Analysis of prognostic factors associated with injection-site sarcomas in cats: 57 cases (2001–2007)

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Objective—To identify prognostic factors in cats with injection-site sarcomas (ISSs).

Design—Retrospective case series.

Animals—57 cats with ISSs.

Procedures—Medical records of cats were reviewed with regard to sex, age, anatomic site of tumor, tumor size, histologic grade, excision of a primary tumor versus excision of a recurrent ISS, use of excision alone versus excision plus adjuvant therapy, local tumor recurrence, and development of distant metastasis to predict overall survival time (ie, time from tumor excision to death).

Results—In univariate analyses, local recurrence and development of distant metastasis were significantly associated with survival time in cats. On multivariate analysis, development of distant metastasis remained a significant prognostic factor. Histologic grade was associated with distant metastasis, with cats having grade 3 tumors being significantly more likely to develop metastasis than cats with grade 1 and 2 tumors. Factors associated with local recurrence of ISSs were not identified.

Conclusions and Clinical Relevance—The development of distant metastasis, which may occur later during the course of the disease, was identified as a prognostic factor for overall survival time in cats with ISSs. In addition, cats with histologic grade 3 ISSs should be considered for further interventional studies with chemotherapy to prevent the high rate of distant metastasis. (*J Am Vet Med Assoc* 2008;232:1193–1199)

Injection-site sarcomas in cats are unique tumors first described in 1991 by Hendrick and Goldschmidt.[1] The postvaccinal local inflammation induced by vaccine adjuvants seems to play a causative role by leading to uncontrolled fibroblast proliferation and, ultimately, to a process of cancer formation.[2–4] Although only vaccines were initially implicated in sarcoma development, investigators have elucidated that any injected compound causing local inflammation may play a role in oncogenesis.[4] This theory is supported by microscopic observation of transition zones from inflammation to sarcoma.[4] Injection-site sarcomas are aggressive tumors with a wide spectrum in terms of histologic type, including fibrosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, extraskeletal osteosarcoma, chondrosarcoma, and undifferentiated sarcoma.[5] In general, histologic subtype often correlates with biological behavior; however, in the case of ISSs, the prognostic value of histogenetic classification is questionable.[4]

Because of aggressive biological behavior, most pathologists consider ISSs as high-grade sarcomas, independent of histologic characteristics. Nevertheless, some authors have tried to identify low- and high-risk groups as well as factors associated with survival, metastatic spread, and local tumor recurrence.[6–9]

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Abbreviations

ISS	Injection-site sarcoma
STS	Soft tissue sarcoma

In humans with STSs, histologic grading is the most important prognostic factor and the best indicator of metastatic risk,[10] thereby being an important part of the pathologic report. It is generally accepted that assessment of histologic grading is also a useful tool for directing treatment because it identifies patients that may benefit from adjuvant therapy, such as radiotherapy and chemotherapy.

In veterinary medicine, grading has also become a key component of the pathologic report; however, the same system is applied for all STSs, which are considered as a single entity. Indeed, the most commonly used system is by Kuntz et al[11] that is derived from human guidelines[12] and has been adapted to dogs. This is a 3-grade system (with grade 1 being the least aggressive and grade 3 the most), and it is based on degree of differentiation, mitotic activity, and amount of tumor necrosis.[11] For ISSs, the value of classic grading may be limited.[13] In fact, despite accurate pretreatment staging procedures and proper histologic evaluation, outcome is often difficult to predict.[2]

To date, limited studies have analyzed prognostic factors for different end points, such as disease-free interval and overall survival. An analysis of prognosis for 61 cats treated by surgery alone was retrospectively provided in a study.[6] According to these investigators, factors that in-

creased the risk of local tumor recurrence were marginal first excision and anatomic site other than appendicular, whereas prognostic factors associated with overall survival time were not identified. In 2 further studies,[9,14] the only significant factor found to be related to disease-free interval was completeness of excision. Factors associated with overall survival time were not identified. In a large retrospective study,[15] the effect of various factors on survival time were evaluated; findings in that study indicated that sex, type of surgery, delay between surgery and initiation of radiotherapy, development of distant metastasis, and size of the tumor had a significant effect on survival time. More recently, aberrant immunohistochemical p53 expression was correlated with shorter time to local tumor recurrence, compared with normal nuclear p53 staining.[8]

The aim of the study reported here was to retrospectively evaluate whether factors such as sex, age, anatomic site of tumor, tumor size, histologic grade, excision of primary tumors or excision of recurrent ISSs, use of excision alone or excision plus adjuvant therapy, and development of local recurrent ISSs or distant metastasis were prognostic factors of survival time in cats with ISSs. In addition, factors associated with the development of local tumor recurrence and distant metastasis were investigated.

Materials and Methods

Case selection—Medical records of cats with a histologic diagnosis of ISSs referred to the Clinica Veterinaria Nerviano between 2001 and 2007 for definitive treatment were reviewed. Cats were eligible for inclusion if the staging procedure was complete, if follow-up information was obtained, and if tumor specimens were available for histologic review.

Medical records review—For each cat included in the study, data recorded and evaluated included the following: signalment; history; physical examination findings; anatomic location of tumor; 3-dimensional measurements of tumor as determined by use of calipers or from a computed tomographic scan; tumor shape, consistency, and mobility; histologic appearance of tumor; palpation results of regional lymph nodes; CBC and differential; results of serum biochemical analysis and urinalysis; findings on plain thoracic radiographs (3 views) and abdominal ultrasonography; and in selected cases (ie, cats with tumors in the scapular region and cats with recurrent ISSs), findings on computed tomographic scans of tumor region as a means to delineate tumor extent. Furthermore, pathologic, treatment, and outcome details for cats were evaluated by review of medical records. If this was not possible, direct contact with the referring veterinarians or with the owners was established.

Treatment had been by wide excision where possible, with 4- to 5-cm margins laterally and 1 fascial plane deep to the tumor. For ISSs originating in the scapular region, the extent of resection included partial scapulectomy and removal of dorsal spinous processes. In the case of an appendicular ISS, the affected limb was amputated. All resections had been performed by the same surgeon (GR). The cut surfaces of resected tumors were inked with yellow dye,[a] oriented with sutures, and allowed to dry before fixation.

A single pathologist (DO) reported microscopic findings for all tumors. For each cat included in the study, the resected tumor in its whole had been fixed in neutral-buffered 10% formalin and routinely processed. For all specimens, sections were stained with H&E and, if required, immunohistochemical staining was performed to obtain a definitive diagnosis. The pathologic report included histopathologic subtypes according to the classification scheme of the World Health Organization,[16] status of resection margins, and grade of tumor (low = 1, intermediate = 2, and high = 3) based on assessment of tumor differentiation, mitotic activity, and amount of tumor necrosis.[11] Regarding the status of resection margins, tumor cells that extended to the surgical edge were considered incomplete margins, tumor cells that extended within 1 cm of the margins or were observed just outside of the pseudocapsule were considered marginal (or clean but close) margins, and 1 to 3 cm of normal tissue observed around the tumor was considered wide (or complete) margins.

For optimizing local tumor control, postoperative radiotherapy had been advised for cats in which a marginal resection was performed, cats with a recurrent tumor, and cats with incomplete surgical margins, as determined by the presence of neoplastic cells extending to ≥ 1 surgical margin. Chemotherapy had been advised for cats with recurrent or high-grade tumors.

For each cat, follow-up information regarding tumor recurrence or metastasis was obtained through physical examinations and thoracic radiography and repeated every 3 months during the first year and every 6 months thereafter. Any growth at the surgical site or developing elsewhere was biopsied. Metastasis was defined as radiographic or histologic evidence of ISSs in a noncutaneous tissue.

Statistical analysis—The following factors were investigated to verify whether they had an influence on overall survival time, which was defined as time elapsed between surgery and death: sex, age, anatomic site of tumor (scapular vs thorax or abdominal), tumor size measured at its major diameter (< 2 cm, ≥ 2 to < 4.9 cm, or ≥ 5 cm), histologic grade, excision of primary tumor versus excision of a recurrent ISS, use of excision alone versus excision plus adjuvant therapy (chemotherapy or radiotherapy), local tumor recurrence, and development of distant metastasis. The influence of these factors was studied by use of the Kaplan-Meier product-limit followed by the log-rank test. Prognostic factors that on univariate analysis had a value of $P < 0.1$ were further used to evaluate their independence by use of the Cox proportional hazard model. Cats were censored if they were still alive or if they died because of causes that were unrelated to the disease (eg, trauma). In addition, factors associated with the development of local recurrence and distant metastasis were investigated by use of the χ^2 or Fisher exact test and r × c contingency tables, followed by Bonferroni correction. Among them, anatomic site, size, and histologic grade of tumor; excision of primary tumor versus ex-

cision of a recurrent ISS; and use of adjuvant therapy were included. For distant metastasis, the development of local recurrence was also studied. Statistical analysis was conducted by use of a software program.[b] Values of $P < 0.05$ were considered significant.

Results

Patient and tumor characteristics—Fifty-seven cats with ISSs met the criteria for inclusion in this study. Of 55 cats, 26 (47%) were castrated males, 24 (44%) were spayed females, 3 (5%) were sexually intact males, and 2 (4%) were sexually intact females (male to female ratio, 1:0.9). Sex had not been recorded for 2 cats. Included in the study were 54 (95%) domestic shorthair, 2 (3%) Persians, and 1 (2%) Turkish Van. Median age was 10 years (range, 3 to 16 years).

Of 57 cats, 28 (49%) had developed ISSs in the thoracic region, whereas 23 (40%) had ISSs located in the scapular region (including the lateral aspect of the scapula and interscapular regions), 5 (9%) had ISSs on the abdomen (including the flank region), and 1 (2%) had an ISS on the caudal aspect of the thigh. Masses were palpable in all cats. Dimension of the tumor had not been recorded for 4 cats. Median size of tumors at the greatest diameter was 2.0 cm (range, 0.4 to 11.0 cm).

Preoperative staging procedures had been performed in all cats by the time of referral and ≤ 1 week prior to excision. Computed tomography was always suggested but had been performed in 31 cats only, mainly because of financial reasons. Among cats undergoing computed tomography, 13 cats had ISSs in the scapular region, 10 had ISSs in the thoracic region, 7 had ISSs in the flank region, and 1 had an ISS on the limb. Of these 31 cats, 18 had primary ISSs and 13 had recurrent tumors. None of the enrolled cats had evidence of distant metastases.

Treatment—Among the 57 cats, 30 (53%) had primary previously untreated ISSs, whereas the remaining 27 (47%) cats had local tumor recurrence after earlier attempts at treatment at outside institutions (range, 1 to 14 months), usually with limited staging information. In 10 of 27 (37%) cats, it was the first recurrence; in 13 (48%), it was the second recurrence; and in 4 (15%), it was the third recurrence. Previous treatments consisted of excision (n = 26) and additional postoperative radiotherapy (1).

Wide radical resection of ISSs had been performed in all cats. The 1 cat with an appendicular ISS underwent limb amputation. Depending on histologic grade, resection margin status, whether the tumor was primary or recurrent, and compliance of the owner, postoperative treatment varied. Overall, 42 of 57 (74%) cats underwent excision only, 9 (16%) received surgery followed by radiotherapy, 3 (5%) had surgery followed by chemotherapy, and 3 (5%) were treated by a combined modality treatment of surgery followed by radiotherapy and chemotherapy.

Regarding radiotherapy, a full-course protocol consisting of 12 fractions of 4 Gy each (on a Monday through Thursday schedule) for a total dose of 48 Gy was applied. Cats received radiotherapy 10 to 14 days after surgery. Regarding chemotherapy, carboplatin was administered to 4 cats, whereas 2 cats with chronic renal disease received liposome-encapsulated doxorubicin.

Histopathologic findings—Of 57 tumors, 53 (93%) were histologically identified as fibrosarcomas, 2 (3.5%) as malignant fibrous histiocytomas, and 2 (3.5%) as chondrosarcomas. Forty-one of 57 (72%) ISSs were classified as grade 1 tumors, 13 (23%) as grade 2 tumors, and 3 (5%) as grade 3 tumors.

Fifty-four of 57 (95%) ISSs were completely resected, whereas in the remaining 3 (5%) tumors, neoplastic cells were identified at the surgical margins. For the 41 grade 1 ISSs, 39 (95%) were completely resected, whereas 1 of 3 grade 3 ISSs was incompletely resected. All grade 2 tumors were completely resected, and neoplastic cells were not detected at the surgical margins.

Outcome—Among 57 cats, 31 (54%) returned to our hospital for follow-up examination, whereas the remaining 26 (46%) were rechecked by their local veterinarian. At the end of the study, 28 of 57 (49%) cats were dead and 29 (51%) were alive.

Among the 28 cats that died, 12 (43%) had died because of distant metastatic disease, 9 (32%) were euthanatized for the lack of local tumor control in the absence of distant metastasis, 4 (14%) had died from tumor-unrelated causes, and 3 (11% of cats that died; 5% of the total 57 cats) had died in the immediate postoperative period. Local tumor recurrence developed in 7 cats admitted with primary ISSs and in 8 cats admitted with recurrent ISSs. With regard to histologic grade, tumor recurrence developed in 12 of 18 cats with grade 1 ISSs, 2 of 7 cats with grade 2 ISSs, and 1 of 3 cats with grade 3 ISSs. Six cats with distant metastases also had local tumor recurrence. The lungs was the most common site for metastases (n = 12), followed by regional lymph nodes (2). With regard to histologic grade, 7 of 12 cats that developed distant metastasis had grade 1 tumors, 2 had grade 2 tumors, and 3 had grade 3 tumors. In addition, 5 of 12 cats with distant metastasis had been admitted with previously untreated ISSs, and the remaining 7 cats had already been treated before admission. Median follow-up time for cats that died was 272 days (range, 5 to 1,170 days).

Among the 29 cats that survived, 22 (76%) had no evidence of disease at data analysis closure, whereas 7 (24%) developed local tumor recurrence in the absence of distant metastasis during the follow-up period. Tumor recurrence developed in 2 cats that were admitted with primary ISSs and in 5 cats that were admitted with recurrent ISSs. With regard to histologic grade, recurrent ISSs developed in 5 of 23 (22%) cats with grade 1 tumors and in 2 of 6 cats with grade 2 tumors. None of the surviving cats developed distant metastasis. Median follow-up of survivors was 600 days (range, 129 to 1,768 days).

The median follow-up for all 57 cats was 366 days (range, 5 to 1,768 days). Overall, local tumor recurrence developed in 22 of 57 (39%) cats, whereas 12 (21%) cats developed regional or distant metastases. Recurrent ISSs developed in 17 of 41 (42%) cats with grade 1 tumors, in 4 of 13 cats with grade 2 tumors, and in 1 of 3 cats with a grade 3 tumor. Metastasis developed in 7 of 41

(17%) cats with grade 1 ISSs, in 2 of 13 cats with grade 2 tumors, and in all 3 cats with grade 3 tumors.

Analysis of prognostic factors—Prognostic factors for overall survival time were evaluated by use of univariate analysis (**Table 1**). Cats that developed local tumor recurrence or metastasis during the follow-up period had a significantly shorter survival time ($P < 0.001$; **Figures 1 and 2**), compared with cats that did not develop tumor recurrence or metastasis. With the adopted model, results of multivariate analysis revealed that only the development of distant metastasis remained of prognostic value ($P = 0.002$; **Table 2**). Metastasis increased the risk of death in cats with ISSs by approximately 3-fold.

Table 1—Kaplan-Meier analysis of factors potentially associated with survival time (ie, time from surgery to death) in 57 cats with ISSs.

Factor	No. of cats*	Median survival time (d)	Hazard ratio	95% CI	*P* value
Sex†					
Male	30	707			
Female	25	848	0.96	0.47–1.94	0.90
Age					
< 10 y	22	707			
≥ 10 y	35	721	0.91	0.45–1.81	0.78
Anatomic site					
Scapula	19	953			
Thorax or abdomen	37	396	0.51	0.26–1.07	0.07
Tumor size					
< 2 cm	28	929			
≥ 2 to < 5 cm	18	728			
≥ 5 cm	7	184	NA	NA	0.15
Histologic grade					
1 (low)	41	728			
2 (intermediate)	13	365			
3 (high)	3	370	NA	NA	0.43
Tumor excision					
First surgery	30	952			
Surgery of a recurrent ISSs	27	707	0.62	0.30–122	0.16
Type of treatment					
Surgery alone	41	804			
Surgery plus adjuvant therapy	15	707	1.77	0.85–4.56	0.11
Development of local tumor recurrence					
Yes	22	365			
No	32	1,098	3.08	1.91–9.62	< 0.001
Occurrence of distant metastasis					
Yes	12	165			
No	45	929	3.58	2.62–19.6	< 0.001

*Total number of cats in the table does not add up to 57 for each variable because for some cats, data were missing from the record. †Including neutered and sexually intact cats.
CI = Confidence interval. NA = Not available.

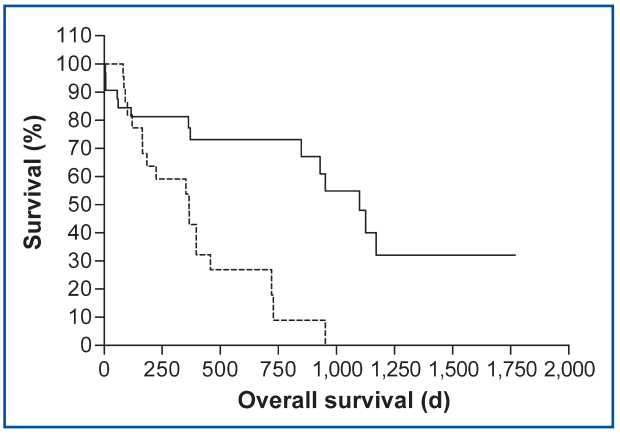

Figure 1—Overall survival time in cats with ISSs that developed local tumor recurrent (dashed line; n = 22) and cats without local recurrent ISSs (solid line; 32).

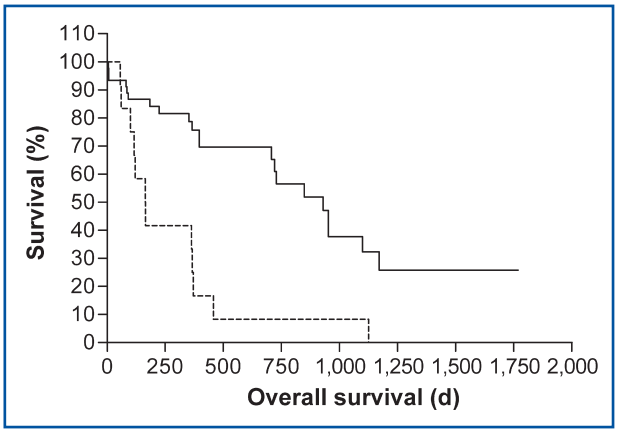

Figure 2—Overall survival time in cats with ISSs that developed distant metastasis (dashed line; n = 12) and cats without distant metastasis (solid line; 45).

Table 2—Cox proportional hazard model analysis of factors potentially associated with survival time in 57 cats with ISSs.

Factor	Odds ratio	95% CI	*P* value
Anatomic site			
Scapula			
Thorax or abdomen	1.80	0.82–3.95	0.15
Development of local tumor recurrence			
Yes			
No	1.00	NA	NA
Occurrence of distant metastasis			
Yes			
No	0.31	0.15–0.66	0.002

See Table 1 for key.

Analysis of factors associated with local tumor recurrence and distant metastasis—With regard to factors associated with the development of distant metastasis, cats with ISSs of grade 3 were more likely to develop metastasis than cats with lower grades ($P = 0.009$; **Table 3**). The investigated factors were not associated with the development of local tumor recurrence (**Table 4**).

Discussion

Injection-site sarcomas in cats are included in the group of STSs; however, they are histologically heterogeneous, have distinctive biological behavior, and are typically considered aggressive.[17] The key determinant of survival is control of local tumor recurrence as well as distant metastatic spread. Injection-site sarcomas dis-

Table 3—Factors potentially associated with the development of distant metastasis in 57 cats with ISSs.

Variable	No. of cats with metastasis*	No. of cats without metastasis*	*P* value
Anatomic site			
Scapula	3	16	
Thorax or abdomen	9	28	0.73
Tumor size			
< 2 cm	3	25	
≥ 2– < 5 cm	6	12	
≥ 5 cm	1	6	0.15
Histologic grade			
1 (low)	6	33	
2 (intermediate)	2	9	
3 (high)	3	0	< 0.001†
Tumor excision			
First surgery	5	25	
Surgery of a recurrent ISSs	7	20	0.51
Type of treatment			
Surgery alone	5	36	
Surgery plus adjuvant therapy	7	8	0.001‡
Development of local tumor recurrence			
Yes	6	16	
No	6	26	0.52

†$P < 0.01$ and ‡$P > 0.05$ with Bonferroni correction.
See Table 1 for remainder of key.

Table 4—Factors potentially associated with the development of local tumor recurrence in 57 cats with ISSs.

Variable	No. of cats with tumor recurrence*	No. of cats without tumor recurrence*	*P* value
Anatomic site			
Scapula	6	13	
Thorax or abdomen	16	19	0.39
Tumor size			
< 2 cm	10	16	
≥ 2– < 5 cm	6	12	
≥ 5 cm	4	2	0.34
Histologic grade			
1 (low)	17	19	
2 (intermediate)	4	7	
3 (high)	1	2	0.76
Tumor excision			
First surgery	9	20	
Surgery of a recurrent ISSs	13	12	0.17
Type of treatment			
Surgery alone	12	27	
Surgery plus adjuvant therapy	9	5	0.05‡

See Tables 1 and 3 for key.

seminate primarily via the hematogenous route, particularly to the lungs with a reported incidence of 15% to 28%.[17,18] Needless to say, early detection and treatment based on accurate diagnosis and staging procedure are the basic principles of management of ISSs.[19] The treatment approach is usually multidisciplinary, with radical excision of the primary tumor representing the most efficacious treatment.[17,20] Depending on histologic grade, effective treatment usually also requires postoperative radiotherapy, chemotherapy, or both.[9,14,15,17–19,21–24]

In several studies,[6,8,9,14,15] prognostic factors concerning local control and survival times for cats with STSs have been analyzed. In humans and dogs, development of distant metastasis is generally the most limiting event in sarcomas and is mostly dependent on tumor size and histologic grade.[11,25] Consequently, high-grade tumors are often managed by postoperative chemotherapy.

Efforts have been made in the last decade to establish prognostic factors for cats with ISSs. For ISSs, anatomic site, size of tumor, completeness of resection, radical first excision, postsurgical adjuvant therapies, and histologic type and grade are agreed to be of importance for local control.[8,9,17,24] According to the findings in 1 study,[15] spayed female cats, cats undergoing conservative surgery immediately followed by radiotherapy, and cats with small ISSs that did not develop distant metastasis were reported to have the longest survival.

In the study reported here, we retrospectively evaluated 57 cats with ISSs to explore the prognostic factors associated with overall survival time. Given the fact that recurrent tumors do not necessarily assume a more anaplastic phenotype, with histologic grade remaining generally the same,[13] we decided to include cats with recurrent ISSs.

As was found in a previous study,[15] we found that development of distant metastasis was significantly correlated with overall survival, on univariate as well as on multivariate analyses. In the study reported here, we also found that high-grade tumors were associated with an increased risk of distant metastasis.

In human medicine and veterinary medicine, it has been reported that pathologic grade is an important prognostic factor for STSs.[11,25] The grading system proposed by Kuntz et al,[11] derived from human medicine and adapted for dogs, is the most widely used in veterinary medicine and comprises 3 grades of malignancy that reflect the degrees of risk of local tumor recurrence and distant metastasis. It has been shown that an accurate, reliable, and reproducible grading system is crucial for tumor management. In fact, medical oncologists place increasing importance on histologic grading in terms of selecting cats for chemotherapy and setting goals for treatment. Furthermore, the grading system is increasingly important to allow the comparison of clinical experiences among treatments and among oncologists. Unfortunately, grade assignment is often somewhat subjective with no universally accepted roster of standard inclusive pathologic criteria; thereby, the development of objective and standardized methods for grading is greatly needed. In addition, the commonly used criteria to define the grade of tumor, such as degree of differentiation, mitotic activity, and amount of necrosis, do not apply uniformly to all STSs.

In the study reported here, pathologic grade was associated with the metastatic rate and all cats with grade 3 ISSs developed pulmonary metastasis. Undoubtedly, the finding that 7 cats with grade 1 ISSs had metastatic spread was unexpected. Overall, 21% (12/57) of cats developed distant metastases, a finding that is in agreement with that of other studies.[8,14,17,18] Specifically, 7 of 41 (17%) cats with grade 1 ISSs and 2 of 13 cats with grade 2 ISSs developed distant metastases, suggesting that relying on histologic grade for treatment decision may not be safe. In fact, lack of recognition of the metastatic potential of grade 1 ISSs may be the result of examination errors, given that small foci of potentially metastatic cells may not be appreciated.

In general, local control status has moderate influence on the development of metastasis.[26,27] It has been documented that local tumor recurrence may select for a more aggressive phenotype, thus increasing the metastatic potential.[8,15,28,29] However, in the study reported here, among the 12 cats that developed metastatic disease, 5 had previously untreated ISSs and 9 had no neoplastic cells detected at the surgical margins. Occurrence of metastasis was not influenced by extent of surgical margins or local control status, and this outcome may support the thesis that more variables need to be taken into account to predict metastatic behavior of ISSs in cats and, ultimately, to drive treatment decisions.

Primary tumor size is an important risk factor for metastasis in humans,[27] with large tumors being associated with an increased metastatic rate. According to findings in 1 study,[15] tumor size has been found to be a prognostic factor in cats with ISSs. In our study, primary tumor size was not prognostically relevant. A conceivable explanation for this observation is that tumor size was mostly measured manually by use of calipers. In fact, if size is to be used to guide treatment decisions, the next issues to be considered are how the size of ISSs should be measured (ie, manually or by use of computed tomographic calculations) and how the prognostic cutoff point in terms of tumor diameter or volume should be determined. It is our opinion that measurements obtained by preoperative computed tomographic-scans are more objective and more readily reproducible, and that tumor size should therefore be established by this technique in a prospective study of cats with ISSs and adequate follow-up. We hypothesize that tumor size, if accurately measured, will likely prove to be a good prognostic indicator. By objectively measuring the complex interaction between tumor and host (eg, the presence of projections of neoplastic cells into the surrounding tissues) the degree of invasiveness of the tumor can be assessed. This theory needs to be evaluated in future prospective studies.

In the study reported here, factors associated with the development of local tumor recurrence were not identified, possibly because of the nonuniform nature of the study population, with some cats having previous surgery with unknown previous size of original tumor, previous histologic grade, and nonuniform use of adjuvant therapy. It is a common observation that complete resection is likely to afford the best chance for disease-free interval and that incomplete gross resection increases the risk for treatment failure.[8,11,17,18,26,28,29] According to the findings in a retrospective study,[8] excision of the primary ISS at referral institutions results in an increased disease-free interval. In Italy, inadequate

initial surgery is still common before consultation with referral centers, thus accounting for a high incidence of local tumor recurrence. In the study reported here, 27 of 57 (47%) cats were admitted with local tumor recurrence following previous surgery elsewhere. However, analysis in our study failed to show a worsening of prognosis in cats initially admitted with locally recurrent disease. Moreover, in the study reported here, complete resection of the tumor was achieved in 54 of 57 (95%) cats; however, although the presence of a contaminated surgical margin led in all cases to local tumor recurrence, local tumor recurrence also developed in 19 cats with complete excision, thereby suggesting that solely an aggressive surgical procedure will not significantly improve the local tumor recurrence rate. An additional consideration is the difficulty in histologically assessing all of the surgical margins from a surgical section.

Primary tumor location has prognostic value, with appendicular ISSs having the best prognosis after radical surgery.[8] This finding may be attributable to the efficacy of amputation. In our cohort of cats, only 1 appendicular ISS was found, and this may be the result of the unfortunate practice of vaccinating in the scapular space, despite the current recommendations.[4] In the study reported here, aggressive surgical procedures may have led to the high postoperative risk of death. These findings reflect the heterogeneous, and in most instances, unpredictable biological behavior of ISSs. According to our results, a high histologic grade increases the probability of distant metastasis, which in turn bears a shorter overall survival. However, a low histologic grade does not rule out the development of local tumor recurrence or distant metastasis. Although clinicians expect pathologists to provide a histologic grade for ISSs, additional information is needed to predict outcome reasonably well. Consequently, it can be assumed that histologic grading alone is not enough to guide treatment decisions. We also believe that assessment of ISSs in cats may not be amenable to the Kuntz grading system, as it does not provide accurate prognostic information. To improve the predictive value of histologic grade, additional morphologic criteria (eg, cellularity, severity of nuclear atypia, presence of malignant giant cells, presence of vascular emboli, and microscopic resection margins) as well as relevant clinical factors (eg, tumor size, depth of infiltration, site of development, and presence or absence of distant metastases) and possibly molecular variables should be considered for inclusion in staging systems. The retrospective design of the study reported here limited our ability to select a uniform population in terms of timing of initial treatment and treatment received; therefore, further evaluation in a prospective study in which treatments are randomized is required.

a. Davidson Marking System, Bradley Products Inc, Bloomington, Minn.
b. SPSS, version 10.0, SPSS Inc, Chicago, Ill.

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