Objective: To report outcome in dogs after internal fixation of a sarcoma-related pathologic fracture of the appendicular skeleton.

Study Design: Multi-institutional case series.

Animals: Dogs (n = 16).

Methods: Medical records of participating VSSO members were reviewed for dogs with pathologic fracture associated with a confirmed bone sarcoma of the appendicular skeleton repaired by external or internal fixation. Dogs were included if they had a histological diagnosis of osteosarcoma or sarcoma and excluded if they had radiation before fracture. Data collected were analyzed for signalment, fracture location, staging performed, method of fracture fixation, histopathology, adjunctive treatment and outcome.

Results: Signalment and fracture location of 16 dogs that met the inclusion criteria was similar to dogs with appendicular OSA without fracture. One of 14 dogs had pulmonary metastasis and 3 of 5 dogs had bone metastasis. Bone plate or interlocking nail were used for repair in 12 dogs. Limb use immediately after surgery in 13 dogs was good (4), weight-bearing but lame (7) and non-weight bearing (2). Adjunctive therapy was administered in 5 dogs (chemotherapy, 3; radiation, 4; pamidronate, 3). Survival time ranged from 18 to 897 days; median survival was 166 days.

Conclusions: Repair of pathologic fracture can result in palliation and prolonged survival.

Current therapy for canine osteosarcoma (OSA) includes removal of the primary tumor and treatment of presumed micrometastatic disease with adjunctive chemotherapy. In dogs, pathologic fracture of the appendicular skeleton associated with OSA is usually treated by amputation or the dog is euthanatized. Rarely, are these fractures repaired. Fracture repair may be attempted if severe concurrent orthopedic or neurologic disease precludes amputation, if the pathologic nature of the fracture is only recognized postoperatively, or with informed consent of an owner aware of the risks.

Pathologic fracture is relatively rare in human appendicular OSA; 5–10% of cases present as a pathologic fracture or develop a fracture during treatment. The equivalent incidence in dogs is unknown but is suspected to be low. In a retrospective study covering 20 years, there were 76 dogs with pathologic fractures treated by amputation with or without chemotherapy. In a 10-year study, there were 25 dogs with pathologic fracture, only 7 of which were treated, 3 by internal fixation. It is our clinical impression that some dogs with repaired pathologic fractures have good limb use and a relatively long survival. Although uncommon in veterinary medicine, the stabilization of bone cancer for impending pathologic fracture because of metastatic cancers has now become standard practice in human cancer patients.

Given the relatively low incidence of pathologic fractures associated with appendicular OSA in dogs, we pooled cases across multiple institutions through the Veterinary Surgery.
Society of Surgical Oncology (VSSO) Research Committee to improve understanding of outcome after repair of these fractures by external or internal fixation and to potentially develop management guidelines.

MATERIALS AND METHODS

Inclusion Criteria

Medical records (1995–2009) of participating institutions were reviewed for dogs with appendicular OSA or undifferentiated sarcoma that had a fracture of the appendicular skeleton repaired by external or internal fixation. Dogs were included if there was a histologic diagnosis of OSA or undifferentiated sarcoma, a pathologic fracture of the appendicular skeleton associated with the tumor, and repair of the fracture by external or internal fixation.

Dogs were excluded if a histologic diagnosis was not available or if they were administered palliative or full-course radiation before identification of pathologic fracture.

Data retrieved were: signalment, body weight, site affected, description of the fracture, staging tests completed and results, histopathology report confirming diagnosis of OSA or sarcoma at the fracture site, description of the fracture fixation method, adjunctive therapy (chemotherapy, radiation, or pamidronate) administered, concurrent systemic disease, concurrent treatments, intercurrent disease, limb use after repair, serum alkaline phosphatase (ALP) concentrations on admission, metastasis-free interval (MFI), cause of death, and survival time (ST). Case information was collected using a standardized case accrual form filled out by the contributing authors.

Serum ALP concentration was considered normal if it was within the reference interval of 22–143 U/L. Postoperative limb use was described by the attending clinician as poor, fair, good, or excellent. Disease-free interval (DFI) was defined as the number of days from fracture repair to evidence of metastatic disease. ST was defined as the number of days from fracture repair to death. Date of death was confirmed by the contributing author, who was, in most cases, the surgeon who repaired the fracture. Death dates were determined by file review, contact with the referring veterinarian or owner. Cases were censored if they were lost to follow-up or if the cause of death was not considered neoplasia-related.

Statistical Analysis

The cause of death was classified as neoplasia-related, or nonneoplasia-related. Dogs with unknown causes of death were presumed to have died from neoplasia-related disease. For survival calculations, dogs that had neoplasia-related death were considered completed events and dogs lost to follow-up, died of causes other than sarcoma (confirmed by necropsy), or were still alive without evidence of metastasis were censored at the time of last contact.

This was largely a descriptive study, depicting signalment, age, weight, fracture location, serum ALP concentration, repair method, staging tests, histopathologic diagnosis, adjunctive therapy, and outcome. The Kaplan–Meier method was used to determine median ST. ST for dogs that had adjunctive treatment was compared with dogs not administered adjunctive treatment using a Wald χ²-test from a Cox proportional hazard model. A P-value of < .05 was considered statistically significant. Software (SAS OnlineDOC® 9.1.3., SAS Institute Inc., Cary, NC, 2004) was used for statistical analysis.

RESULTS

Sixteen dogs (Table 1) met the inclusion criteria; follow-up information was available for 14 dogs. Breeds were Rotweiler (4), Greyhound (3), and 1 each of various other breeds. There were 8 spayed females, 6 castrated males, and 2 intact males. Age at admission ranged from 6 to 12 years (median, 9 years). Median weight was 37.6 kg.

Fractures

Bones involved were femur (n = 7; 3 distal, 3 diaphyseal, and 1 proximal), humerus (n = 4; 2 proximal, 1 distal, 1 diaphyseal), distal aspect of the radius (n = 3), and distal aspect of the tibia (n = 2). One dog (dog 12) had a mid-diaphyseal femoral fracture at the distal tip of a femoral implant for total hip replacement. No other cases of implant-related sarcoma were noted. In 12 dogs, there was a known neoplastic lesion at time of repair based on presence of an aggressive bone lesion radiographically at the fracture site. In dogs 3 and 14, neoplasia was suspected, but was not obvious radiographically or at the time of surgical repair. In dogs 12 and 16, neoplasia was not suspected at time of repair and did not become apparent until clinical and radiographic signs progressed after fracture repair. OSA was diagnosed in 13 dogs and 3 dogs (dogs 4, 14, 15) had a histologic diagnosis of bone sarcoma. OSA subtype diagnosis was not performed except in dog 12, which had a telangiectactic OSA.

Metastatic Disease

No evidence of pulmonary metastasis was identified in 13 of 14 dogs that had preoperative thoracic radiographs; dog 13 had radiographic and CT evidence of pulmonary metastasis. Dog 6 had radiographic evidence of an enlarged sternal lymph node. Long bone survey radiography was not performed in any of the dogs. Bone scintigraphy was performed in 5 (31%) dogs; bone metastasis was identified in 3 dogs. In dog 5, a distal radial pathologic fracture was stabilized and palliative radiation administered to the site. In this dog, preoperative scintigraphy showed no evidence of bone metastasis. The bone scan was repeated at 11 months. When evaluated together, both scans showed increased uptake of radiopharmaceutical in the affected.
### Table 1  Summary Data for 16 Dogs with Sarcoma-Related Pathologic Fracture

<table>
<thead>
<tr>
<th>Dog</th>
<th>Signalment</th>
<th>Weight (kg)</th>
<th>Fracture Site</th>
<th>Repair Method</th>
<th>ALP (U/L)</th>
<th>Metastasis</th>
<th>Adjunctive Treatment</th>
<th>Survival Time (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 y FS Rottweiler</td>
<td>50</td>
<td>L proximal humerus</td>
<td>Interlocking nail</td>
<td>144</td>
<td>No</td>
<td>ND</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>6 y FS German Shepherd</td>
<td>34.8</td>
<td>L proximal humerus</td>
<td>Interlocking nail</td>
<td>98</td>
<td>No</td>
<td>Yes</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>9.5 y FS Greyhound</td>
<td>37</td>
<td>L midhumerus</td>
<td>Plate-rod</td>
<td>33</td>
<td>No</td>
<td>ND</td>
<td>&gt; 39</td>
</tr>
<tr>
<td>4</td>
<td>7 y M Flat-coated Retriever</td>
<td>42</td>
<td>R humeral condyle and diaphysis</td>
<td>Plates, screws</td>
<td>Normal</td>
<td>No*</td>
<td>ND</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>6 y MC Newfoundland</td>
<td>58</td>
<td>L distal radius</td>
<td>Bone plate with carpal arthrodesis</td>
<td>39</td>
<td>No</td>
<td>No</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>7.5 y MC mixed breed</td>
<td>36.4</td>
<td>R distal radius</td>
<td>Steinman pin and rush pins</td>
<td>83</td>
<td>No*</td>
<td>ND</td>
<td>C, R†</td>
</tr>
<tr>
<td>7</td>
<td>8 y MC Borzoi</td>
<td>38.2</td>
<td>R distal radius</td>
<td>Circular skeletal fixator</td>
<td>84</td>
<td>No</td>
<td>Yes*</td>
<td>&gt; 659</td>
</tr>
<tr>
<td>8</td>
<td>9 y MC Rottweiler</td>
<td>51.8</td>
<td>R proximal femur</td>
<td>Bone Plate</td>
<td>—</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>6 y MC Rottweiler</td>
<td>43</td>
<td>R distal femur</td>
<td>Plate femur and radius (met)</td>
<td>219</td>
<td>No</td>
<td>Yes</td>
<td>C, R, P</td>
</tr>
<tr>
<td>10</td>
<td>12 y FS Springer Spaniel</td>
<td>23</td>
<td>R distal femur</td>
<td>Interlocking nail</td>
<td>127</td>
<td>No</td>
<td>ND</td>
<td>R, P</td>
</tr>
<tr>
<td>11</td>
<td>12 y FS Greyhound</td>
<td>30.6</td>
<td>L diaphyseal femur</td>
<td>Interlocking nail</td>
<td>20</td>
<td>No</td>
<td>No</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>11 y FS Rottweiler</td>
<td>44</td>
<td>R diaphyseal femur§</td>
<td>Plate, screws</td>
<td>69</td>
<td>No</td>
<td>ND</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>10 y M Mastiff</td>
<td>84</td>
<td>R femur</td>
<td>Locking plate</td>
<td>105</td>
<td>Yes (CT confirmed)</td>
<td>ND</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>12 y FS Shetland Sheepdog</td>
<td>18</td>
<td>L distal femur</td>
<td>Condyle plate</td>
<td>96</td>
<td>No</td>
<td>ND</td>
<td>&gt; 110</td>
</tr>
<tr>
<td>15</td>
<td>9 y FS Labrador Retriever</td>
<td>27</td>
<td>R distal tibia</td>
<td>Double plate</td>
<td>—</td>
<td>No</td>
<td>ND</td>
<td>&gt; 17 months</td>
</tr>
<tr>
<td>16</td>
<td>11 y MC Greyhound</td>
<td>26.2</td>
<td>R distal tibia</td>
<td>External fixator</td>
<td>141</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
</tr>
</tbody>
</table>

*Enlarged sternal lymph node.
†Dog had a primary lesion of the right distal radius, bone scan showed increased uptake in the opposite radius as well, indicating either a metastatic or synchronous lesion.
§Previous total hip replacement at this site.
F, female; M, male; FS, spayed female; MC, castrated male; R, right; L, left; ND, not done, indicating that either 3-view thoracic radiography or bone scan were not performed; N, none, indicating no adjunctive therapy; C, chemotherapy; R, radiation therapy; P, pamidronate; ALP, alkaline phosphatase; LTF, lost to follow-up; y, year.
lesion, but the region was significantly less intense in the 2nd scan, indicating some response to treatment.

In dog 7, with a distal radial pathologic fracture, scintigraphy identified a 2nd region of increased radiopharmaceutical uptake in the contralateral radius; and although it was not possible to determine if this was a metastatic or synchronous bone lesion, it was considered a metastatic site for this study. There was insufficient information to accurately determine date of metastasis in these dogs, and therefore determine MFI.

Preoperative serum ALP concentration was measured in 13 dogs. It was described as within the normal range (no value recorded) for 1 dog and was not reported in 2 dogs. For 11 dogs, ALP was within the reference interval of 22–143 U/L and increased in 2 dogs (dog 1 = 144 U/L; dog 9 = 291 U/L).

Fracture Repair
Methods of fracture repair were: bone plate (n = 8), interlocking nail (4), combined plate-rod (1), Steinman pin with rush pins (1), circular fixator (1), and external fixator (1). Curettage and bone cement was not used in any repair. Postoperatively, dogs subjectively appeared to use the limb similarly to that expected after repair of a traumatic fracture. Four dogs were described as having good limb function or a mild lameness postoperatively, 7 dogs as having weight-bearing lameness, and 2 dogs as nonweight bearing on the limb immediately postoperatively.

Adjunctive Therapy
Chemotherapy (alternating doxorubicin/carboplatin) was administered in 3 dogs, pamidronate in 3 dogs, and radiation in 5 dogs (with a palliative-intent in 4 and full-course radiation in 1). All dogs treated with adjunctive therapy received > 1 treatment type (chemotherapy, radiation and pamidronate; Table 1). Five dogs had adjunctive therapy and 11 dogs did not.

Outcome
Information on long-term limb use in was difficult to acquire. Dogs 9, 12, and 16 were euthanized because of progression of local disease at 394, 64 and 113 days postoperatively, respectively.

Two dogs ultimately had limb amputation. Dog 15 had amputation 17 months after fracture repair because of recurrence of lameness and disease progression. This dog had not been lame until just before amputation. Dog 3 had amputation 33 days postoperatively after OSA was confirmed on histopathology. There was no obvious radiographic evidence of a bone tumor preoperatively, the fracture developed after minimal trauma and the site was biopsied because of the attending clinician’s suspicion of a bone tumor. The decision to amputate was based on the diagnosis and treatment recommendations, rather than unsatisfactory limb use. Radiographic evidence of fracture healing was observed in dog 10. Information on fracture healing was not available for the other dogs.

Date of death was known in 8 dogs; 7 were euthanized because of local disease or poor quality of life and dog 13 died from respiratory arrest 18 days after fracture repair. This dog had thoracic metastasis on admission. Four dogs were lost to follow-up and were censored at the date of last contact (range, 218–897 days after fracture repair). Two dogs were still alive (39 and 110 days). Two dogs were lost to follow-up immediately after hospital discharge.

Survival ranged from 18 to 897 days with a median survival of 166 days. Median ST for the 5 dogs administered adjunctive treatment (chemotherapy, radiation and/ or pamidronate) was 394 days and was not significantly different from median ST of 110 days for the 11 dogs that did not (P = .13)

DISCUSSION
We found that dogs that had repair (internal or external fixation) of a pathologic appendicular skeleton fracture associated with OSA or undifferentiated sarcoma was technically feasible, appeared to reduce pain and in some cases, led to a prolonged ST. Median survival was 166 days, and 5 dogs survived > 1 year. Although there was not a significant difference in median survival, likely reflecting low power in this study, adjunctive therapy seemingly resulted in longer median survival. One dog in this series had evidence of gross pulmonary metastasis and this patient had a very short ST (18 days). This poor outcome was interpreted to be associated with the stage of disease, rather than the treatment of the pathologic fracture. Overall, these findings suggest that similar to approaches used in people, repair of such fractures in dogs should be considered, and guidelines for case selection should be developed. Whereas this recommendation might be viewed as controversial and of ethical concern, there is evidence in human oncology to support such an approach.

Between 5% and 10% of people with OSA are diagnosed with a pathologic fracture either at admission or during treatment. Historically, pathologic fractures in people were treated by immediate amputation, because of concern that progression of the fracture and fracture hematoma will increase the risk of tumor local or hematogenous dissemination of tumor, pre- or intraoperatively. This remains controversial, with some authors favoring immediate amputation for improved survival and decreased risk of local recurrence and others suggesting that similar rates of local recurrence and survival occur when pathologic fractures are treated with either amputation or limb spare. When limb spare is performed, external coaptation or, more rarely, internal fixation and neoadjuvant chemotherapy are used before limb spare with mega-prosthesis. , the DFI and ST are decreased in people with pathologic fracture from OSA compared with nonfractured, age-matched OSA patients that present without a pathologic fracture. However, the method of
surgical treatment (amputation or limb salvage) did not appear to have an effect on local recurrence or survival.9,11

When treated with external coaptation and chemotherapy, pathologic fractures in people appear to heal9 in most cases, with an increased healing seen in patients with an increased percentage of tumor necrosis histologically.9 This supports the notion that similar bone tumors in dogs may heal when treated with a combination of fracture stabilization and chemotherapy to induce tumor necrosis. Radiographic evidence of fracture healing was observed in the only dog evaluated, suggesting that similar outcomes are possible in dogs with appropriate stabilization and adjunctive treatment.

Aside from this report there is limited information in dogs to guide development of approaches to management of these fracture types. A dog with 3 concurrent pathologic fractures from multiple myeloma was treated successfully with surgical stabilization and cementoplasty, resulting in good limb function and a ST of 8 months with concurrent chemotherapy.12 The signalment and location of the primary bone tumor in 16 dogs we describe is similar to dogs with appendicular OSA without pathologic fracture.1

Fracture stabilization directly addresses pain by preventing fracture motion as well as tumor micromotion, allowing weight-bearing forces to be transferred through the implant, rather than the fracture or tumor. This strategy has been used in people with metastatic bone cancer to treat and prevent pathologic fracture, to palliate the pain associated with bone metastasis and impending fracture, and to improve quality of life and limb function in most patients.13–17 This approach is so successful that it is currently recommended for human patients with metastatic bone cancer, regardless of their long-term prognosis.13–17 This treatment approach could be adopted for dogs with pathologic fracture and concurrent orthopedic or neurological disease that preclude amputation when the owner’s goal is palliation despite a guarded long-term prognosis.

Fractures (4 diaphyseal, 12 metaphyseal) in these locations lend themselves to fixation with an interlocking nail or bone plate and method of repair will depend on a number of considerations. Curettage and bone cement was not used in any of these dogs. This is noteworthy, because this method has been reported in people14,18–20 and also in dogs12 for treatment of pathologic fractures. Bone cement may be useful when bone lysis has resulted in a deficiency of bone stock for reconstruction and repair. The disadvantage of conventional bone cement (polymethylmethacrylate) is that the interposition of bone cement between the fractured remnants of bone will preclude the possibility of bone healing. Newer generation bone cement materials made of calcium phosphate may provide a more biocompatible option for augmentation of pathologic fracture repair.21

Deciding whether or not to repair a pathologic fracture is challenging and will depend on many factors. The owners will influence decision making to some degree if they are unwilling to consent to amputation. Aside from having a fracture configuration that is amenable to reconstruction and fixation, other factors need to be considered. Identification of metastatic disease is important but also challenging from a management perspective, especially the use of bone scintigraphy, before fracture repair. Of 5 dogs that had bone scintigraphy, 3 had bone metastasis. This high frequency was surprising and may simply reflect chance and a small sample size, or that canine OSA associated with pathologic fracture has a slightly different metastatic pattern. Further investigation of this is needed. Regardless, these findings highlight the importance of evaluating all OSA patients for evidence of pulmonary and bone metastasis before fracture repair, especially when knowledge of metastatic disease may change the owner’s treatment choice. However, scintigraphy poses challenges when used for staging because of the need to isolate dogs after radiopharmaceutical administration, which delays definitive fracture treatment and limits the ability to assess the patient and administer parental analgesics. Alternatively, long bone survey radiographs or CT under anesthesia are options that could be recommended before considering pathologic fracture repair.

It is tempting to speculate that leaving the primary tumor in situ may also be responsible for some of the relatively long STs we observed, because the presence of the primary tumor may suppress the progression of metastatic disease. Termed concomitant resistance, this phenomenon has been reported in animal models of OSA22–24 and in human OSA patients.25–27 Further evaluation of concomitant resistance is warranted in canine OSA. It is likely mediated by suppression of angiogenesis by the primary tumor.23,24,26

We saw a longer median ST (394 days) when adjunctive therapy (chemotherapy, pamidronate, and/or radiation) was used with fracture repair compared with 110 days in dogs not administered adjunctive treatment; however this difference was not significant. This may be because there is no improvement in survival with the addition of adjunctive therapy, or may represent a type II error, because of small case numbers and low statistical power. However, we believe that adjunctive therapy may improve survival and patient comfort and should be considered in combination with pathologic fracture repair.

Based on this series and until more clinical experience is gained, we have developed initial guidelines for case selection. There are 4 factors to consider when determining the best treatment option for a patient with a pathologic fracture: the capacity for amputation, the stage of disease, the fracture conformation, and owner commitment to pursue chemotherapy to treat micrometastatic disease. The overall condition of the dog and the concurrent neurologic or orthopedic conditions that might preclude amputation. Owners may also categorically rule out amputation, despite this being the recommended treatment. All dogs admitted with a suspected pathologic fracture should be staged for evidence of metastasis. A minimum of 3-view thoracic radiographs and long bone survey radiographs should be performed. Although bone scan is considered more sensitive, it is difficult to perform when there is pathologic fracture for reasons mentioned previously. The 1 dog in this
series that had pulmonary metastasis had a short ST and succumbed to respiratory arrest 18 days postoperatively, likely because of the metastases and on this evidence, pathologic fracture repair in this setting will predictably be associated with a guarded prognosis. However, even with the guarded prognosis, rigid stabilization of the fracture may subjectively be less painful than external coaptation in cases when euthanasia is refused. Although management of this case is controversial, palliation of pain was the primary focus and euthanasia was recommended to the owner, but refused.

Fractures in a diaphyseal location are more amenable to fracture fixation; however, most cases of OSA and therefore pathologic fractures are metaphyseal and this location should not exclude fracture fixation. The degree of bone lysis is also a factor to consider and severe lysis may make fracture repair more challenging. Curettage and filling the defect with bone cement was not used in any of these dogs, but could be considered in a severely lytic tumor. Although bone healing has been seen with pathologic fracture repair, healing may be impaired or slower than normal, or may not occur. For this reason, internal fixation may be a better option for repair than an external fixator if this repair technique is feasible.

Finally, the time, effort, morbidity, and finances invested in pathologic fracture repair necessitates a firm commitment to improve survival by pursuing conventional chemotherapy postoperatively. It should be stated that this is always considered a palliative procedure and that every case should be evaluated individually. Chemotherapy is not a requirement of this palliative procedure, but may help improve survival and comfort. These are not intended to be rigid guidelines, but a starting point when faced with a pathologic fracture when amputation is not an option. As with any treatment with a goal of palliation, continual reassessment to gauge limb use and quality of life is essential.

Summarily, case selection criteria for pathologic fracture repair include: cases where amputation has been ruled out for patient or owner reasons, those negative for gross metastasis, those with a fracture amenable to repair with minimally morbid techniques, and those owners who will commit to conventional chemotherapy after surgery.

We are aware that the decision to repair a suspected pathologic fracture in dogs with OSA or bone sarcoma is likely to be controversial. The repair of a pathologic fracture will raise ethical concerns that are valid, but beyond the scope of this article. The current system and veterinarian–client–patient relationship dictate that the role of a veterinarian is to evaluate the patient and advise the client based on medical knowledge and, hopefully to a much lesser extent, personal beliefs. Our clients then make treatment decisions on their pets’ behalf. Within this current system, we can do much more for our patients’ welfare by working with, rather than against our clients’ wishes and belief system, recognizing that this may not be in alignment with our own. The aim and scope of this retrospective study was to evaluate the frequency of this procedure and report on its outcome. We believe that the outcome in these 16 dogs is encouraging and suggests that this is a reasonable approach and alternative to amputation and euthanasia in select cases. Repair resulted in palliation of pain associated with fracture and prolonged STs in some dogs. Prospective evaluation of a larger series of dogs will allow further refinement of guidelines for case selection.

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REFERENCES