Cyclooxygenase-2 expression is not associated with clinical outcome in synovial sarcoma

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Abstract. Several studies have identified cyclooxygenase-2 (COX-2) expression in a variety of sarcomas, including rhabdomyosarcoma, osteosarcoma and chondrosarcoma. Although overexpression of COX-2 has been associated with poor prognosis and decreased survival in chondrosarcoma and osteosarcoma, no relationship between COX-2 expression and patient outcome has been demonstrated in rhabdomyosarcoma or adult soft tissue sarcomas. Little is known concerning the expression of COX-2 in synovial sarcoma. Therefore, the aim of this study was to examine the expression of COX-2 in synovial sarcoma and if shown, to identify any association with tumor stage and oncologic outcome. Paraffin-embedded specimens from 27 patients with synovial sarcoma who were treated with surgical resection or biopsy were obtained. Specimens were evaluated for the degree of COX-2 expression after immunohistochemical staining. Specimens were assigned an immunoreactivity score (IS) based on the percent positivity of the specimen. A retrospective chart analysis was performed to determine the clinical stage at presentation, incidence of local recurrence, presence of metastatic disease and overall survival. Statistical analysis was then performed to determine whether there was a significant relationship between IS and stage at presentation or patient outcomes. COX-2 expression was detected in 18 of 27 (66.67%) of the pathological specimens. There was a statistically significant relationship between COX-2 expression and patient clinical stage at presentation; however, we were unable to identify a significant relationship between IS and patient survival. We also found no significant relationship between IS and development of metastases or local recurrence. COX-2 was expressed to some degree in 67% of the tumor specimens. There was a significant relationship between IS and patient stage at presentation, but no significant relationship between COX-2 expression and clinical outcome could be identified. The fact that these tumors do express COX-2, however, suggests the potential for an additional target for more effective therapy.

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Introduction

Although rare, with only 9,000 new cases occurring each year in the US, soft tissue sarcoma is a devastating disease (1). Of these new cases, approximately 6-9% are synovial sarcomas (2). Despite advancements in surgical techniques, radiation therapy and chemotherapy, we have accomplished little to change the ultimate outcomes in patients with synovial sarcoma. Metastasis develops in approximately 50% of patients, most often to lung, although metastasis to lymph nodes also occurs in these tumors in approximately 10% of cases. (3-8). Reported 5-year survival rates for synovial sarcoma range from 36 to 76% and 10-year survival ranges from 20 to 63% (9-12). Unlike the success of adjuvant chemotherapy for osteosarcoma, results of chemotherapy for synovial sarcoma have been inconsistent, and have generally been reserved for the most severe cases. To date, no chemotherapy regimen has been shown to consistently improve survival in patients with synovial sarcoma (13-15).

Cyclooxygenase is responsible for the synthesis of prostaglandins from arachadonic acid. Two isoforms of cyclooxygenase have been described. Cyclooxygenase-1 is expressed constitutively in most tissues and is responsible for the production of prostaglandins required for normal physiologic functions (16). Cyclooxygenase-2 (COX-2) is not expressed in most normal tissues, but is induced in inflammatory and tumor cells by several cytokines and growth factors (17). COX-2 production has been associated with decreased apoptosis, as well as increased angiogenesis and matrix metalloproteinase production (18-21) all of which contribute to tumor growth and increased tumorigenicity. COX-2 has been shown to be expressed in a variety of adult solid tumors, such as squamous cell, cervical, lung and colon carcinomas (22-25). COX-2 has also been shown to be expressed in a variety of sarcomas, including rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma and chondrosarcoma (26-28). Furthermore, inhibition of COX-2 both *in vivo* and *in vitro* has shown significant antiproliferative effects against multiple

tumor types (29-35). Although overexpression of COX-2 has been associated with poor prognosis in chondrosarcoma (36), esophageal squamous cell carcinoma (37) and osteosarcoma (38,39), no relationship between COX-2 expression and patient outcomes has been identified in either rhabdomyosarcoma or most adult soft tissue sarcomas (40).

Little is known about COX-2 expression in adult soft tissue sarcomas, and even more specifically synovial sarcoma. Whether COX-2 expression has any relationship with the clinical outcomes of patients with synovial sarcoma has not been determined. We examined pathological specimens from 27 patients with synovial sarcoma, from our institution, for the degree of COX-2 expression. The primary aim of this study was to evaluate COX-2 expression patterns in synovial sarcoma. Additionally, we attempted to define a relationship between known prognostic variables, including histological grade, tumor stage and clinical outcome, with the intensity of COX-2 expression upon immunohistochemical staining.

Materials and methods

Immunoreactivity score. This study was approved by the Institutional Review Board of the University of Florida. Twenty-seven synovial sarcoma tissue specimens were obtained from the tissue bank in the Department of Pathology at the University of Florida. All tissue samples were formalin-fixed and paraffin-embedded. After immunohistochemical staining for the presence of COX-2, all specimens were evaluated by the head musculoskeletal pathologist (J.R.) who had no knowledge of patient identity or patient clinical outcome. Immunoreactivity of COX-2-stained cells was graded according to the following scale, indicating percent positive cells: 0, 0-4%; 1, 5-24%; 2, 25-49%; 3, 50-74%; 4, 75-100%.

Immunohistochemical staining. Formalin-fixed paraffin-embedded tissue sections were prepared from tissue specimens obtained at the time of surgery. Sections (5-μm) were cut and allowed to dry overnight at room temperature. After drying, the slides were sequentially deparaffinized, rehydrated, and blocked for endogenous peroxidase activity. Optimal staining required 25 min of heat antigen retrieval in 10 mM citrate buffer at a pH of 6.0. Ready-to-use rabbit monoclonal anti-COX-2 antibody (Neomarkers, Freemont, CA) was applied to the sections, and they were incubated overnight at 4˚C. Slides were then stained using the ABC-Elite kit (Vector Laboratories, Burlingame, CA) according to the manufacturer's protocol. Positive staining was detected with DAB (Vector Laboratories) as the chromogen and hematoxylin 560 (SurgiPath, Richmond, IL) as the counter stain. Colon cancer was used as the positive control.

Clinical data correlation. Twenty-seven consecutive patients from 1998 to 2007, diagnosed with synovial sarcoma, were identified using the Department of Pathology specimen database. All of the patients in the study received surgical treatment and follow-up care at the University of Florida. Clinical details were obtained by reviewing the patient medical charts. The patient group was comprised of 18 men and 9 women between the ages of 7 and 78 (mean age 46). The tumors were located in the axial skeleton in 2 cases (1 chest wall mass and 1 paraspinal mass), the upper extremity in 10 cases, and the lower extremity in 15 cases. Nineteen patients underwent wide resection, 7 patients underwent amputation, and 1 patient underwent biopsy only, as this patient died of disease during pre-operative radiation therapy and never underwent definitive surgery. Four patients presented with metastatic disease.

Table I. Immunoreactivity score for COX-2 expression in soft tissue sarcoma pathological specimens.

Immunoreactivity score	Percent positive cells
0	<5
1	5-24
2	25-49
3	50-74
4	75-100

The follow-up period was dated from the time of diagnosis. Follow-up ranged from 3 to 113 months (mean follow-up 48 months). Disease-specific survival was recorded from the date of diagnosis until the time of death from tumor-related causes. Immunoreactivity scores were calculated as described above. Immunoreactivity scores were then correlated with the patient clinical stage at presentation (both the Musculoskeletal Tumor Society and American Joint Committee on Cancer staging systems were used), development of local recurrence, development of metastasis and disease-specific survival. In this study disease-specific survival and overall survival were identical as all patients who expired, died of their disease.

Statistical analysis. Clinicopathological correlations were calculated using χ^2 analysis. Overall survival was determined using the Kaplan-Meier method. Statistical significance was defined as $P<0.05$.

Results

COX-2 expression in synovial sarcoma pathological specimens. We previously examined 20 soft tissue sarcoma specimens of various histological subtypes. Of these, only the synovial sarcoma specimens consistently expressed COX-2 (data not shown). Therefore, subsequent study focused on COX-2 expression in synovial sarcoma. An immunoreactivity score was assigned to each specimen based on the percentage of cells within the specimen staining positive for COX-2 (Table I). Representative sections of COX-2-staining patterns are illustrated in Fig. 1. Overall, 18 of 27 (66.67%) synovial sarcoma specimens showed some immunoreactivity for COX-2. Of these, 5/27 (18.52%) had an immunoreactivity score of 1, 7/27 (25.93%) had an immunoreactivity score of 2, 6/27 (22.22%) had an immunoreactivity score of 3, and 1/27 (3.70%) had an immunoreactivity score of 4 (Fig. 2). All specimens were considered high grade according to the American Joint Committee on Cancer grading system.

COX-2 expression and clinical stage at presentation. Clinical information was analyzed for all 27 patients and the clinical

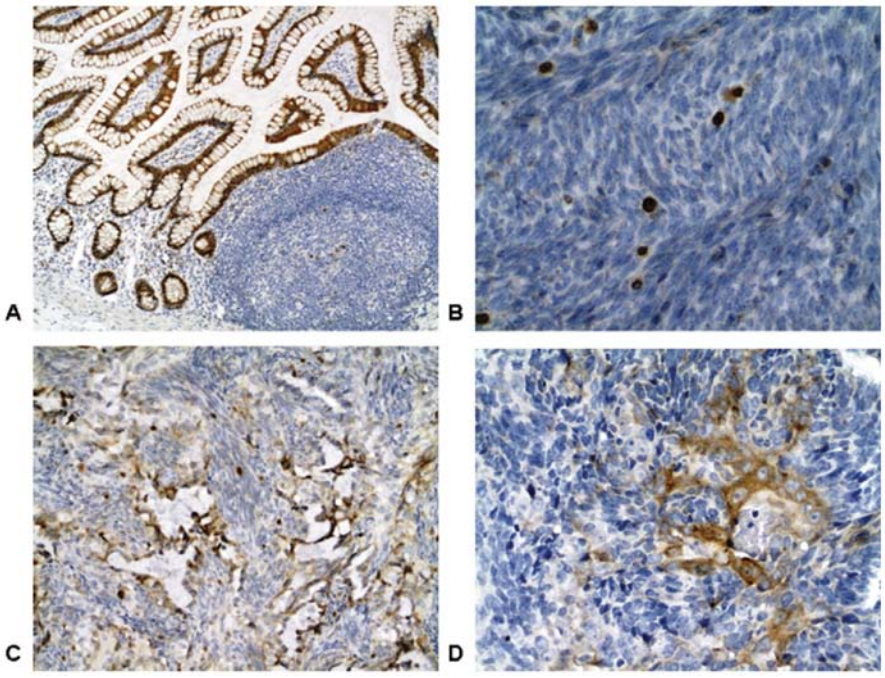

Figure 1. Cyclooxygenase-2 (COX-2) expression in synovial sarcoma tissue specimens. (A) Small bowel positive control (x20). (B) Negative specimen with only mast cells staining positive (x40). Immunoreactivity score (IS), 0. (C) Representative specimen IS, 2 (x20). (D) Representative specimen IS, 3 (x40).

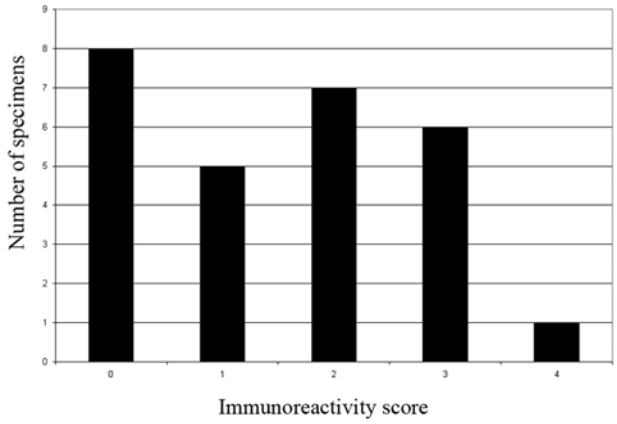

Figure 2. Cyclooxygenase-2 (COX-2) immunoreactivity. Scores in the synovial sarcoma specimens. This graph depicts the results of 27 specimens.

stage of the patients at presentation, according to both the Musculoskeletal Tumor Society (MSTS) and the American Joint Committee on Cancer (AJCC) classification systems, was identified. COX-2 immunoreactivity score and clinical stage for each staging system are provided in Tables II and III. Based on the MSTS staging system 6/27 (22.2%) presented at stage IIa, 17/27 (63.0%) presented at stage IIb, and 4/27 (14.8%) presented at stage III. When using the AJCC staging system, 7/27 (7.4%) of patients presented at stage II, 21/27 (77.8%) presented at stage III, and 4/27 (14.8%) presented at stage IV. COX-2 staining intensity tended to be higher in patients who presented at a more advanced clinical stage. Patients with immunoreactivity scores of 3 and 4 presented at a higher clinical stage. This correlation was statistically significant (P=0.03).

Table II. Intensity of COX-2 expression according to MSTS stage.

		COX-2 expression (IS)				
MSTS stage	n	0	1	2	3	4
IIa	6	4	2	0	0	0
IIb	17	4	1	6	5	1
III	4	0	2	1	1	0
Total samples	27	8	5	7	6	1

Table III. Intensity of COX-2 expression according to AJCC stage.

		COX-2 expression (IS)				
AJCC stage	n	0	1	2	3	4
II	2	0	2	0	0	0
III	21	8	1	6	5	1
IV	4	0	2	1	1	0
Total samples	27	8	5	7	6	1

COX-2 expression and clinical outcome. At the last follow-up, 14 of the 27 patients (52%) had died as a result of their disease, 11 patients (41%) were alive with no evidence of disease, and 2 patients (7%) were alive with disease. When examining the patient group as a whole, there was no significant difference (P=0.65) in survival in patients who had COX-2-positive versus COX-2-negative specimens (Fig. 3). When examining

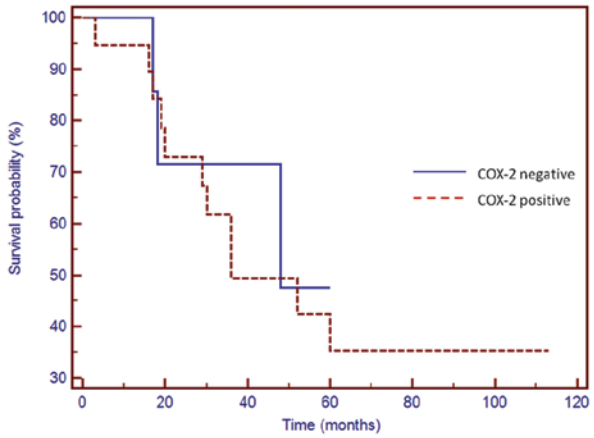

Figure 3. Overall survival rate of all patients (n=27) using the Kaplan-Meier method. COX-2 expression was not associated with survival (P=0.65).

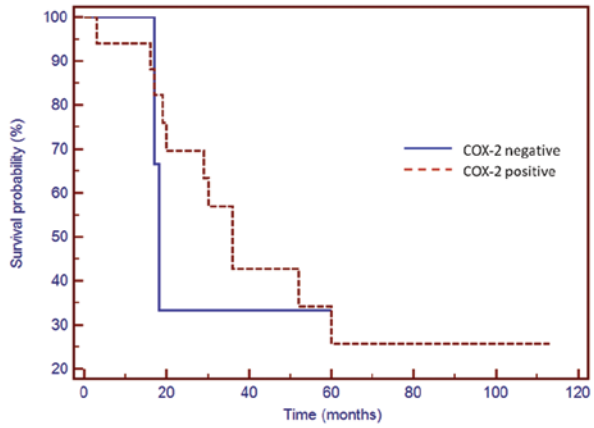

Figure 4. Overall survival rate of patients who presented at MSTS stage IIb or AJCC stage III or higher using the Kaplan-Meier method. COX-2 expression was not associated with decreased survival in patients presenting at a more advanced stage (P=0.78)

only patients who presented with an MSTS stage IIb or an AJCC stage III or higher (Fig. 4), there was no significant difference in survival between patients with COX-2-positive vs. COX-2-negative specimens (P=0.78). Sixteen of 27 patients (59%) either presented with or developed pulmonary metastasis. Of these, 14 of the 16 (88%) died from their disease. There was no significant correlation between development of pulmonary metastasis and COX-2 expression. No patients developed a local recurrence.

Discussion

COX-2 is expressed in a variety of solid tumors including osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma and chondrosarcoma. In addition, overexpression of COX-2 is associated with poor clinical outcome in several types of cancer. However, little is known regarding COX-2 expression in adult soft tissue sarcomas, and even more specifically in synovial sarcoma. Therefore, we examined the expression of COX-2 in synovial sarcoma and its relationship to clinical stage at presentation, development of local recurrence, distant metastasis and overall survival.

Our data revealed that a significant number of the synovial sarcoma specimens had some degree of COX-2 expression, although, the degree of expression varied greatly. A previous study by Lassus *et al* (41) examined 103 soft tissue sarcomas for COX-2 expression. Of those, roughly 50% had some degree of COX-2 expression, but all 10 of the biphasic synovial sarcomas expressed COX-2 to some level. In that study, only the epithelial components of these tumors were positive. Notably, it was the epithelial component of the biphasic tumors in our specimens that stained the most robustly for COX-2. However, the non-epithelial component of some biphasic tumors, and several of the monophasic specimens expressed COX-2 as well.

Previous studies have linked COX-2 expression to poor clinical outcomes in a variety of solid tumors. Despite our statistically significant correlation between COX-2 expression and clinical stage at presentation, we were unable to correlate COX-2 expression with the clinical outcome of the patients. Our data suggest that although patients with a higher degree of COX-2 expression presented at a more advanced clinical stage, this did not affect the development of metastasis, local recurrence or survival. This is similar to the results of both Lassus *et al* and Herceg *et al* (41,42) who found no relationship between COX-2 expression in soft tissue sarcoma, and more specifically leiomyosarcoma, with the clinicopathological parameters evaluated.

Although COX-2 expression may not be useful as a prognostic tool in synovial sarcoma it still may be important in treating the disease. The fact that the majority of the synovial sarcoma specimens in our study expressed COX-2 to some degree implies that it may still be a potential target for chemotherapeutic intervention. Further investigation is needed to determine potential roles for COX-2 in the treatment of synovial sarcoma.

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