/total no. of patients (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male: 38/247 (15) Female: 39/213 (18)</td>
<td>38/84 (45)</td>
<td>39/67 (58)</td>
</tr>
<tr>
<td>Size a (cm)</td>
<td>&lt;5: 8/12 (7) 5–10: 33/198 (17) &gt;10: 33/124 (27)</td>
<td>8/26 (31)</td>
<td>33/82 (53)</td>
</tr>
<tr>
<td>Grade</td>
<td>Benign: 0/239 (0) 1: 0/70 (0) 2: 20/55 (36) 3: 57/96 (59)</td>
<td>0/67 (0)</td>
<td>20/55 (36)</td>
</tr>
</tbody>
</table>
| a Patients with unknown data are not included. b Adipocytic = liposarcoma, atypical lipomatous tumor, lipoma, lipoblastoma, hematoma. c Myogenic = leiomyosarcoma, rhabdomyosarcoma, myogenic sarcoma, NOS, leiomyoma. d Fibroblastic = fibrosarcoma, myofibroblastoma, dermatofibrosarcoma protuberans, benign and malignant solitary fibrous tumors, deep and superficial fibromatoses, elastofibroma, benign fibrous histiocytoma, benign fibrous tumor NOS. e Synovial = synovial sarcoma, localized and diffuse tenosynovial giant cell tumors. f Vascular = angiosarcoma, hemangiopericytoma, angiomat. g Nerve sheath = malignant peripheral nerve sheath tumor, schwannoma, neurofibroma. h Miscellaneous = malignant fibrous histiocytoma, pleomorphic sarcoma NOS, malignant mesenchymoma, benign and malignant soft tissue chondromas and osteogenic tumors, benign and malignant soft tissue tumors NOS.

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**Clinical Outcome.** Of the 460 patients with follow-up data, 77 (17%), all of whom had grade 2 or 3 sarcomas, developed metastases (Table 1). Median time to first metastasis was 10 (range 0–180) months; 12 of the patients had metastases already at diagnosis; and an additional 64 of them developed metastases within 84 months. The 383 patients without metastases had a median follow-up time of 56 (range 0–384) months. The median follow-up time for the 74 patients with grade 2 or 3 tumors that did not metastasize was 76 (range 0–307) months.

**Cytogenetic Analysis.** G-banded metaphase spreads from short-term cultured tumor cells were obtained as reported previously (9). Karyotypes were described according to the ISCN (1995; Ref. 13). For the statistical analyses, we classified each karyotype with respect to complexity (sole anomaly; simple karyotype, here defined as 2–5 clonal aberrations; or complex karyotype, i.e., >5 aberrations), ploidy level(s), type of aberrations (structural only, numerical only, or both structural and numerical), and the presence of cytogenetic signs of gene amplification, i.e., double minutes and homogeneously staining regions, and ring chromosomes. Furthermore, for each case, the chromosomal regions, as defined by ISCN (1995), affected by breaks, gains, and losses were recorded.

**Statistical Analyses.** The prognostic effect of each clinicopathological and cytogenetic variable was examined by Kaplan-Meier curves and the log-rank test (14). Cox regression modeling was applied to explore the effects of several variables on metastasis development (14, 15). Because none of the 70 grade 1 sarcomas metastasized, the modeling was based on data from the patients with grade 2 and 3 tumors. We used the following model-building strategy: First, the clinicopathological variables (Table 1) were analyzed. Secondly, we screened the cytogenetic variables; variables with at least five positive patients who developed metastases and that implied a log-rank \( P \leq 0.10 \) were selected for additional analyses. Thirdly, the additional prognostic value of each selected variable, besides the clinicopathological variables of importance, was explored. Finally, to obtain the most important prognostic factors, the relevant clinicopathological variables and the cytogenetic variables that showed a statistically significant additional effect were forwardward in a stepwise selection procedure (entry only if \( P \leq 0.05 \) and removal only if \( P \geq 0.10 \)). Modeling of the final prognostic factors was checked graphically (15). We used the log likelihood ratio test as well as Wald’s test for obtaining Ps from the modeling (16). Hazard ratios with 95% confidence intervals are presented as effect measures. The statistical computations were carried out using SPSS for Windows (release 10.0.5; SPSS Inc., Chicago).
nancy grade and tumor size, or malignancy grade and tumor depth, resulted in 17 variables that showed a significant additional effect on risk for metastasis development (Table 3). Some of these variables were gains of neighboring regions and were always simultaneously involved. Hence, they were combined in the following analyses. In the final, stepwise Cox regression analysis, five markers, breakpoints in 1p1, 1q4, 14q1, and 17q2 and gain of 6p1/p2, became statistically significant besides grade and size/depth. A summary index, “additional complexity,” was constructed by counting, for each case, the number (0, 1, or ≥2) of positive variables selected in the final step. The results show that the additional complexity provided prognostic information besides grade and size/depth (Table 4). The prognostic value of additional complexity was seen also when dichotomizing the patients into one group with disadvantageous clinicopathological predictors (i.e., grade 3 and size ≥5 cm or deep-seated; n = 85, 55 of

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Besides grade and size</th>
<th>Besides grade and depth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>B1p1</td>
<td>2.5 (1.3–4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>B1q4</td>
<td>3.2 (1.2–8.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>B10p1</td>
<td>1.9 (1.0–3.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>B10q1</td>
<td>2.7 (1.1–6.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>B14q1</td>
<td>2.8 (1.3–6.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>B17q2</td>
<td>3.6 (1.7–7.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>L10p1</td>
<td>1.9 (1.1–3.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>G1q2</td>
<td>2.7 (1.0–7.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>G1p1</td>
<td>2.7 (1.2–6.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>G1q1</td>
<td>2.4 (1.1–5.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>G6p1</td>
<td>2.8 (1.4–5.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>G6q1</td>
<td>2.6 (1.1–6.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>G7p1/p2</td>
<td>1.8 (0.9–3.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>G9q2/q3</td>
<td>4.2 (1.2–14)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

a The screening (see “Statistical Analyses”) of the 268 cytogenetic variables in a series of 151 patients (77 of whom developed metastases) resulted in 37 markers of potential interest. These 17 variables that were significant in the multivariate Cox analyses are included in the Table. The following 20 variables were not significant: ploidy level, double minutes/homogeneously staining region, B6q1, B6q2, B6q1, B17p1, B20p1, L5p1, L6p2, L6q1, L10q1, L10q2, L20p1, G1p3, G1q2, G1q3, G1q4, G3p2, G3p1, and G9q1.

b First letter in names of variables: B, breakpoint in chromosome region; L, loss of chromosome region; G, gain of chromosome region. Gains of regions 6p1/p2, 7p1/p2, and 9q2/q3, respectively, were always present together and were, hence, combined.

c HR, hazard ratio estimate (yes versus no) obtained from trivariate Cox regression analysis; CI, confidence interval; P, P from Wald’s test. The hazard ratios of grade and size/depth were consistently similar to the corresponding hazard ratios given in Table 2.

d The no. of cases/no. of cases with metastasis are given in parentheses.

Table 4

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>HR* (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(with metastasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55 (20)</td>
<td>1.0⁸</td>
</tr>
<tr>
<td>3</td>
<td>96 (57)</td>
<td>3.1 (1.7–5.8)</td>
</tr>
<tr>
<td>Size⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>26 (8)</td>
<td>1.0⁸</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>121 (66)</td>
<td>3.7 (1.7–8.0)</td>
</tr>
<tr>
<td>Additional complexity⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>104 (43)</td>
<td>1.0⁷</td>
</tr>
<tr>
<td>1</td>
<td>34 (22)</td>
<td>2.8 (1.6–5.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>13 (12)</td>
<td>9.3 (4.3–20)</td>
</tr>
<tr>
<td>Additional complexity in myogenic sarcomas⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (8)</td>
<td>1.0⁷</td>
</tr>
<tr>
<td>1</td>
<td>12 (8)</td>
<td>3.6 (1.1–12)</td>
</tr>
<tr>
<td>≥2</td>
<td>6 (5)</td>
<td>4.9 (1.2–20)</td>
</tr>
</tbody>
</table>

* Hazard ratio estimate obtained from the multivariate Cox regression analysis.

† Confidence interval.

‡ P obtained from Wald’s test.

§ Reference category.

¶ Similar effects were obtained when size was replaced by tumor depth (deep versus superficial).

Table 4 Effects of malignancy grade (only grade 2–3 tumors), tumor size, and additional complexity on the hazard of having a metastasis diagnosed

Fig. 1. Kaplan-Meier curves showing the prognostic effect of karyotypic complexity in soft tissue tumors (dotted curve, sole anomaly; broken curve, simple karyotype; solid curve, complex karyotype). A. All of the patients (sole anomaly, 185/11 (total no. of patients/no. of patients with metastases); simple karyotype, 153/15; complex karyotype, 94/51; P = 0.27).

Additional Prognostic Value of Cytogenetic Variables for Grade 2 and 3 Sarcomas. The Cox regression analyses, including each of the 37 selected cytogenetic variables, together with malignancy grade and tumor size, or malignancy grade and tumor depth, resulted in 17 variables that showed a significant additional effect on risk for metastasis development (Table 3). Some of these variables were gains of neighboring regions and were always simultaneously involved. Hence, they were combined in the following analyses. In the final, stepwise Cox regression analysis, five markers, breakpoints in 1p1, 1q4, 14q1, and 17q2 and gain of 6p1/p2, became statistically significant besides grade and size/depth. A summary index, “additional complexity,” was constructed by counting, for each case, the number (0, 1, or ≥2) of positive variables selected in the final step. The results show that the additional complexity provided prognostic information besides grade and size/depth (Table 4). The prognostic value of additional complexity was seen also when dichotomizing the patients into one group with disadvantageous clinicopathological predictors (i.e., grade 3 and size ≥5 cm or deep-seated; n = 85, 55 of
which metastasized; see Table 2) and one complementary group (i.e.,
grade 2 or grade 3, and size < 5 cm or deep-seated tumor). Clinical pathology
variables (0 variables, 1/5; 1 variable, 21/17; 2 variables, 65/51; P < 0.001).

When the entire material, i.e., both benign and malignant tumors,
was considered, we found the majority (167 of 268) of cytogenetic
variables, including the level of karyotypic complexity, to be associ-
ated with metastasis development (Fig. 1). Although not formally
demonstrated in earlier studies, this finding was not entirely unex-
pected, bearing in mind that malignant soft tissue tumors in general
have more complex karyotypes than benign soft tissue tumors.

Furthermore, in the present series none of the patients with tumors
classified as grade 1 sarcomas developed metastases. Hence, we
restricted additional statistical analyses to the clinically most relevant
subgroup of 151 patients with grade 2 or 3 sarcomas. That this subset
constituted a clinically representative series of high-grade sarcomas
was demonstrated by the finding that previously established clinic-
opathological variables, such as malignancy grade, tumor histotype,
size and depth, and gender, but not patient age or tumor location,
turned out to be significantly associated with metastasis development
(Table 1).

By focusing on the subset of 151 patients with high-grade soft
tissue sarcomas, 37 cytogenetic variables turned out to provide prog-
nostic information, 17 of which were significant besides tumor grade
and size/depth (Table 3). In contrast to what has been suggested for
many other types of solid tumors (17), general karyotypic features,
such as ploidy level or complexity level, or cytogenetic markers of
gene amplification (double minutes and homogeneously staining re-
gions), did not reach statistical significance when analyzed together
with grade and size. Instead, the identified independent prognostic
variables were breakpoints, losses, or gains of specific chromosome
regions. These variables showed considerable overlap with each other,
and some of them were always simultaneously involved. This strongly
indicates that these aberrations are not independently acquired,
a conclusion corroborated by recent results of statistical analyses on
clonal evolution in solid tumors (18). The close relationships between
some of the variables was further demonstrated in the stepwise re-
gression analysis, in which five of the variables were found to be
strong, independent predictors of metastasis development.

We could also show that the risk for metastasis development
increased with the increasing involvement of cytogenetic variables
(Table 4), including when the material was dichotomized into one
disadvantageous and one advantageous clinical subgroup. Further-
more, for some of the histopathological types, i.e., myogenic, adipocytic,
synovial, and nerve sheath sarcomas, case numbers were large
enough to allow separate statistical analysis. In all of them, the
presence of any of the selected cytogenetic variables provided addi-
tional prognostic information, and in the largest group, the myogenic
sarcomas, the risk for metastasis development increased with increas-
ing involvement of the five independent prognostic cytogenetic vari-
able (Table 4).

Although our findings strongly suggest that prognostic information
may be gained from cytogenetic analysis of soft tissue sarcomas, the
specific cytogenetic variables that were identified as predictors of

Chromosomal aberrations may provide additional prognostic information, independent of histopatho-
logical diagnosis, tumor grade, or previously established clinical
variables associated with poor outcome. Chromosomal banding anal-
ysis, like comparative genomic hybridization, provides information on
all chromosomes, and has the further advantage of detecting both
balanced and unbalanced rearrangements. However, because of the
outgrowth of normal stromal cells, a cell culture may yield only
normal metaphase cells. Hence, only cases with clonal, acquired
aberrations were included. Because of the lack of previous informa-
tion on possible clinicocytogenetic correlations, the karyotypic infor-
mation on each tumor was categorized into a large number (n = 268)
of cytogenetic variables, including both general cytogenetic features,
such as level of karyotypic complexity and ploidy level, and specific
information on each chromosome region.

Our aim was to determine whether chromosomal aberrations may
provide additional prognostic information, independent of histopatho-
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DISCUSSION

For some types of neoplasia, notably the hematological malignan-
cies, it is now well established that the chromosomal aberrations
detected at diagnosis are important predictors of clinical outcome.
Although still far less extensively analyzed, preliminary results
strongly indicate that the variability in the spectrum of somatic mu-
tations that are encountered in solid tumors is also reflected in different
risks of metastasis development and/or treatment response (17). In
the management of patients with soft tissue sarcoma, the prediction of
tumor aggressiveness and the ensuing treatment strategy presently
relate on a combination of histopathological and clinical findings.
Reports in which attempts have been made to extract additional
information from genetic features are scarce and have all been based
on small numbers of patients, or have focused on rearrangements that
are relevant only for particular histological subsets of sarcoma.

Our aim was to determine whether chromosomal aberrations may
provide additional prognostic information, independent of histopatho-
logical diagnosis, tumor grade, or previously established clinical
variables associated with poor outcome. Chromosomal banding anal-
ysis, like comparative genomic hybridization, provides information on
all chromosomes, and has the further advantage of detecting both
balanced and unbalanced rearrangements. However, because of the
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tion on possible clinicocytogenetic correlations, the karyotypic infor-
mation on each tumor was categorized into a large number (n = 268)
of cytogenetic variables, including both general cytogenetic features,
such as level of karyotypic complexity and ploidy level, and specific
information on each chromosome region.

Although our findings strongly suggest that prognostic information
may be gained from cytogenetic analysis of soft tissue sarcomas, the
specific cytogenetic variables that were identified as predictors of

CHROMOSOMES AND PROGNOSIS IN SARCOMAS

which metastasized; see Table 2) and one complementary group (i.e.,
grade 2 or grade 3, and size < 5 cm and superficial; n = 66, 22 of
which metastasized; Fig. 2). Furthermore, also when high-grade myo-
genic sarcomas were investigated separately, an association between
the increasing number of cytogenetic variables and the increasing risk
for metastasis development was seen (Table 4). Although the number
of cases was smaller, similar results were obtained for adipocytic sarcomas,
malignant peripheral nerve sheath tumors, and synovial sarcomas (data not shown).
metastasis development need to be evaluated in additional large series of sarcoma patients before their true prognostic impact can be established. Many cytogenetic variables were investigated, and, although precautions were taken in the statistical analyses (19), it cannot be excluded that some of the associations detected are chance findings. Conversely, it should also be noted that additional prognostically important genetic aberrations, occurring too rarely to be fully evaluated in the present study, may exist.

Apart from the potential clinical relevance of the identified genetic variables, our findings could also prove helpful in the elucidation of cellular mechanisms influencing the metastatic process of sarcoma cells. Bearing in mind, however, that the chosen level of investigation, i.e., chromosome regions, represents a fairly large segment of DNA, any speculation concerning the possible molecular genetic consequences of the aberrations would be premature. However, obvious candidates for refined molecular genetic investigation would be sarcomas with breakpoints in chromosomal regions 1p1, 1q4, 14q1, and 17q2, to find out whether these rearrangements target specific gene loci, and sarcomas with gain of material from the short arm of chromosome 6, to investigate whether cases with overrepresentation of this segment display specific gene expression profiles. Furthermore, if the limited set of prognostically significant cytogenetic variables that we identified is confirmed by other studies, alternative approaches, such as molecular cytogenetic investigation, to detect them could be developed to provide more rapid and reliable identification than may be obtained by a cytogenetic analysis of cultured cells. On the other hand, it should be noted that the involvement of particular chromosome bands is difficult to demonstrate using comparative genomic hybridization, and interphase fluorescence in situ hybridization is cumbersome when several loci need to be investigated. Thus, it may well be found that chromosome banding analysis is the more efficient technique.

REFERENCES

